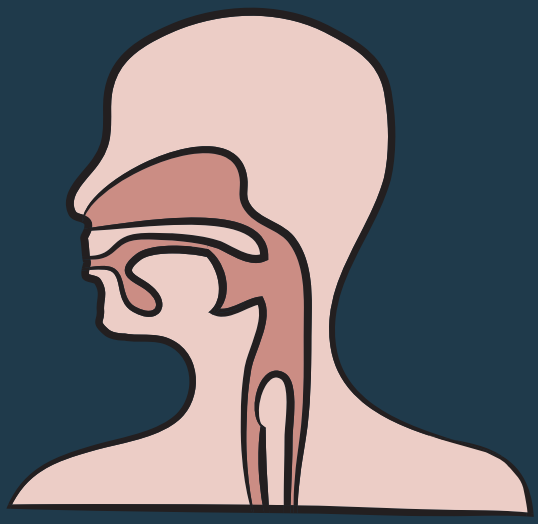
Functional Impairment and Cues for Rehabilitation of Head and Neck Cancer Patients



Rebecca Tosca Karsten

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COLOFON

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Chapter 1

General introduction

GENERAL INTRODUCTION

Head and neck cancer

Head and neck cancer (HNC), cancer of the upper aerodigestive tract above the level of the clavicles, annually affects around 3.000 people in the Netherlands with over 900 head and neck cancer (HNC) related deaths reported each year (1). The most common histopathological subtype, comprising over 90% of all HNCs, is squamous cell carcinoma, which originates from the mucosal lining of the upper aerodigestive tract. HNC is categorized by the anatomical subsite it originates from, including the oral cavity, oropharynx, larynx, hypopharynx, nasopharynx, and nasal cavity and paranasal sinuses (figure 1). The most common risk factors are alcohol and tobacco abuse. However, also viral infections with the Human Papilloma Virus (HPV) and Epstein Barr Virus (EBV) play an important role in the carcinogenesis of oropharyngeal and nasopharyngeal cancer (2, 3).

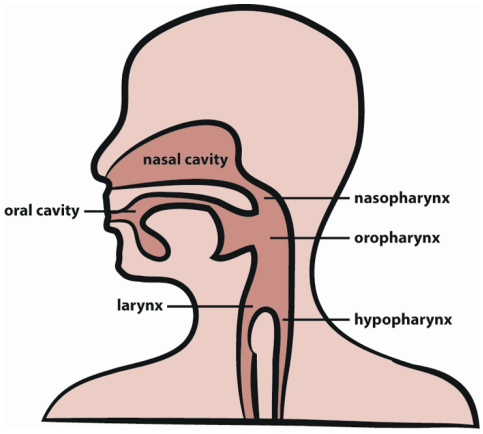

Figure 1 Schematical overview of the subsites of the head and neck area.

Treatment and functional impairment

Historically, surgery alone was the first choice for early stage HNC treatment, combined with radiotherapy for advanced disease. Some thirty years ago, organ-preserving therapy protocols, including (chemo)radiotherapy ((C)RT), emerged into clinical practice and came to play an increasingly important role in the treatment of HNC. However, it soon became clear that organ preservation was not synonymous with function preservation. Despite organ preservation, vital functions of the head and neck area (e.g., swallowing, chewing, and speaking) are often affected, not only due to the (extent of) the tumor but also due to the side effects of the treatment (4-6). One of the vital functional limitations after HNC treatment is swallowing impairment, or dysphagia. Together with the associated weight loss and feeding tube dependency, dysphagia is often referred to as the most serious and debilitating side effect, which can cause (silent) aspiration and, with that, pneumonia (5, 7-10). Impaired mouth opening, or trismus, also commonly occurs after treatment for HNC – especially when radiotherapy is used – and can interfere with daily functioning (11-16). Furthermore, voice and speech, vital in (social) communication, may get affected (17). Apart from these side effects, many patients have health

issues such as lymphedema, sticky saliva and xerostomia, and altered taste and sensibility in the treated areas. As imaginable, these negative side effects may cause serious deterioration of the quality of life of HNC survivors.

Although tumor- and treatment-related functional limitations are most likely to occur in advanced stage (III and IV) HNC, knowledge on functional limitations in early stage (I and II) is also needed to inform (shared) treatment decisions. For early-stage oropharyngeal cancer, for example, surgery as well as radiotherapy are equivalent concerning oncological outcomes, but different with respect to severity and timing of short- and long-term morbidity (18-24). To our knowledge, only one study has assessed differences in self-reported functional outcomes using a randomized comparison between these treatment modalities. This study showed no clinically meaningful difference in the swallowing-related quality of life, one year after treatment (25). In the near future, currently ongoing (randomized) comparative studies, such as the EORTC-1420-HNCG-ROG trial (NCT02984410) and the ORATOR trial (NCT03210103), comparing surgery and RT, will increase the body of evidence and hopefully provide more definitive conclusions on the optimal patient selection for surgery or radiotherapy (26, 27). In the meantime, further observational analyses comparing self-reported swallowing and other functional outcomes would be informative.

Muscles involved in eating and drinking

Treatment in the head and neck area is prone to causing functional limitations because this area has a high density of vital functions, which are regulated by complex mechanisms. Swallowing, for instance, is enabled by subsequent activation of over thirty different muscles, with the need for close coordination to ensure a safe swallow (28, 29). The first of the four phases of swallowing, the oral preparatory phase includes chewing and preparing the food bolus for transportation to the oropharynx. This transportation by the tongue occurs during the subsequent oral phase. These first two phases are facilitated by facial, masticatory, and tongue muscles innervated by the facial, trigeminal, and hypoglossal nerve. Afterwards, during the pharyngeal phase, velopharyngeal closure occurs, and the bolus is transported down to the upper esophageal sphincter by reflexive contractions of the pharyngeal muscles. Also, the airway is protected by forward elevation and closure of the larynx. Muscles involved include the pharyngeal, laryngeal, palatal and supra- and infrahyoid muscles, innervated by the glossopharyngeal, accessory and vagal nerve, respectively. During the last phase, the esophageal phase, the bolus is transported to the stomach by peristaltic contractions of the esophageal muscles. This complex mechanism of swallowing may be interrupted on multiple levels, with dysphagia as a result, which may lead to aspiration and pneumonia.

Assessment of swallowing function

To identify and assess the extent of functional limitations, and swallowing in particular, currently, numerous objective (e.g., videofluoroscopy and functional oral intake scale) and subjective (e.g., Swallowing Quality of Life Questionnaire (SWAL-QOL) and MD Anderson Dysphagia Inventory (MDADI), evaluation methods are available (39). However, there is a

low correlation between objective measures of swallowing function, and subjective/patient-reported swallowing outcomes, suggesting the need for an objective measure that better captures swallowing function in daily life (37, 38). The objective methods mainly measure the physical functions needed for swallowing, and thus for eating and drinking, such as the (safe) transportation of the food bolus to the esophagus. Patient-reported or subjective measures, on the other hand, measure the perceived swallowing (dis)ability and its impact on daily functioning. This perception is an expression of performance in daily life which relates not only to physical function, but also the level of adaptation to any dysfunction. In addition, patient-reported outcomes also reflect the perceived level of (dis)ability which may differ regardless of underlying function. Thus, to fully understand an individual's swallowing problem, assessment of swallowing capacity - reflecting both function and the ability to adapt to possible dysfunction - in addition to function and perception is important. An objective measurement tool for swallowing capacity would be very helpful for identifying discrepancies and/or interactions between an individual's physical functions, capacity, and perception and could help to guide the choice of rehabilitation interventions (40). Also, the assessment of swallowing capacity, in addition to function and perception, can help evaluate the effectiveness of swallowing rehabilitation over time. However, few tests are available for this purpose, and none of these tests includes the full range of consistencies used in daily life.

Minimizing functional loss

Considerable efforts have been put into reducing functional losses after HNC treatment. First, (organ-preserving) HNC treatment nowadays is more targeted and precise than in the early years of its conception. With the introduction of Intensity Modulated RT (IMRT) and Volumetric Modulated Arc Therapy (VMAT), it became technically possible to reduce the radiotherapy dose on functional structures adjacent to the tumor, including salivary glands and swallowing muscles (30, 31).

Second, efforts have been put into the development of rehabilitation programs to treat and, better yet, prevent the aforementioned functional losses. Numerous exercises and maneuvers are available targeting different aspects of the swallowing and mouth opening function (29). In the Netherlands Cancer Institute – Antoni van Leeuwenhoek (NKI-AVL) exercises such as jaw range of motion exercises (using tongue spatulas or the TheraBite® Jaw Motion rehabilitation System™ (Atos Medical AB, Hörby, Sweden)), the effortful swallow, Shaker (head raise) exercise, super-supraglottic swallow, Mendelsohn maneuver, and Masako (tongue hold) maneuver are traditionally used in daily practice. Depending on the etiology and degree/severity of the functional impairment, different exercises can be used to train and optimize function. The Shaker exercise, for example, targets the suprahyoid muscle to increase laryngeal elevation (29, 32). The super-supraglottic swallow helps to improve airway closure to prevent aspiration, but also seem to improve tongue strength (33, 34). In the MD Anderson Swallowing Boot Camp Program, an individualized choice of swallowing exercises is combined with taking foods with increasing difficulty with regard to texture and viscosity.

Despite the effort put into minimalizing the toxicity of treatment in combination with the optimization of individualized training programs, the impaired function of the head and neck area is still an important issue in the lives of HNC survivors, suggesting considerable room for further improvement. For this reason, research efforts have been made in the NKI-AVL over the last one and a half decade, with the aim to unravel the remaining clinical and physiological questions behind the functional losses related to HNC.

First, van der Molen et al. performed a randomized controlled trial (RCT) comparing two types of rehabilitation strategies (with and without the addition of the medical tool/training device TheraBite®) to prevent (long-term) side effects of CRT for HNC (figure 2). The TheraBite® device enables performing passive range of motion exercises that appeared to improve mouth opening as well as swallowing function in a comfortable position (figure 2) (35-37). The hypothesis was that with a dedicated exercise program using the TheraBite®, trismus, swallowing, and speech problems in HNC patients treated with CRT could be better prevented than with a standard exercise program. However, comparing the results of the two arms of this RCT no significant differences were found. Nevertheless, the preventive rehabilitation program with the addition of the TheraBite® was feasible with good compliance, and in comparison with historical controls of a preceding in-house study that included patients who did not receive any preventive rehabilitation suggested that there were benefits of both forms of preventive rehabilitation on functional limitations at one-year post-treatment. Additionally, a cost-effectiveness study indicated that the addition of the TheraBite® to the rehabilitation program was cost-effective compared to exercises alone (38). Studies on preventive rehabilitation from other institutes showed predominantly positive results, although meta-analysis could not be performed due to the heterogeneity of outcome measures and a statistically significant effect could not be detected in the Cochrane Review by Perry et al. (39). The lack of convincing evidence is not necessarily due to the lack of observed effectiveness, however, but partially due to limited precision caused by the small sample sizes of the included studies.

Kraaijenga et al. further built on the results of van der Molen et al., by assessing functional outcomes of the study participants, six years after inclusion in the aforementioned RCT. Results showed that the positive effects of the preventive rehabilitation program were maintained. Compared to the ten-year results of the historical cohort of patients who did not receive preventive rehabilitation, the patients who had received preventive rehabilitation had maintained better functional outcomes (40).

Despite the positive outcomes provided in the studies by van der Molen et al. and Kraaijenga et al., inevitably, several clinical, methodological, and physiological questions remained deserving further research. Especially given the increased survival of patients treated for HNC, due to improving treatment strategies and changing etiology (i.e., more HPV-associated cases and thus younger patients being affected), a better understanding of long-term functional outcomes is gaining relevance (41). Besides, earlier studies have suggested that functional impairment after (C)RT may develop, or continue to worsen, even years after the end of treatment. This is possibly due to a combination of ageing, continuing fibrosis of swallowing

structures, cranial neuropathies, and non-use atrophy (5, 42, 43). Knowledge on the course of the functional status on the long-term (that is: longer than six years post-treatment) after state-of-the-art HNC treatment (IMRT with preventive rehabilitation) will help to provide patients with adequate information on long-term effects of treatment. It will also inform clinicians about which functional problems might be expected several years after treatment, so they can timely act accordingly by, for example, initiating rehabilitation. To date, data on such long-term functional outcomes after CRT with preventive swallowing rehabilitation are still scarce.

Figure 2 TheraBite® is used by placing the mouthpieces between the teeth and squeezing the lever open halfway, swallow afterward with the tongue up and forward as far as possible, then close mouth again.

Rehabilitation program

In 2010, a dedicated rehabilitation program for HNC patients was developed in the NKI-AVL, which includes specific swallowing, voice, and speech rehabilitation modules. Unfortunately, the TheraBite® could not be included in the dysphagia protocol used in this program, since it is not imbursed by the health insurance authorities for this indication, despite the apparent cost-effectiveness (44). The multidisciplinary program not only focuses on the aforementioned functional issues but also addresses health problems with regard to overall physical, psychosocial and occupational functioning, in a personalized rehabilitation plan for each individual patient, with the ultimate aim to regain an acceptable quality of life and participation in society (45).
Knowledge of the degree and course of functional limitations after HNC treatment will facilitate optimization of the program to target remaining functional problems. Also, identification of (pre-treatment) risk factors (e.g., functional status before treatment and specific tumor characteristics such as HPV status) associated with specific functional outcomes can be identified to enable individualized (preventive) rehabilitation.

Swallow Exercise Aid

Besides evaluating preventive rehabilitation, Kraaijenga et al. also developed a new swallowing rehabilitation tool, the Swallow Exercise Aid (SEA) (figure 3). Some of the prementioned swallowing exercises have been proven to be effective for improving swallowing function; especially the Shaker exercise (32, 46). However, the major disadvantage of this exercise is

that the supine position it has to be performed in is not always feasible, especially for the HNC population, limiting compliance. As a solution, Yoon et al. developed the *chin tuck against resistance* exercise. For this exercise, the patient is seated in an upright position while tucking the chin against a rubber ball (47). For an effective gain of muscle strength, it is important to practice at 60-70% of the maximal 1 repetition maximum (48, 49). This means that during the course of an exercise program, as muscle strength increases, the resistance against which is exercised should be increased as well; an exercise principle known as progressive overload. While the *chin tuck against resistance* method tackles the uncomfortable position, it does not easily enable progressive overload. Multiple balls were used, but this is a rather crude and awkward way of increasing resistance. Also, the number of repetitions or contraction duration could be increased, but while this is effective for hypertrophy, it is less so for improving maximal strength (49). To tackle these problems, Kraaijenga et al. developed an exercise device based on the handheld TheraBite® (figure 3) (35-37). The device was modified in such a way that it enabled performing multiple active exercises (figure 4), targeting the suprahyoid, tongue, pharyngeal, and jaw opening musculature in a comfortable sitting position (50). Also, the device enables precise application and increase of exercise load. It is hypothesized that this combination will improve the effectiveness of conventional swallowing strength training. Results of two prospective studies on the SEA including healthy participants (n = 10) and patients with chronic, therapy-refractory dysphagia (*n* = 17) respectively, showed good compliance and feasibility as well as improved subjective and objective swallowing outcomes, after a training period of 6-8 weeks. One of the physiological questions remaining about the newly developed SEA was whether the relevant swallowing muscle groups targeted by this rehabilitation tool, as well as by the conventional exercises, are indeed activated. Adjustment of the (combination of) exercises could be made if, for example, a relevant muscle group appears not to be sufficiently activated.

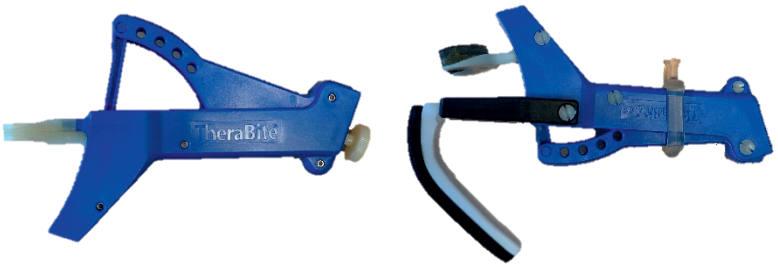

Figure 3 TheraBite® (left) and Swallow Exercise Aid (right).

Predicting feeding tube dependency

It is common knowledge that unused muscles lose mass and function; a phenomenon referred to as non-use atrophy and aptly summarized in the saying 'use it or lose it'. This reversibility principle also applies to the swallowing muscles (51). Therefore, maintaining oral intake during HNC treatment is believed to be beneficial for functional outcomes afterward (51, 52). Feeding tube dependency during CRT for advanced-stage head and neck cancer (HNC) is common; but still, a considerable proportion of patients can maintain their oral intake during CRT (53, 54). Reactive feeding tube (RFT) placement, i.e., placement of a feeding tube in response to excessive weight loss, dehydration, or aspiration, has a role in decreasing the incidence of

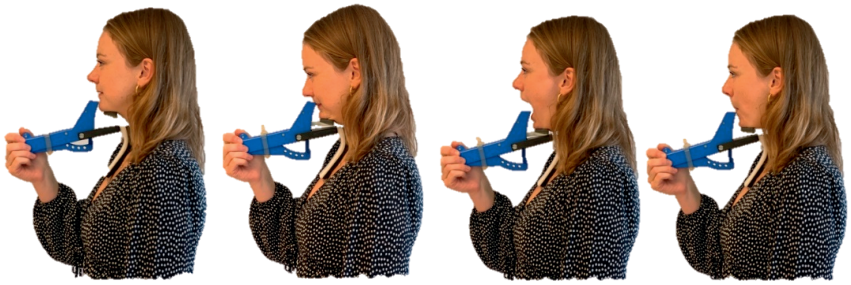

Figure 4 Exercises performed with the swallow exercise aid. Left: start position; middle left: chin tuck against resistance (CTAR) exercise; middle right: jaw opening against resistance (JOAR) exercise; right: effortful swallow (ES) exercise.

(long-term) functional problems. RFT policies stimulate the patient to maintain oral intake as long as possible, which prevents non-use atrophy of the swallowing muscles (36, 40, 51, 55). On the other hand, prophylactic feeding tube placement strategies have been advocated and used to prevent treatment interruption due to dehydration (56). However, with this strategy, all patients are given tube feeding. As this would likely be unnecessary in a substantial proportion of these patients, this unnecessarily increases their risk for non-use atrophy of the swallowing muscles (57-59). Both protocols thus have advantages and disadvantages and it would be beneficial if one could predict whether a reactive or prophylactic approach would be most appropriate for a given patient (i.e., personalized medicine) (60). Predictive factors for tube placement and (prolonged) dependency have been identified before (59, 61-70). These factors include radiotherapy variables, tumor, and nodal stage, and weight loss prior to treatment. However, a clinically applicable prediction model to select patients for proactive tube feeding in high-risk patients is still lacking.

Sarcopenia

Besides the currently available (predominantly clinical) parameters, new biomarkers are making their way into daily practice, and these might be of value in the risk assessment for functional loss and tube dependency specifically. Sarcopenia, loss of skeletal muscle mass and function, might be one of those relevant biomarkers related to functional loss. Recently, it was shown that sarcopenia is associated with inferior cancer treatment outcomes, also for HNC patients (71-77). Sarcopenia could also be a factor associated with functional impairment by co-causing (long-term) swallowing dysfunction, as patients suffering from sarcopenia have limited reserves with regard to muscle mass and function. Consequently, in these patients, non-use atrophy of the swallowing muscles may even sooner lead to prolonged functional impairment (78, 79). Therefore, sarcopenia might be a relevant predictive factor which can be used to select high-risk patients for (early) rehabilitation or proactive feeding tube placement.

Outline of the thesis

This thesis aimed to provide answers to the abovementioned knowledge gaps by further exploring functional impairment in patients treated HNC, find relevant risk factors for functional loss and aid in the improvement of rehabilitation to ultimately improve quality of life of HNC survivors.

In **chapter 2**, surgery and radiotherapy for early-stage stage oropharyngeal carcinoma are compared with respect to patient-reported swallowing function outcomes; to enable informed decisions on treatment choice and inform patients prior to treatment on the likely outcome of their intended treatment.

To extend the options for objective assessment of swallowing ability and to improve insight of the interplay between function, capacity, and perceived ability, the Swallowing Proficiency for Eating And Drinking (SPEAD) test was developed, as described in **chapter 3**. This test entails the timed ingestion of thin liquid, thick liquid and solid and is hypothesized to provide a link between objective and subjective swallowing outcomes.

In **chapter 4,** swallowing, trismus and speech function ten years after CRT and preventive rehabilitation for head and neck cancer are described, and sustainability of the effect of preventive rehabilitation in this cohort of HNC patients is discussed.

Chapter 5 describes the functional limitations, including dysphagia, trismus, and speech problems, within the first year after (C)RT for oropharyngeal carcinoma. This cohort includes patients from the implementation of a dedicated preventive rehabilitation program until now, and facilitates the evaluation of implementation of such a program in clinical practice.

In **chapter 6**, further insight is obtained in which muscles are activated during the training with the SEA, using Magnetic Resonance Imaging.

In **chapter 7** a prediction model is developed to predict the risk for long-term feeding tube dependency before CRT for head and neck cancer, to select patients for proactive tube placement and to avoid unnecessary prophylactic tube placement.

In **chapter 8**, the association between pretreatment low muscle mass, i.e., sarcopenia, and long-term feeding tube dependency is explored. Sarcopenia might be an important lead for pretreatment optimization of patient condition to prevent long-term functional (swallowing) impairment.

Chapter 9 is a general discussion of the results of the studies within this thesis and a summary is provided in **chapter 10.**

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Chapter 2

Patient-reported swallowing function after treatment for early-stage oropharyngeal carcinoma: a population-based study

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ABSTRACT

Background: Single-modality treatment (surgery or radiotherapy) are curative treatment options for early-stage oropharyngeal carcinoma (OPC) with comparable (excellent) oncological outcomes. This study aimed to compare self-reported swallowing function.

Methods: Participants with a T1-2N0-2bM0 OPC offered single-modality treatment recruited to the Head and Neck 5000 study were included. Prospectively collected self-reported swallowing function was compared between surgery and RT.

Results: Those offered RT (n = 150) had less favourable baseline characteristics than those offered surgery (n = 150). At 12-month follow-up, RT participants reported more swallowing problems (35% vs. 23%, RR 1.3; 95% CI 0.8–2.3, p = .277) in models adjusted for baseline characteristics. In those allocated to surgery who received adjuvant therapy (n = 78, 52%), the proportion with swallowing problems was similar to those allocated to RT alone.

Conclusions: Participants offered surgery alone had similar mortality but improved swallowing, although not statistically significant. However, over half of participants offered surgery alone received surgery and adjuvant therapy.

INTRODUCTION

The incidence of oropharyngeal cancer (OPC) has risen over recent decades, mainly due to the increase in human papilloma virus (HPV) associated cases (1, 2). In some people with early stage OPC, single-modality treatment with surgery or radiotherapy (RT) can be a curative treatment with a high probability of disease-free survival. Because of these excellent survival outcomes, survivors are expected to live with the long-term effects of treatment.

When in the past open surgery was the usual surgical treatment for early-stage OPC, complication rates and morbidity favoured RT (3). However, since the introduction of transoral surgery, the two treatment modalities became more comparable in terms of adverse effects. Several meta-analyses of observational studies showed similar results for survival but differences in severity and timing of short- and long-term morbidity (4-10). Only one study has compared differences in self-reported functional outcomes in a randomized comparative study. Results of this ORATOR-trial (NCT01590355), including 68 patients, showed no clinically meaningful difference in swallowing related quality of life one year after treatment, despite statistically significantly better results in the RT arm (11). Other ongoing (randomized) comparative studies, such as the EORTC-1420-HNCG-ROG trial (NCT02984410) and the ORATOR2 trial (NCT03210103), are also comparing surgery and RT, and will increase the body of evidence and hopefully provide more definitive conclusions on optimal patient selection (12, 13). In the meantime, further observational analyses with self-reported functional outcomes are informative.

Given the comparable disease-free survival, clinicians and patients need information on toxicity profiles to make informed treatment decisions. OPC and its treatment often affect swallowing function (14, 15). Impaired swallowing has proven to be an important problem in people with OPC having significant impact on their quality of life (15, 16). Information on swallowing and oral function would be potentially important for clinicians and patients when making treatment decisions.

The objective of this study is to compare self-reported swallowing function in people planned for single-modality treatment with surgery or RT for early T classification OPC, regardless of received treatment, in order to inform patients prior to treatment on likely outcome of their intended treatment. Data from an existing large UK-wide multicentre study HN5000 were used, resulting in a large cohort, but detailed data on treatment were not included in this study.

MATERIALS AND METHODS

Study design, population and patient selection

Data from the Head and Neck 5000 (HN5000) prospective clinical cohort study were used in this analysis. The study has been described in detail elsewhere (17, 18). Briefly, data from people with newly diagnosed head and neck cancer from 76 participating centres throughout the United Kingdom (UK) were collected. Participants were recruited from April 2011 to December 2014. The study received formal ethical approval from the South West Frenchay Ethics Committee (reference 10/H0107/57) and was performed in accordance with Helsinki Declaration of 1983. The participants selected from the database for this study were diagnosed with oropharyngeal squamous cell carcinoma and were treated with curative intent. We divided the group into two subsets. The first subset, called 'early-stage', had early T classification (T1 and T2) and excluded N2c and N3 participants. The remaining participants (T3-4 or N2c-N3) were called 'advanced-stage'. This analysis focusses on the early-stage subset.

Treatment characteristics

Details on intended, received and intent of treatment were collected from participants' medical records by research staff. Participants' intended treatment was the treatment initially intended by clinicians at diagnosis; changes may have been made due to further staging scans or patient choice. Received treatment was collected at 4-month follow-up. Whether participants received IMRT was extracted from data taken from the Radiotherapy Dataset NatCanSAT© (19).

Baseline characteristics

Participants were asked to complete three questionnaires at baseline that included questions on date of birth, gender, smoking status (never used, former user, or current user), amount of alcohol consumed, and postal code. Alcohol consumption was grouped into four categories using the number of units per week the participants reported they drank (none, moderate (less than 14 units per week for men and women), hazardous (14-50 units per week for men, 14-35 units per week for women) of harmful (more than 50 units per week for men, more than 35 units per week for women)) (20). The Index of Multiple Deprivation (IMD) was derived from postal codes with 1 indicating the most deprived areas and 5 the most affluent areas (21). The following baseline characteristics were collected from the hospital information system and notes by research nurses: Adult Comorbidity Evaluation-27 (ACE-27) index (22), (oropharyngeal) tumour site, tumour (T) and nodal (N) classification, and TNM stage of Malignant Tumours stage (7^{th} edition). The primary measure of human papillomavirus (HPV) status was seropositivity of HPV antibodies using a glutathione S-transferase multiplex assay carried out at the German Cancer Research Centre (DKFZ) in Heidelberg, Germany (23). Seropositivity was defined as a HPV16 E6 > 1000 Median Fluorescence Intensity units (MFI).

Outcome measures

For this analysis, the following outcomes were used: self-reported swallowing function, secondary self-reported functional outcomes, and survival and absence of disease. The primary outcome of this study was self-reported swallowing function reported as problems

with swallowing liquids, pureed and/or solid food. Secondary functional outcomes were dry mouth, weight loss during the past week, use of tube feeding during the past week, pain (in mouth, jaw or throat), coughing, trouble opening mouth, bothersome appearance, and altered taste. These data were extracted from the European Organization for Research and Treatment of Cancer Quality of Life Head and Neck 35 questionnaire (EORTC-QLQ-H&N35), completed by participants at baseline and at 4- and 12-month follow-up (24). Questions with four possible answers were dichotomized into no (not at all and a little) or yes (quite a bit and very much) to increase interpretability of the risk ratio (RR). Analyses were repeated after dichotomizing the outcome into no (not at all) and yes (a little, quite a bit and very much). Also, research nurses asked participants whether they had a percutaneous endoscopic gastrostomy (PEG) or tracheostomy at 4- and 12-month follow-up. Research nurses assessed the presence of residual/recurrent disease from the medical records at 4- and 12-month follow-up. All participants were flagged with the NHS Digital for 6-monthly updates on mortality and date of death.

Statistical analysis

Analyses were performed using IBM® SPSS® Statistics 24.0. First, intended and received treatment were described. Baseline characteristics and baseline functional outcomes were compared, grouped by treatment modality and whether data on (swallowing) function were available. The independent samples *t*-test was used to compare continuous variables of two groups, the one-way ANOVA was used to compare continuous variables of more than two groups, and the Chi-square test was used to compare categorical variables.

Differences in self-reported swallowing and secondary functional outcomes at both 4- and 12-months follow-up were compared using Poisson regression analysis with a robust error variance to estimate RRs and confidence intervals (CI). Poisson regression was used as odds ratios (obtained from logistic regression) are poor approximations of RRs if the outcome prevalence is high (25). First, the RR with 95% CI and *p* values, adjusted for age and gender only were calculated (minimally adjusted). Second, results after also adjusting for ACE-27, smoking status, oropharyngeal tumour site, TNM-stage, HPV-status, and pre-treatment swallowing problems were presented (adjusted). The minimally adjusted analyses were repeated on the participants included in the adjusted analyses to ensure that any changes in estimated RRs in the adjusted models were attributable to confounding rather than missing data.

Hazard ratios (HRs) were calculated using minimally adjusted Cox regression analyses (adjusted for age and gender only) as well as adjusted Cox regression analyses (adjusted for ACE-27, TNM stage, HPV-status, and smoking status also). Again, the minimally adjusted analyses were repeated on the participants included in the adjusted analyses. Survival was defined as time between date of consent and date of death or date of last mortality follow-up.
Patterns in baseline characteristics and functional outcomes of participants with T1N0 OPC only were compared to those of all early-stage OPC participants. Also, HPV-negative and –positive participants were compared.

RESULTS

In total, 5511 participants were recruited into the HN5000 study. Of these, 1816 participants were treated with curative intent for a squamous cell carcinoma of the oropharynx without distant metastases (Appendix 1). Of these participants, 1014 had early-stage and 802 had advanced-stage OPC. Of the early-stage participants, 150 were offered surgery only and 150 were offered RT only. Of the 150 participants offered surgery as single modality, 66 (44%) received surgery only whereas 78 (52%) received adjuvant (chemo (C))RT (50 RT and 28 CRT). Treatment of the remaining 6 participants was converted to (C)RT. Of the 150 early-stage participants offered RT as single modality, 126 participants (84%) received this. The other patients received either CRT ($n = 17$) or surgery with adjuvant (C)RT ($n = 7$). Reasons for treatment change or adjuvant treatment were not available. Intended and received treatment are listed in Appendix 2.

Treatment characteristics

Unfortunately, detailed description of surgical techniques were not available for most participants. In 20 (30%) of the 66 participants who received surgery only, the surgery was performed with transoral laser of whom 10 (50%) received a neck dissection and none a reconstruction with a free flap. Of the 46 participants not treated with laser surgery, 15 (33%) received a neck dissection and 8 (17%) a reconstruction with a free flap. Median total RT dose on the tumour and lymph nodes was 65 Gy (range 18–71 Gy). Dose of the elective neck irradiation was not available.

Of the 126 participants who received RT as intended, 9 (7%) received brachytherapy. Of the 204 participants who received RT (either primary or postoperatively), 142 (70%) were treated with Intensity Modulated Radiotherapy (IMRT) (73% of primary RT and 76% of postoperative RT). For 12 participants (6%), it was unknown whether they were treated with IMRT. Of the 126 participants who received RT as intended, 122 (97%) had data on completion of prescribed course of RT available. Three (2%) did not complete the prescribed course due to toxicity ($n = 1$) or patient choice ($n = 2$). Of the 78 participants who received postoperative RT, 65 (89%) had data on completion of RT available of whom all completed the prescribed course.

Baseline characteristics

Baseline characteristics are presented in Table 1. Participants who were offered RT only were older, had more comorbidities, were more likely to have a tumour localized in the base of tongue, a T2 tumour, higher TNM-stages, and reported more pre-treatment swallowing problems compared to those offered surgery only. Participants who received RT as intended were also older, more often had a tumour localized in the base of tongue, had more T2 tumours, and higher TNM stages compared to participants who received surgery only as planned. Participants who received postoperative adjuvant treatment had higher T and N classifications and TNM stages, consumed less alcohol, had fewer comorbidities, and were more likely to be HPV positive compared to those who only received surgery only. See Appendix 3 for functional outcomes at baseline.

Table 1 Baseline characteristics of participants with early-stage OPC. *P* values shown for comparisons between groups. [a]Chi-square test, [b]independent samples *t*-test, [c]one-way ANOVA. Percentages and statistical tests for available cases only.

		Intended treatment Number of participants (%)				***P* value** S vs. RT	***P* value** All groups	**Intended and received treatment** Number of participants (%)			***P* value** S vs. RT	***P* value** S vs. S + (C)RT
		Surgery (*n* = 150)	RT (*n* = 150)	CRT (*n* = 431)	Surgery + (C)RT (*n* = 283)			Surgery (*n* = 66)	RT (*n* = 126)	Intended S and received S + (C)RT (*n* = 78)		
Gender	Male	113 (75)	114 (76)	329 (76)	208 (74)	.893[a]	.854[a]	48 (73)	96 (76)	60 (77)	.599[a]	.562[a]
	Female	37 (25)	36 (24)	102 (24)	75 (27)			18 (27)	30 (24)	18 (23)		
Age at diagnosis (years) Mean (SD)		59 (10)	63 (10)	57 (8)	58 (9)	< .001[b]	< .001[c]	60 (11)	64 (10)	58 (10)	.006[a]	.434[a]
Deprivation index	1 (most deprived)	32 (24)	30 (21)	74 (18)	39 (15)	.332[a]	.200[a]	16 (25)	27 (23)	15 (21)	.499[a]	.340[a]
	2	33 (24)	31 (22)	80 (19)	50 (19)			17 (27)	24 (20)	15 (21)		
	3	26 (19)	34 (24)	84 (20)	63 (24)			9 (14)	30 (25)	16 (23)		
	4	20 (15)	30 (21)	92 (22)	52 (20)			12 (19)	23 (19)	8 (11)		
	5 (most affluent)	25 (18)	17 (12)	85 (21)	57 (22)			9 (14)	15 (13)	16 (23)		
	Unknown	14	8	16	22			3	7	8		
Smoking	Never used	22 (23)	23 (22)	116 (36)	57 (28)	.940[a]	.020[a]	8 (19)	19 (22)	13 (26)	.503[a]	.091[a]
	Former user	55 (57)	62 (59)	173 (53)	120 (59)			22 (52)	49 (57)	31 (62)		
	Current user	20 (21)	20 (19)	38 (12)	26 (13)			13 (30)	18 (21)	6 (12)		
	Unknown	53	45	104	80			23	40	28		
Alcohol	Non-drinker	23 (24)	28 (25)	93 (28)	41 (19)	.632[a]	.512[a]	10 (23)	26 (28)	11 (22)	.327[a]	.014[a]
	Moderate	25 (26)	28 (25)	74 (23)	55 (26)			7 (16)	25 (27)	17 (33)		
	Hazardous	40 (41)	38 (34)	122 (37)	82 (39)			18 (41)	29 (31)	22 (43)		
	Harmful	10 (10)	17 (15)	40 (12)	34 (16)			9 (21)	13 (14)	1 (2)		
	Unknown	52	39	102	71			22	33	27		
ACE-27	None	68 (47)	44 (30)	240 (57)	156 (56)	.002[a]	< .001[a]	23 (36)	34 (28)	42 (56)	.602[a]	.043[a]
	Mild	51 (35)	55 (37)	133 (31)	85 (31)			26 (41)	51 (42)	23 (31)		
	Moderate	20 (14)	44 (30)	49 (12)	28 (10)			13 (20)	34 (28)	6 (8)		
	Severe	6 (4)	4 (3)	3 (1)	9 (3)			2 (3)	4 (3)	4 (5)		
	Unknown	5	3	6	5			2	3	3		

Table 1 Continued

		Intended treatment Number of participants (%)				***P* value** S vs. RT	***P* value** All groups	**Intended and received treatment** Number of participants (%)			***P* value** S vs. RT	***P* value** S vs. S + (C)RT
		Surgery ($n = 150$)	RT ($n = 150$)	CRT ($n = 431$)	Surgery + (C)RT ($n = 283$)			Surgery ($n = 66$)	RT ($n = 126$)	Intended S and received S + (C)RT ($n = 78$)		
Oropharyngeal tumour site	Base of tongue	18 (12)	31 (21)	133 (31)	50 (18)	.076	<.001[a]	10 (15)	28 (22)	8 (10)	< .001[a]	< .001[a]
	Tonsil	76 (51)	76 (51)	245 (57)	204 (72)			20 (30)	58 (46)	52 (67)		
	Other	56 (37)	43 (29)	53 (12)	29 (10)			36 (55)	40 (32)	18 (23)		
T classification	T1	64 (43)	41 (27)	120 (28)	100 (35)	.005[a]	.003[a]	35 (53)	32 (25)	27 (35)	< .001[a]	.026[a]
	T2	86 (57)	109 (73)	311 (72)	183 (65)			31 (47)	94 (75)	51 (65)		
N classification	N0	79 (53)	91 (61)	49 (11)	44 (16)	.457[a]	< .001[a]	49 (74)	84 (67)	27 (35)	.609[a]	< .001[a]
	N1	26 (17)	20 (13)	80 (19)	38 (13)			7 (11)	17 (13)	19 (24)		
	N2 (not bilateral)	2 (1)	3 (2)	10 (2)	14 (5)			0 (0)	2 (2)	1 (1)		
	N2a	7 (5)	9 (6)	63 (15)	51 (18)			3 (5)	3 (2)	4 (5)		
	N2b	36 (24)	27 (18)	229 (53)	136 (48)			7 (11)	20 (16)	27 (35)		
TNM stage	I	39 (26)	25 (17)	9 (2)	8 (3)	.014[a]	< .001[a]	31 (47)	24 (19)	7 (9)	.001[a]	< .001[a]
	II	40 (27)	66 (44)	40 (9)	36 (13)			18 (27)	60 (48)	20 (26)		
	III	26 (17)	20 (13)	80 (19)	38 (13)			7 (11)	17 (14)	19 (24)		
	IV	45 (30)	39 (26)	302 (70)	201 (71)			10 (15)	25 (20)	32 (41)		
HPV status						.652[a]	< .001[a]				.137[a]	< .001[a]
	Negative	55 (44)	59 (47)	74 (20)	49 (21)			33 (64)	54 (51)	21 (30)		
	Positive	69 (56)	66 (53)	294 (80)	190 (80)			19 (37)	52 (49)	48 (70)		
	Unknown	26	25	63	239			14	20	9		
Received treatment	Surgery	66 (44)	0 (0)	0 (0)	14 (5)	NA	NA	66 (100)	0 (0)	0 (0)	NA	NA
	RT	1 (1)	126 (84)	11 (3)	3 (1)			0 (0)	126 (100)	0 (0)		
	CRT	5 (3)	17 (11)	390 (91)	18 (6)			0 (0)	0 (0)	0 (0)		
	Surgery + (C)RT	78 (52)	7 (5)	28 (7)	248 (88)			0 (0)	0 (0)	78 (100)		
	No treatment	0 (0)	0 (0)	2 (1)	0 (0)			0 (0)	0 (0)	0 (0)		

Table 1 Continued

		Intended treatment Number of participants (%)				***P* value** S vs. RT	***P* value** All groups	**Intended and received treatment** Number of participants (%)			***P* value** S vs. RT	***P* value** S vs. S + (C)RT
		Surgery (*n* = 150)	RT (*n* = 150)	CRT (*n* = 431)	Surgery + (C)RT (*n* = 283)			Surgery (*n* = 66)	RT (*n* = 126)	Intended S and received S + (C)RT (*n* = 78)		
Received treatment intent	Curative	150 (100)	149 (99)	429 (100)	283 (100)	NA	NA	66 (100)	125 (99)	78 (100)	NA	NA
	Palliative	0 (0)	1 (1)	1 (0)	0 (0)			0 (0)	1 (1)	0 (0)		
	Unknown	0	0	1	0			0	0	0		
Pre-treatment swallowing problems	No	73 (73)	84 (75)	270 (81)	173 (82)	.740	.157	33 (75)	73 (79)	38 (73)	.567	.831
	Yes	27 (27)	28 (25)	62 (19)	39 (18)			11 (25)	19 (21)	14 (27)		
	Unknown	50	38	99	71			22	34	26		

NB: Not all percentages sum up exactly to 100% due to rounding. Outcome 'pre-treatment swallowing problems' is defined as problems with swallowing liquids, pureed and/or solid food assessed by means of questions from the EORTC-QLQ-H&N35 questionnaire.
Abbreviations: ACE-27 = Adult Comorbidity Evaluation-27, (C)RT = (chemo)radiotherapy, HPV = human papilloma virus, S = surgery, SD = standard deviation.

Available data

Of the 150 participants offered surgery, 102 (68%), 87 (58%), and 83 (55%) had EORTC-QLQ-H&N35 data available at baseline, 4- and 12-month follow-up respectively. Of the 150 participants offered RT, EORTC-QLQ-H&N35 data was available for 114 (76%), 93 (62%), and 80 (53%) participants respectively. Characteristics of participants with data available at 12-month follow-up (Appendix 4) were comparable to those of the total group, except the participants who completed the questionnaire lived in more affluent areas. Of the 163 participants with data available at 12-month follow-up, 138 (85%) also had data available at 4-month follow-up.

Self-reported swallowing outcomes – 'not at all' and 'a little' versus 'quite a bit' and 'very much'

Self-reported swallowing outcomes are presented in Appendix 5. Figure 1 illustrates the RRs per outcome measure at 4- and 12-month follow-up. At 4-month follow-up, more participants offered RT reported problems swallowing, especially with solid foods than those offered surgery (55% vs. 35%, minimally adjusted RR 1.6; 95% CI 1.0–2.5, $p = .051$, adjusted RR 1.3; 95% CI 0.8–2.0, $p = .249$). At 12-month follow-up, these proportions decreased to 35% and 23% for RT and surgery participants respectively (minimally adjusted 1.3; 95% CI 0.7–2.3, $p = .362$ and adjusted RR 1.3; 95% CI 0.8–2.3, $p = .277$).

Self-reported swallowing outcomes - 'not at all' versus 'a little', 'quite a bit' and 'very much'

Appendix 6 shows self-reported swallowing outcomes (and secondary outcomes) with no including 'not at all' (instead of 'not at all' and 'a little') and yes including 'a little', 'quite a bit', and 'very much' (instead of only 'quite a bit' and 'very much'). The difference in RRs are presented in Figure 2. At 4-month follow-up, differences between surgery and RT participants are similar. At 12-month follow-up, however not consistent, differences between surgery and RT participants are more prominent when the cut-off is between 'not at all' and 'a little'. At 12-month follow-up the differences between surgery and RT participants with problems swallowing all consistencies and solids appeared were smaller when more severe symptoms are considered, while the differences with problems swallowing liquids and purees were greater.

Differences between RT and surgery regarding swallowing problems were more prominent when only participants were included who received their intended single-modality treatment (Appendix 7). Participants who received surgery with adjuvant (C)RT were more likely to report swallowing problems than participants who received surgery only. Swallowing outcomes of participants receiving surgery with (C)RT and those who received RT were comparable.

Self-reported swallowing outcomes (from EORTC-QLQ-H&N35)	4-month follow-up (grey)		12-month follow-up (black)	
	RR (95% CI)	*P* value	RR (95% CI)	*P* value
Problems swallowing liquids, pureed or solid food	1.3 (0.8–2.0)	.249	1.3 (0.8–2.3)	.277
Problems swallowing liquids	1.1 (0.4–3.1)	.869	1.6 (0.2–11.1)	.628
Problems swallowing pureed food	2.0 (0.8–5.2)	.157	2.1 (0.4–10.3)	.361
Problems swallowing solid food	1.3 (0.8–2.1)	.287	1.3 (0.8–2.2)	.308
Secondary functional outcomes (from EORTC-QLQ-H&N35)				
Weight loss	1.5 (0.9–2.4)	.093	2.1 (1.0–4.6)	.051
Tube feeding	0.9 (0.4–2.2)	.766	NA	NA
Pain mouth, jaw or throat	1.3 (0.8–2.0)	.311	1.5 (0.7–3.1)	.319
Coughing	2.3 (0.8–7.2)	.137	2.7 (0.7–10.3)	.145
Trouble opening mouth	0.5 (0.2–0.9)	.025	0.8 (0.3–2.0)	.655
Dry mouth	1.5 (1.1–2.0)	.011	2.0 (1.4–3.1)	.001
Bothersome appearance	1.8 (0.8–4.1)	.139	0.8 (0.4–2.0)	.663
Altered taste	1.3 (0.9–2.1)	.184	1.9 (1.0–3.4)	.035

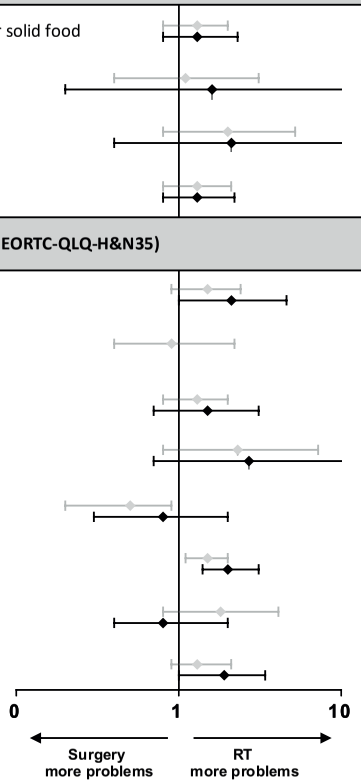


Figure 1 Adjusted Poisson regression analysis (adjusted for age, gender, ACE-27, smoking status, tumour site, TNM-stage, HPV-status and pre-treatment swallowing problems) of self-reported swallowing and secondary functional outcomes at 4- and 12-month follow-up grouped by intended surgery (reference) and RT. Answers to questions of the EORTC-QLQ-H&N35 questionnaire were dichotomized into no problems ('not at all' and 'a little') and problems ('quite a bit' and 'very much').

Self-reported swallowing outcomes (from EORTC-QLQ-H&N35)	'not at all' vs. rest (grey)		'not at all' and 'a little' vs. rest (black)	
	RR (95% CI)	*P* value	RR (95% CI)	*P* value
Problems swallowing liquids, pureed or solid food	1.6 (1.2–2.2)	.001	1.3 (0.8–2.3)	.277
Problems swallowing liquids	1.3 (0.6–2.8)	.453	1.6 (0.2–11.1)	.628
Problems swallowing pureed food	1.5 (0.7–3.2)	.332	2.1 (0.4–10.3)	.361
Problems swallowing solid food	1.7 (1.3–2.3)	.001	1.3 (0.8–2.2)	.308
Secondary functional outcomes (from EORTC-QLQ-H&N35)				
Weight loss	2.0 (0.9–4.2)	.071	2.1 (1.0–4.6)	.051
Tube feeding	NA	NA	NA	NA
Pain mouth, jaw or throat	1.2 (0.9–1.7)	.207	1.5 (0.7–3.1)	.319
Coughing	2.5 (1.3–4.6)	.005	2.7 (0.7–10.3)	.145
Trouble opening mouth	0.8 (0.5–1.3)	.415	0.8 (0.3–2.0)	.655
Dry mouth	1.1 (1.0–1.3)	.036	2.0 (1.4–3.1)	.001
Bothersome appearance	0.6 (0.3–0.9)	.026	0.8 (0.4–2.0)	.663
Altered taste	1.3 (1.0–1.7)	.019	1.9 (1.0–3.4)	.035

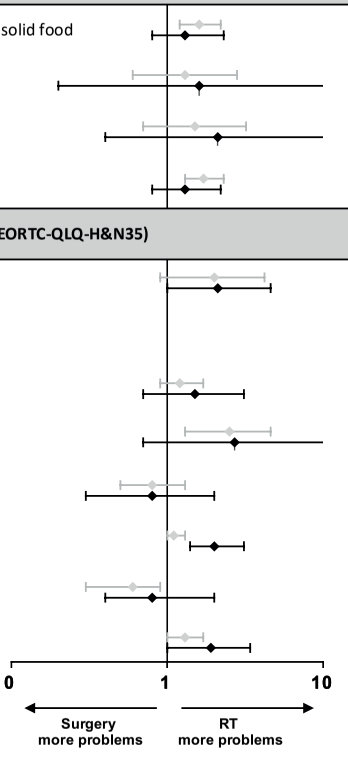


Figure 2 Adjusted Poisson regression analysis (adjusted for age, gender, ACE-27, smoking status, tumour site, TNM-stage, HPV-status and pre-treatment swallowing problems) of self-reported swallowing outcomes and secondary functional outcomes at 12-month follow-up of participants who were offered surgery (reference) and RT of two different cut-offs. Grey: no includes 'not at all' and yes includes 'a little', 'quite a bit', and 'very much'. Black: no includes 'not at all' and 'a little' and yes includes 'quite a bit' and 'very much'.

Secondary functional outcomes

Secondary functional outcomes of participants offered surgery or RT only are shown in Appendix 5. Figure 1 illustrates the RRs per outcome measure at 4- and 12-month follow-up. Participants offered RT reported more problems with weight loss and dry mouth compared to those who were offered surgery. In contrast, participants offered surgery had more trouble opening their mouth, especially at 4-month follow-up. Eight (33%) of the 24 participants with mouth opening problems at 4-month follow-up had a reconstruction with a free flap in contrast to 11 (18%) of the 61 participants who did not have trouble opening their mouth. At 12-month follow-up, only 4% of the participants used tube feeding in both groups.

As with the self-reported swallowing problems, differences between functional outcomes were more prominent between RT and surgery when only participants were included who received their intended single-modality treatment (Appendix 7). Participants who received adjuvant treatment after surgery had more secondary functional problems than participants who received surgery only, especially weight loss, feeding tube use, pain, dry mouth, and altered taste.

Functional outcomes of participants with T1N0 OPC

When baseline characteristics as well as functional outcomes between participants with T1N0 offered surgery and RT were compared, the same patterns in differences between surgery and RT were seen compared to those of all early-stage OPC participants (Appendix 8 and 9).

Presence of disease and survival

The 1-year overall survival (OS) was 96% vs. 93% for participants offered surgery and RT respectively. The 3-year OS was 89% and 79% for surgery and RT and the 5-year OS was 80% and 68% respectively. At 12-month follow-up, 89% and 87% of the participants offered surgery and RT respectively were alive without any signs of residual/recurrent disease. The adjusted HR for death of participants who were offered RT compared to participants who were offered surgery was 1.7 (95% CI 0.7–3.8, $p = .219$). Participants who were both offered and received RT had an adjusted HR of death of 2.2 (95% CI 0.7–7.2, $p = .189$) compared to participants who both were offered and received surgery. The associations were similar in minimally adjusted models. Kaplan Meier curves are presented in Figure 3 (survivor functions were more unstable with increasing follow-up time since the latter estimates are based on smaller sample sizes).

Influence of HPV-status

Baseline characteristics of participants stratified by HPV-status are presented in Appendix 10. In both the HPV-negative and -positive group, participants offered RT were older, had more comorbidities, and more pre-treatment swallowing problems. Within the HPV-positive group, RT participants had more T2-tumours, lower N classification, and HPV-positive participants offered surgery needed adjuvant (C)RT more often than HPV-negative participants (70% vs. 38%).

In both the HPV-negative and -positive participants, those who were offered RT reported more swallowing problems at 12-month follow-up (see Figure 4 and Appendix 11). However, differences were smaller within the HPV-positive group, probably due to a higher proportion of participants who received adjuvant treatment after surgery.

HPV-negative participants who were offered RT had a potentially worse survival than those who were offered surgery (HR 2.5; 95% CI 0.8–7.5, $p = .100$). There was no evidence of a difference in survival in HPV-positive participants offered surgery compared to those offered RT (HR 0.7; 95% CI 0.2–3.4, $p = .683$) (Appendix 12).

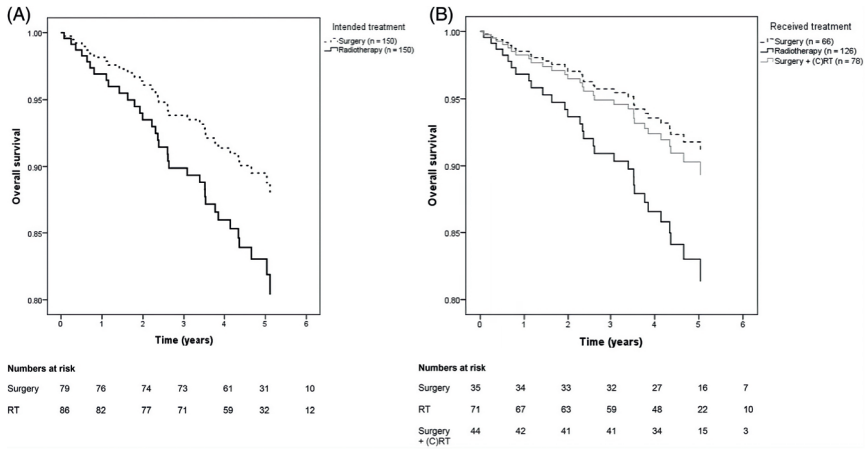
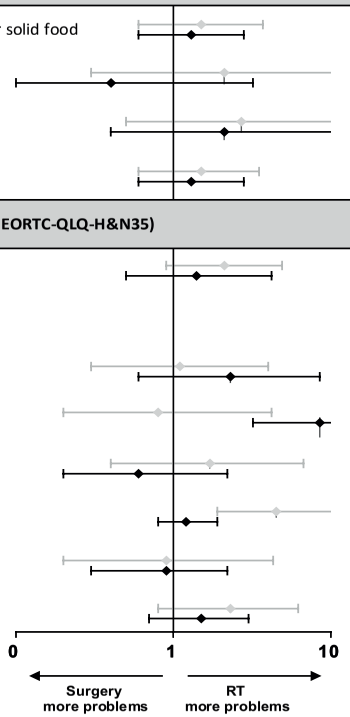


Figure 3 Kaplan Meier Curves. Left: Survival by intended treatment ($p = .219$). Right: Survival by received treatment ($p = .189$).



Self-reported swallowing outcomes (from EORTC-QLQ-H&N35)	HPV negative (grey)		HPV positive (black)	
	RR (95% CI)	*P* value	RR (95% CI)	*P* value
Problems swallowing liquids, pureed or solid food	1.5 (0.6–3.7)	.344	1.3 (0.6–2.8)	.490
Problems swallowing liquids	2.1 (0.3–13.6)	.405	0.4 (0.1–3.2)	.421
Problems swallowing pureed food	2.7 (0.5–13.4)	.229	2.1 (0.4–10.3)	.374
Problems swallowing solid food	1.5 (0.6–3.5)	.401	1.3 (0.6–2.8)	.490
Secondary functional outcomes (from EORTC-QLQ-H&N35)				
Weight loss	2.1 (0.9–4.9)	.074	1.4 (0.5–4.2)	.509
Tube feeding	NA	NA	NA	NA
Pain mouth, jaw or throat	1.1 (0.3–4.0)	.850	2.3 (0.6–8.5)	.198
Coughing	0.8 (0.2–4.2)	.781	8.5 (3.2–23.0)	<.001
Trouble opening mouth	1.7 (0.4–6.7)	.460	0.6 (0.2–2.2)	.420
Dry mouth	4.5 (1.9–10.6)	.001	1.2 (0.8–1.9)	.327
Bothersome appearance	0.9 (0.2–4.3)	.933	0.9 (0.3–2.2)	.744
Altered taste	2.3 (0.8–6.2)	.103	1.5 (0.7–3.0)	.269

Figure 4 Adjusted Poisson regression analysis (adjusted for age, gender, ACE-27, smoking status, tumour site, TNM-stage, HPV-status and pre-treatment swallowing problems) of self-reported swallowing outcomes and secondary functional outcomes at 12-month follow-up of participants who were offered surgery (reference) and RT only grouped by HPV status. Answers to questions of the EORTC-QLQ-H&N35 questionnaire were dichotomized into no problems ('not at all' and 'a little') and problems ('quite a bit' and 'very much')).

DISCUSSION

This is the first study to compare self-reported swallowing function in people with early-stage OPC who are offered single-modality treatment with surgery or RT. Existing prospective data from 300 participants in the multi-institutional HN5000 study were used, with 150 participants offered surgery and 150 offered RT. Trismus was more prevalent in participants offered surgery. However, participants offered surgery had better other functional outcomes including swallowing, dry mouth and altered taste, compared to those offered RT, both at 4- and 12-month follow-up. This difference was more prominent when comparing participants who received their intended single modality surgery or RT. This was probably because 52% of the participants offered surgery received adjuvant treatment while 84% of those offered RT received their intended single modality treatment. There was no evidence of a difference in survival between surgery and RT. Differences in swallowing problems, however, did not result in substantial differences in tube feeding use.

The 150 participants offered surgery were younger, had less comorbidities, earlier tumour- and, TNM-stage and had less pre-treatment swallowing problems compared to the 150 offered RT. However, despite these baseline differences, adjustment for these confounders resulted in only modest attenuation of RRs. It is possible that these baseline characteristics contributed to treatment selection offering participants with favourable baseline characteristics surgery more often. In addition, participants selected for surgery have more favourable characteristics not captured by the measured confounders such as tumour volume or the distance from tumour to swallowing structures, than participants offered RT. Even in the T1N0 participants, these T1 tumours may have had other characteristics not adjusted for, such as tumour volume or location near swallowing related structures. While the lack of attenuation on adjustment is reassuring, randomized trials are required to exclude the possibility of residual confounding.

Previous observational studies have shown that people who are offered surgery only for early-stage OPC are likely to receive adjuvant treatment (4, 9). Also, studies have shown that adjuvant treatment after surgery for oropharyngeal cancer is associated with a decreased quality of life and cost-effectiveness (26-29). In our cohort, 52% of participants offered surgery received adjuvant (C)RT and they reported comparable functional impairments to participants treated with RT only. Our study confirms that the favourable functional outcomes in people offered surgery, are only present when adjuvant treatment is avoided.

The indications to use adjuvant RT are not well defined. In general, in the case of close resection margins, re-excision is favoured over postoperative RT. In the case of neck metastases, a single metastasis is often treated with a selective neck dissection, but multiple lymph node metastases are usually seen as an indication for postoperative RT (30). However, in the case of HPV positive tumours, multiple lymph node metastases without extranodal spread are staged as N1, and the role of postoperative RT has not been well defined (31).

The only randomized comparative study investigating differences in clinical outcomes after surgery or radiotherapy for early stage oropharyngeal carcinoma was the ORATOR-trial, including 68 patients, of which the results were published recently (11). Differences in swallowing related quality of life were not clinically meaningful and the authors concluded that both treatment options have different toxicity profiles. A recent retrospective study focusing on patient reported outcomes was performed by Amit et al. who compared symptom burden and quality of life of low-intermediate risk OPC treated either surgically or nonsurgically (32). Patients were analysed by received treatment rather than intended treatment. Results of the 24 patients treated with singly modality, a significantly smaller sample size than our current analyses, showed that surgery participants had less interference of symptoms on daily functioning at 6 month post treatment. Also, studies have focused on patient reported outcomes and swallowing in more advanced staged OPC and concluded that surgery seems beneficial over CRT . Many other studies have reported on outcomes after single-modality treatment for early-stage OPC, but most have focused on either surgery or RT separately (28, 35), or only examined survival and disease recurrence (5, 10, 36-39). Results from the systematic review of observational studies by de Almeida et al. (4) showed different adverse events after either surgery or RT for early-stage OPC including oesophageal stenosis and osteoradionecrosis after (adjuvant) RT, and haemorrhage and fistula after surgery. The review of Huang et al. (9) reported on a feeding tube dependency rate of 5% one-year post treatment for both surgery and RT in early-stage OPC, which was comparable to the 4% in our cohort.

Previous studies have shown that HPV-positive and -negative OPC are distinct diseases with respect to both aetiology and prognosis (40). Currently, treatment de-intensification trials are underway for early-stage oropharyngeal carcinoma that aim to reduce toxicity while maintaining excellent survival (31). In our study, although participant numbers were low within groups, functional outcomes between HPV-positive and -negative participants seemed comparable. Also, no substantial differences in survival were seen. The possible difference in survival in HPV-negative participants between those who were offered RT or surgery might be caused by differences in age, comorbidities, and tumour biology or it could be due to chance.

This study has several limitations. Firstly, 49% of those eligible were actually enrolled ($n = 5511$) (18). This may result in selection bias and a lack of generalisability. Secondly, of the 300 OPC participants offered single-modality treatment, only 163 patients had data on self-reported swallowing and secondary functional outcomes available at 12-month follow-up. These missing data reduced the sample size and there may have been differences in those that provided complete data and those with missing data. Thirdly, because data from an existing large UK-wide multicentre study HN5000 were used, collecting a broad range of data from participants, detailed data on treatment and the process of clinical decision making were not collected. So data on treatment characteristics (e.g., surgical approach, and RT details such as time to and reason for adjuvant RT) that would have been valuable to this study were not available. Also, since most swallowing problems occurred in eating solids, information on dental status would provide more insight in the aetiology of the swallowing difficulties. Fourthly, multiple

comparisons were carried out in this study increasing the risk of reporting false positive results. For this reason, our presented *p* values should be interpreted with caution.

The study did have a number of strengths. Firstly, this was a multi-institution nationwide prospective study. Secondly, all institutes were eligible to take part so those with different views on management of early-stage OPC were included. Thirdly, this is, to our knowledge, the first study to report on swallowing and oral function (a high priority in people with OPC) after surgery or RT for early-stage OPC within a study that recruited both groups at the same time.

CONCLUSION

In this study we compared a key self-report functional outcome (swallowing) in people with early-stage OPC offered surgery or RT alone. Survival was similar between groups but swallowing was worse with RT, although not statistically significant in multivariable analysis, which did not result in differences of feeding tube use. Trials are required to confirm these observational differences are not a result of residual confounding. In the meantime, these results are helpful in informing treatment decisions by clinicians and patients. Over half of people offered surgery alone received surgery plus adjuvant therapy. More effort should be made to define the indications for postoperative RT and select the patients who will not go on to need adjuvant therapy.

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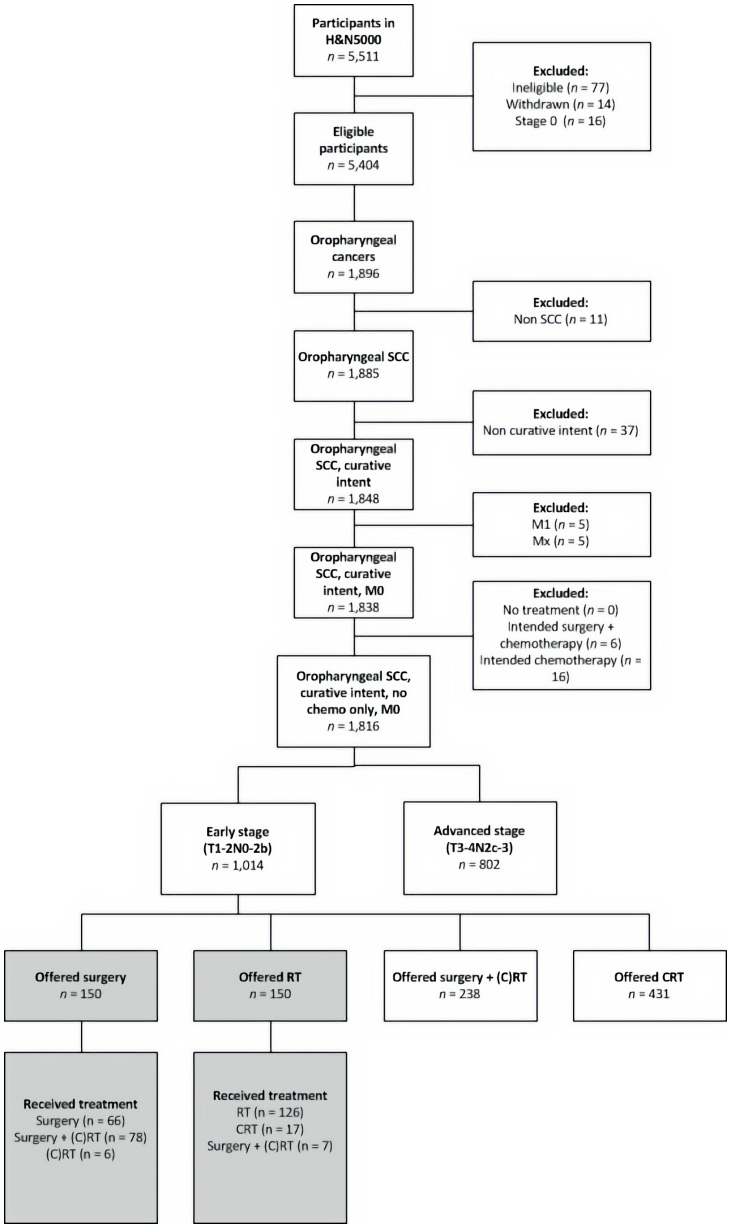
APPENDICES

Appendix 1 Flow chart. NB 6 participants were offered surgery with adjuvant chemotherapy and 16 were offered chemotherapy only. These were excluded from further analyses, since these treatment were considered likely to be not curative even though the treatment intent was recorded as curative. Gray shaded participants were included in the analyses.



Abbreviations: (C)RT = (chemo)radiotherapy, SCC = squamous cell carcinoma

Appendix 2 Number of participants with intended vs. received treatment

2a Intended vs. received treatment for M0 squamous cell oropharyngeal carcinoma treated with curative intent (without intended (surgery +) chemotherapy).

		Received								Total
		Surgery	CRT	RT	Surgery + RT	Surgery + CRT	Surgery + chemo	Chemotherapy	No treatment	
Intended	Surgery	74	5	1	58	45	0	0	0	183
	CRT	0	933	26	1	39	0	5	4	1008
	RT	0	28	195	10	1	0	0	2	236
	Surgery + RT	15	4	2	119	42	0	0	0	182
	Surgery + CRT	4	33	1	15	154	0	0	0	207
Total		93	1003	225	203	281	0	5	6	1816

2b Intended vs. received treatment for T1-2N0-2bM0 squamous cell oropharyngeal carcinoma treated with curative intent (without intended (surgery +) chemotherapy).

		Received								Total
		Surgery	CRT	RT	Surgery + RT	Surgery + CRT	Surgery + chemo	Chemotherapy	No treatment	
Intended	Surgery	66	5	1	50	28	0	0	0	150
	CRT	0	390	11	0	28	0	0	2	431
	RT	0	17	126	6	1	0	0	0	150
	Surgery + RT	11	1	2	101	30	0	0	0	145
	Surgery + CRT	3	17	1	9	108	0	0	0	138
Total		80	430	141	166	195	0	0	2	1014

2c Intended vs. received treatment for T3-4, N2c-3, M0 squamous cell oropharyngeal carcinoma treated with curative intent (without intended (surgery +) chemotherapy).

		Received								Total
		Surgery	CRT	RT	Surgery + RT	Surgery + CRT	Surgery + chemo	Chemotherapy	No treatment	
Intended	Surgery	8	0	0	8	17	0	0	0	33
	CRT	0	543	15	1	11	0	5	2	577
	RT	0	11	69	4	0	0	0	2	86
	Surgery + RT	4	3	0	18	12	0	0	0	37
	Surgery + CRT	1	16	0	6	46	0	0	0	69
Total		13	573	84	37	86	0	5	4	802

Appendix 3 Self-reported swallowing outcomes and secondary functional outcomes at baseline. *P* values shown for comparisons between group with Chi-square tests.

		Intended treatment Number of participants (%)		***P* value**	**Intended and received treatment** Number of participants (%)			***P* value**
		Surgery (*n* = 150)	RT (*n* = 150)		Surgery (*n* = 66)	RT (*n* = 126)	Surgery and received surgery + (C)RT (*n* = 78)	
Self-reported swallowing outcomes (from EORTC-QLQ-H&N35)								
Problems swallowing liquids, pureed or solid food	No	73 (73)	84 (75)	.740	33 (75)	73 (79)	38 (73)	.831
	Yes	27 (27)	28 (25)		11 (25)	19 (21)	14 (27)	
	Unknown	50	38		22	34	26	
Problems swallowing liquids	No	83 (82)	98 (87)	.358	37 (82)	83 (89)	43 (83)	.952
	Yes	18 (18)	15 (13)		8 (18)	10 (11)	9 (17)	
	Unknown	49	37		21	33	26	
Problems swallowing pureed food	No	88 (88)	100 (89)	.768	40 (91)	83 (90)	45 (87)	.503
	Yes	12 (12)	12 (11)		4 (9)	9 (10)	7 (14)	
	Unknown	50	38		22	34	26	
Problems swallowing solid food	No	77 (76)	86 (75)	.891	36 (80)	75 (80)	39 (75)	.558
	Yes	24 (24)	28 (25)		9 (20)	19 (20)	13 (25)	
	Unknown	49	36		21	32	26	
Secondary functional outcomes (from EORTC-QLQ-H&N35)								
Weight loss	No	79 (78)	78 (72)	.267	34 (77)	68 (76)	42 (79)	.814
	Yes	22 (22)	31 (28)		10 (23)	22 (24)	11 (21)	
	Unknown	49	41		22	36	25	
Tube feeding	No	101 (99)	108 (96)	.126	45 (100)	89 (96)	53 (100)	NA
	Yes	1 (1)	5 (4)		0 (0)	4 (4)	0 (0)	
	Unknown	48	37		21	33	25	
Pain mouth, jaw or throat	No	62 (63)	67 (59)	.555	27 (63)	57 (61)	34 (67)	.695
	Yes	36 (37)	46 (41)		16 (37)	36 (39)	17 (33)	
	Unknown	52	37		23	33	27	
Coughing	No	95 (94)	108 (96)	.616	41 (91)	90 (96)	50 (96)	.304
	Yes	6 (6)	5 (4)		4 (9)	4 (4)	2 (4)	
	Unknown	49	37		21	32	26	
Trouble opening mouth	No	90 (88)	104 (91)	.468	40 (89)	87 (93)	46 (87)	.752
	Yes	12 (12)	10 (9)		5 (11)	7 (7)	7 (13)	
	Unknown	48	36		21	32	25	
Dry mouth	No	77 (76)	86 (75)	.891	34 (76)	71 (76)	40 (77)	.875
	Yes	24 (24)	28 (25)		11 (24)	23 (25)	12 (23)	
	Unknown	49	36		21	32	26	

Appendix 3 Continued

		Intended treatment Number of participants (%)		***P* value**	**Intended and received treatment** Number of participants (%)			***P* value**
		Surgery (*n* = 150)	RT (*n* = 150)		Surgery (*n* = 66)	RT (*n* = 126)	Surgery and received surgery + (C)RT (*n* = 78)	
Bothersome appearance	No	95 (94)	103 (92)	.551	40 (91)	86 (94)	51 (96)	.279
	Yes	6 (6)	9 (8)		4 (9)	6 (7)	2 (4)	
	Unknown	49	38		22	34	25	
Altered taste	No	90 (88)	92 (81)	.129	40 (89)	78 (83)	46 (87)	.752
	Yes	12 (12)	22 (19)		5 (11)	16 (17)	7 (13)	
	Unknown	48	36		21	32	25	

NB: Not all percentages sum up exactly to 100% due to rounding.

Appendix 4 Baseline characteristics of early-stage participants with EORTC-QLQ-H&N35 data available at 12-month follow-up. *P* values shown for comparisons between groups. Percentages and statistical tests for available cases only. [a]Chi-square test, [b]independent samples *t*-test.

		Intended treatment Number of participants (%)		***P* value**	**Intended and received treatment** Number of participants (%)		***P* value**
		Surgery (*n* = 83)	RT (*n* = 80)		Surgery (*n* = 34)	RT (*n* = 68)	
Gender	Male	60 (72)	60 (25)	.695[a]	24 (71)	50 (74)	.754[a]
	Female	23 (28)	20 (75)		10 (29)	18 (27)	
Age at diagnosis (years) Mean (SD)		59 (10)	64 (10)	.003[b]	60 (10)	64 (10)	.045[b]
Deprivation index	1 (most deprived)	13 (17)	7 (10)	.059[a]	5 (15)	6 (9)	.407[a]
	2	20 (26)	15 (20)		9 (27)	14 (21)	
	3	14 (18)	24 (32)		5 (15)	20 (29)	
	4	9 (12)	16 (22)		6 (18)	13 (19)	
	5 (most affluent)	20 (26)	12 (16)		8 (24)	10 (15)	
	Unknown	7	6		1	5	
Smoking	Never used	14 (21)	16 (24)	.294[a]	9 (27)	14 (26)	.208[a]
	Former user	39 (57)	43 (64)		16 (47)	33 (60)	
	Current user	15 (22)	8 (12)		5 (15)	8 (15)	
	Unknown	15	13		4	13	
Alcohol	Non-drinker	16 (23)	20 (28)	.388[a]	8 (26)	18 (30)	.277[a]
	Moderate	17 (24)	19 (27)		4 (13)	17 (28)	
	Hazardous	30 (43)	21 (30)		13 (42)	17 (28)	
	Harmful	7 (10)	11 (16)		6 (19)	8 (14)	
	Unknown	13	9		3	8	

Appendix 4 Continued

		Intended treatment Number of participants (%)		***P* value**	**Intended and received treatment** Number of participants (%)		***P* value**
		Surgery ($n = 83$)	RT ($n = 80$)		Surgery ($n = 34$)	RT ($n = 68$)	
ACE-27	None	38 (48)	25 (31)	.030[a]	14 (42)	19 (28)	.450[a]
	Mild	27 (34)	28 (35)		11 (33)	27 (40)	
	Moderate	10 (13)	24 (30)		6 (18)	19 (28)	
	Severe	5 (6)	3 (4)		2 (6)	3 (4)	
	Unknown	3	0		1	0	
Oropharyngeal tumour site	Base of tongue	13 (16)	20 (25)	.286[a]	6 (18)	18 (27)	.124[a]
	Tonsil	41 (49)	38 (48)		11 (32)	30 (44)	
	Other	29 (35)	22 (28)		17 (50)	20 (29)	
T classification	T1	36 (43)	23 (29)	.052[a]	19 (56)	18 (27)	.004[a]
	T2	47 (57)	57 (71)		15 (44)	50 (74)	
N classification	N0	43 (52)	53 (66)	.217[a]	24 (71)	48 (71)	.684[a]
	N1	16 (19)	8 (10)		5 (15)	7 (10)	
	N2 (not bilateral)	1 (1)	2 (3)		0 (0)	2 (3)	
	N2a	5 (6)	5 (6)		2 (6)	2 (3)	
	N2b	18 (22)	12 (15)		3 (9)	9 (13)	
TNM stage	I	20 (24)	17 (21)	.098[a]	16 (47)	16 (24)	.050[a]
	II	23 (28)	36 (45)		8 (24)	32 (47)	
	III	16 (19)	8 (10)		5 (15)	7 (10)	
	IV	24 (29)	19 (24)		5 (15)	13 (19)	
HPV status	Negative	37 (47)	26 (33)	.233[a]	20 (67)	23 (40)	.016[a]
	Positive	41 (53)	43 (54)		10 (33)	35 (60)	
	Unknown	5	11		4	10	
Received treatment	Surgery	34	0	NA	34	0	NA
	RT	1	68		0	68	
	CRT	1	8		0	0	
	Surgery + (C)RT	47	4		0	0	
	No treatment	0	0		0	0	
Receieved treatment intent	Curative	83 (100)	80 (100)	NA	34 (100)	68 (100)	NA
	Palliative	0 (0)	0 (0)		0 (0)	0 (0)	
	Unknown	0	0		0	0	
Pre-treatment swallowing problems	No	52 (75)	61 (85)	.164	24 (77)	53 (88)	.171
	Yes	17 (25)	11 (15)		7 (23)	7 (12)	
	Unknown	14	8		3	8	

NB: Not all percentages sum up exactly to 100% due to rounding.
Abbreviations: ACE-27 = Adult Comorbidity Evaluation-27, HPV = human papilloma virus, SD = standard deviation.

Appendix 5 Self-reported swallowing and secondary functional outcomes at 4- and 12-month follow-up grouped by intended surgery and RT. Poisson regression analysis comparing RT to surgery (reference).

		4-month follow-up				12-month follow-up			
		Number of participants (%)		Regression analysis		Number of participants (%)		Regression analysis	
		Surgery (n = 150)	RT (n = 150)	RR (95% CI)	P value	Surgery (n = 150)	RT (n = 150)	RR (95% CI)	P value
Self-reported swallowing outcomes (from EORTC-QLQ-H&N35)									
Problems swallowing liquids, pureed or solid food	No	55 (66)	41 (45)	MA: 1.6 (1.0–2.5)	.051	64 (77)	51 (65)	MA: 1.3 (0.7–2.3)	.362
	Yes	29 (35)	50 (55)	A: 1.3 (0.8–2.0)	.249	19 (23)	28 (35)	A: 1.3 (0.8–2.3)	.277
	Unknown	66	59			67	71		
Problems swallowing liquids	No	73 (86)	77 (84)	MA: 1.4 (0.5–4.0)	.493	79 (85)	74 (93)	MA: 1.9 (0.4–9.8)	.167
	Yes	12 (14)	15 (16)	A: 1.1 (0.4–3.1)	.869	4 (5)	6 (8)	A: 1.6 (0.2–11.1)	.628
	Unknown	65	58			67	70		
Problems swallowing pureed food	No	70 (83)	68 (76)	MA: 2.7 (1.0–7.5)	.062	80 (96)	71 (90)	MA: 2.4 (0.5–12.4)	.284
	Yes	14 (17)	21 (24)	A: 2.0 (0.8–5.2)	.157	3 (4)	8 (10)	A: 2.1 (0.4–10.3)	.361
	Unknown	66	61			67	71		
Problems swallowing solid food	No	55 (67)	42 (46)	MA: 1.6 (1.0–2.7)	.040	65 (78)	52 (65)	MA: 1.3 (0.7–2.3)	.388
	Yes	27 (33)	50 (54)	A: 1.3 (0.8–2.1)	.287	18 (22)	28 (35)	A: 1.3 (0.8–2.2)	.308
	Unknown	68	58			67	70		
Secondary functional outcomes (from EORTC-QLQ-H&N35)									
Weight loss	No	54 (64)	42 (46)	MA: 1.6 (1.0–2.6)	.039	67 (83)	52 (68)	MA: 2.0 (1.0–4.0)	.055
	Yes	31 (37)	49 (54)	A: 1.5 (0.9–2.4)	.093	14 (17)	24 (32)	A: 2.1 (1.0–4.6)	.051
	Unknown	65	59			69	74		
Tube feeding	No	74 (85)	75 (81)	MA: 1.1 (0.5–2.6)	.767	80 (96)	75 (96)	MA: 1.5 (0.1–14.3)	.747
	Yes	13 (15)	18 (19)	A: 0.9 (0.4–2.2)	.766	3 (4)	3 (4)	NA	
	Unknown	63	57			67	72		
Pain mouth, jaw or throat	No	50 (60)	50 (54)	MA: 1.4 (0.9–2.3)	.138	62 (79)	61 (77)	MA: 1.1 (0.6–2.2)	.715
	Yes	34 (41)	42 (46)	A: 1.3 (0.8–2.0)	.311	17 (22)	18 (23)	A: 1.5 (0.7–3.1)	.319
	Unknown	66	58			71	71		
Coughing	No	76 (93)	78 (85)	MA: 3.3 (1.0–11.0)	.049	79 (95)	68 (86)	MA: 2.1 (0.7–6.8)	.176
	Yes	6 (7)	14 (15)	A: 2.3 (0.8–7.2)	.137	4 (5)	11 (14)	A: 2.7 (0.7–10.3)	.145
	Unknown	68	58			67	71		

Appendix 5 Continued

		4-month follow-up				12-month follow-up			
		Number of participants (%)		Regression analysis		Number of participants (%)		Regression analysis	
		Surgery (n = 150)	RT (n = 150)	RR (95% CI)	P value	Surgery (n = 150)	RT (n = 150)	RR (95% CI)	P value
Trouble opening mouth	No	61 (72)	75 (82)	MA: 0.5 (0.3–1.0)	.050	71 (86)	69 (87)	MA: 0.7 (0.3–1.7)	.431
	Yes	24 (28)	17 (19)	A: 0.5 (0.2–0.9)	.025	12 (15)	10 (13)	A: 0.8 (0.3–2.0)	.655
	Unknown	65	58			67	71		
Dry mouth	No	38 (44)	18 (20)	MA: 1.5 (1.1–2.1)	.007	46 (55)	18 (23)	MA: 2.0 (1.4–2.9)	<.001
	Yes	48 (56)	74 (80)	A: 1.5 (1.1–2.0)	.011	37 (45)	62 (78)	A: 2.0 (1.4–3.1)	.001
	Unknown	64	58			67	70		
Bothersome appearance	No	73 (85)	73 (79)	MA: 1.9 (0.8–4.4)	.121	71 (86)	69 (89)	MA: 0.8 (0.3–2.1)	.697
	Yes	13 (15)	19 (21)	A: 1.8 (0.8–4.1)	.139	12 (15)	9 (12)	A: 0.8 (0.4–2.0)	.663
	Unknown	64	58			67	72		
Altered taste	No	48 (57)	39 (42)	MA: 1.4 (0.9–2.1)	.116	58 (70)	41 (51)	MA: 1.6 (1.0–2.6)	.069
	Yes	37 (44)	53 (58)	A: 1.3 (0.9–2.1)	.184	25 (30)	39 (49)	A: 1.9 (1.0–3.4)	.035
	Unknown	65	58			67	70		
Study specific outcomes									
PEG tube in situ	No	124 (85)	112 (75)	MA: 1.7 (0.8–3.6)	.142	136 (94)	133 (91)	MA: 1.3 (0.4–4.8)	.682
	Yes	22 (15)	38 (25)	A: 1.5 (0.6–3.7)	.393	9 (6)	13 (9)	A: 0.6 (0.1–2.4)	.442
	Unknown	4	0			5	4		
Tracheostomy in situ	No	142 (97)	150 (100)	NA		142 (98)	146 (100)	NA	
	Yes	5 (3)	0 (0)			3 (2)	0 (0)		
	Unknown	3	0			5	4		
Study specific outcomes									
PEG tube in situ	No	124 (85)	112 (75)	MA: 1.7 (0.8–3.6)	.142	136 (94)	133 (91)	MA: 1.3 (0.4–4.8)	.682
	Yes	22 (15)	38 (25)	A: 1.5 (0.6–3.7)	.393	9 (6)	13 (9)	A: 0.6 (0.1–2.4)	.442
	Unknown	4	0			5	4		
Tracheostomy in situ	No	142 (97)	150 (100)	NA		142 (98)	146 (100)	NA	
	Yes	5 (3)	0 (0)			3 (2)	0 (0)		
	Unknown	3	0			5	4		

NB: Not all percentages sum up exactly to 100% due to rounding.

Abbreviations: A = adjusted model (adjusted for age, gender, ACE-27, smoking status, tumour site, TNM-stage, HPV-status and pre-treatment swallowing problems), CI = confidence interval, MA = minimally adjusted model (adjusted for age and gender), PEG = percutaneous endoscopic gastrostomy, RR = risk ratio, RT = radiotherapy.

Appendix 6 Self-reported swallowing and secondary functional outcomes with no including 'not at all' and yes including 'a little', 'quite a bit', and 'very much'. Outcomes at 4- and 12-month follow-up grouped by intended surgery and RT. Poisson regression analysis comparing RT to surgery (reference).

		4-month follow-up				12-month follow-up			
		Number of participants (%)		Regression analysis		Number of participants (%)		Regression analysis	
		Surgery (n = 150)	RT (n = 150)	RR (95% CI)	P value	Surgery (n = 150)	RT (n = 150)	RR (95% CI)	P value
Self-reported swallowing outcomes									
Problems swallowing liquids, pureed or solid food	No	32 (38)	16 (18)	MA: 1.5 (1.1–1.9)	.004	37 (45)	17 (21)	MA: 1.6 (1.2–2.2)	.001
	Yes	53 (62)	75 (82)	A: 1.3 (1.0–1.7)	.031	46 (55)	63 (79)	A: 1.6 (1.2–2.2)	.001
	Unknown	65	59			67	70		
Problems swallowing liquids	No	48 (57)	44 (48)	MA: 1.5 (1.0–2.2)	.067	67 (81)	58 (73)	MA: 1.4 (0.7–3.0)	.317
	Yes	37 (44)	48 (52)	A: 1.2 (0.8–1.9)	.313	16 (19)	22 (28)	A: 1.3 (0.6–2.8)	.453
	Unknown	65	58			67	70		
Problems swallowing pureed food	No	60 (71)	41 (46)	MA: 2.7 (1.5–4.8)	.001	72 (87)	59 (75)	MA: 1.8 (0.8–4.2)	.150
	Yes	24 (29)	48 (54)	A: 1.9 (1.0–3.5)	.036	11 (13)	20 (25)	A: 1.5 (0.7–3.2)	.332
	Unknown	66	61			67	71		
Problems swallowing solid food	No	33 (40)	18 (20)	MA: 1.5 (1.1–2.0)	.004	40 (48)	17 (21)	MA: 1.7 (1.3–2.3)	<.001
	Yes	49 (60)	74 (80)	A: 1.4 (1.0–1.8)	.029	43 (52)	63 (79)	A: 1.7 (1.3–2.3)	.001
	Unknown	68	58			67	70		
Secondary functional outcomes									
Weight loss	No	54 (64)	42 (46)	MA: 1.6 (1.0–2.6)	.041	67 (83)	52 (68)	MA: 2.1 (1.0–4.4)	.041
	Yes	31 (37)	49 (54)	A: 1.4 (0.9–2.3)	.161	14 (17)	24 (32)	A: 2.0 (0.9–4.2)	.071
	Unknown	65	59			69	74		
Tube feeding	No	74 (85)	75 (81)	MA: 1.1 (1.5–2.6)	.772	80 (96)	75 (96)	NA	
	Yes	13 (15)	18 (19)	A: 0.7 (0.3–1.8)	.482	3 (4)	3 (4)		
	Unknown	63	57			67	72		
Pain mouth, jaw or throat	No	15 (17)	13 (14)	MA: 1.2 (1.0–1.4)	.100	31 (38)	23 (29)	MA: 1.4 (1.0–1.8)	.046
	Yes	71 (83)	79 (86)	A: 1.1 (0.9–1.3)	.302	51 (62)	57 (71)	A: 1.2 (0.9–1.7)	.207
	Unknown	64	58			68	70		
Coughing	No	59 (72)	60 (65)	MA: 1.4 (0.8–2.4)	.249	65 (78)	43 (54)	MA: 2.6 (1.4–4.8)	.003
	Yes	23 (28)	32 (35)	A: 1.1 (0.6–1.9)	.804	18 (22)	36 (46)	A: 2.5 (1.3–4.6)	.005
	Unknown	68	58			67	71		

Appendix 6 continued

		4-month follow-up				12-month follow-up			
		Number of participants (%)		Regression analysis		Number of participants (%)		Regression analysis	
		Surgery ($n = 150$)	RT ($n = 150$)	RR (95% CI)	*P* value	Surgery ($n = 150$)	RT ($n = 150$)	RR (95% CI)	*P* value
Trouble opening mouth	No	35 (41)	49 (53)	MA: 0.8 (0.6–1.2)	.324	47 (57)	49 (62)	MA: 0.8 (0.5–1.3)	.337
	Yes	50 (59)	43 (47)	A: 0.7 (0.5–1.0)	.029	36 (43)	30 (38)	A: 0.8 (0.5–1.3)	.415
	Unknown	65	58			67	71		
Dry mouth	No	26 (30)	2 (2)	MA: 1.4 (1.2–1.7)	.001	18 (22)	5 (6)	MA: 1.2 (1.1–1.4)	.006
	Yes	60 (70)	90 (98)	A: 1.4 (1.1–1.7)	.001	65 (78)	75 (94)	A: 1.1 (1.0–1.3)	.036
	Unknown	64	58			67	70		
Bothersome appearance	No	45 (52)	42 (46)	MA: 1.2 (0.8–1.8)	.264	49 (59)	56 (72)	MA: 0.7 (0.4–1.2)	.233
	Yes	41 (48)	50 (54)	A: 1.1 (0.7–1.6)	.647	34 (41)	22 (28)	A: 0.6 (0.3–0.9)	.026
	Unknown	64	58			67	72		
Altered taste	No	25 (29)	9 (10)	MA: 1.3 (1.1–1.6)	.016	34 (41)	12 (15)	MA: 1.4 (1.1–1.8)	.007
	Yes	60 (71)	83 (90)	A: 1.3 (1.0–1.6)	.041	49 (59)	68 (85)	A: 1.3 (1.0–1.7)	.019
	Unknown	65	58			67	70		

NB: Not all percentages sum up exactly to 100% due to rounding.

Abbreviations: A = adjusted model (adjusted for age, gender, ACE-27, smoking status, tumour site, TNM-stage, HPV-status and pre-treatment swallowing problems), CI = confidence interval, MA = minimally adjusted model (adjusted for age and gender), PEG = percutaneous endoscopic gastrostomy, RR = risk ratio, RT = radiotherapy.

Appendix 7 Self-reported swallowing outcomes and secondary functional outcomes at 4- and 12-month follow-up grouped by intended and received surgery (with or without adjuvant (C)RT) and RT only. Poisson regression analysis comparing RT to surgery (reference).

		4-month follow-up					12-month follow-up				
		Number of participants (%)			Regression analysis		Number of participants (%)			Regression analysis	
		Surgery (*n* = 66)	RT (*n* = 126)	Surgery and received surgery + (C)RT (*n* = 78)	RR (95% CI)	*P* value	Surgery (*n* = 66)	RT (*n* = 126)	Surgery and received surgery + (C)RT (*n* = 78)	RR (95% CI)	*P* value
Self-reported swallowing outcomes (from EORTC-QLQ-H&N35)											
Problems swallowing liquids, pureed or solid food	No	32 (84)	34 (44)	21 (49)	MA: 4.1 (1.4–12.1)	.011	30 (88)	41 (61)	33 (70)	MA: 2.9 (0.9–8.8)	.067
	Yes	6 (16)	44 (56)	22 (51)	A: 3.2 (1.3–8.2)	.013	4 (12)	26 (39)	14 (30)	A: 2.7 (1.1–6.7)	.027
	Unknown	28	48	35			32	59	31		
Problems swallowing liquids	No	36 (95)	67 (85)	35 (80)	NA		34 (100)	63 (93)	43 (92)	NA	
	Yes	2 (5)	12 (15)	9 (21)			0 (0)	5 (7)	4 (9)		
	Unknown	28	47	34			32	58	31		
Problems swallowing pureed food	No	34 (90)	58 (76)	34 (79)	MA: 4.8 (0.7–32.0)	.109	34 (100)	60 (90)	44 (94)	NA	
	Yes	4 (11)	18 (24)	9 (21)	A: 2.7 (0.4–17.8)	.296	0 (0)	7 (10)	3 (6)		
	Unknown	28	50	35			32	59	31		
Problems swallowing solid food	No	32 (87)	35 (44)	21 (50)	MA: 4.1 (1.4–12.1)	.011	30 (88)	42 (62)	34 (72)	MA: 2.8 (0.9–8.6)	.072
	Yes	5 (14)	44 (56)	21 (50)	A: 3.2 (1.3–8.2)	.013	4 (12)	26 (38)	13 (28)	A: 2.7 (1.7–6.7)	.027
	Unknown	29	47	36			32	58	31		
Secondary functional outcomes (from EORTC-QLQ-H&N35)											
Weight loss	No	30 (79)	32 (41)	24 (55)	MA: 2.9 (1.3–6.4)	.009	29 (85)	42 (66)	36 (80)	MA: 2.4 (0.9–6.2)	.065
	Yes	8 (21)	46 (59)	20 (45)	A: 2.7 (1.2–6.0)	.018	5 (15)	22 (34)	9 (20)	A: 2.8 (0.9–8.5)	.077
	Unknown	28	48	34			32	62	33		
Tube feeding	No	37 (97)	65 (81)	35 (76)	NA		34 (100)	64 (96)	44 (94)	NA	
	Yes	1 (3)	15 (19)	11 (24)			0 (0)	3 (4)	3 (6)		
	Unknown	28	46	32			32	59	31		
Pain mouth, jaw or throat	No	28 (74)	47 (60)	21 (49)	MA: 2.2 (0.9–5.6)	.097	26 (79)	51 (76)	34 (77)	MA: 1.4 (0.5–3.9)	.558
	Yes	10 (26)	32 (41)	22 (51)	A: 2.0 (0.9–4.6)	.105	7 (21)	16 (24)	10 (23)	A: 2.3 (0.6–8.2)	.211
	Unknown	28	47	35			33	59	34		

Appendix 7 Continued

		4-month follow-up					12-month follow-up				
		Number of participants (%)			Regression analysis		Number of participants (%)			Regression analysis	
		Surgery (*n* = 66)	RT (*n* = 126)	Surgery and received surgery + (C)RT (*n* = 78)	RR (95% CI)	*P* value	Surgery (*n* = 66)	RT (*n* = 126)	Surgery and received surgery + (C)RT (*n* = 78)	RR (95% CI)	*P* value
Coughing	No	37 (97)	68 (86)	37 (90)	NA		31 (91)	58 (87)	46 (98)	MA: 1.8 (0.4–7.7)	.457
	Yes	1 (3)	11 (14)	4 (10)			3 (9)	9 (13)	1 (2)	A: 1.8 (0.2–18.1)	.623
	Unknown	28	47	37			32	59	31		
Trouble opening mouth	No	28 (74)	65 (82)	31 (71)	MA: 0.6 (0.2–1.5)	.240	33 (97)	59 (88)	36 (77)	MA: 2.1 (0.3–16.7)	.494
	Yes	10 (26)	14 (18)	14 (30)	A: 0.6 (0.3–1.6)	.333	1 (3)	8 (12)	11 (23)	A: 5.0 (0.6–40.5)	.130
	Unknown	28	47	34			32	59	31		
Dry mouth	No	28 (74)	18 (23)	10 (22)	MA: 3.4 (1.5–7.4)	.003	27 (79)	13 (19)	19 (40)	MA: 4.7 (1.9–11.8)	.001
	Yes	10 (26)	61 (77)	35 (78)	A: 3.3 (1.5–7.1)	.003	7 (21)	55 (81)	28 (60)	A: 4.7 (1.9.1–11.6)	.001
	Unknown	28	47	33			32	58	31		
Bothersome appearance	No	32 (84)	63 (80)	38 (84)	MA: 4.5 (0.7–30.1)	.117	29 (85)	60 (91)	40 (85)	MA: 0.6 (0.2–2.7)	.547
	Yes	6 (16)	16 (20)	7 (16)	A: 4.1 (0.7–22.7)	.107	5 (15)	6 (9)	7 (15)	A: 0.5 (0.1–2.0)	.311
	Unknown	28	47	33			32	60	31		
Altered taste	No	32 (84)	33 (42)	16 (36)	MA: 3.2 (1.3–7.9)	.014	28 (82)	33 (49)	30 (64)	MA: 2.9 (1.1–7.4)	.029
	Yes	6 (16)	46 (58)	28 (64)	A: 2.9 (1.2–7.0)	.020	6 (18)	35 (52)	17 (36)	A: 2.6 (1.0–7.1)	.058
	Unknown	28	47	34			32	58	31		
Study specific outcomes											
PEG tube in situ	No	64 (97)	97 (77)	57 (77)	MA: 4.9 (0.7–36.6)	.118	64 (99)	110 (90)	67 (91)	NA	
	Yes	2 (3)	29 (23)	17 (23)	A: 4.2 (0.5–33.7)	.178	1 (2)	12 (10)	7 (10)		
	Unknown	0	0	4			1	4	4		
Tracheostomy in situ	No	63 (96)	126 (100)	73 (97)	NA		63 (97)	122 (100)	73 (99)	NA	
	Yes	3 (5)	0 (0)	2 (3)			2 (3)	0 (0)	1 (1)		
	Unknown	0	0	3			1	4	4		

NB: Not all percentages sum up exactly to 100% due to rounding.

Abbreviations: A = adjusted model (adjusted for age, gender, ACE-27, smoking status, tumour site, TNM-stage, HPV-status and pre-treatment swallowing problems), CI = confidence interval, MA: minimally adjusted model (adjusted for age and gender), PEG = percutaneous endoscopic gastrostomy, RR = risk ratio.

Appendix 8 Baseline characteristics of participants with T1N0 OPC. *P* values shown for comparisons between groups. [a]Chi-square test, [b]independent samples *t*-test. Percentages and statistical tests for available cases only.

		Intended treatment Number of participants (%)		***P* value** Surgery vs. RT	**Intended and received treatment** Number of participants (%)		***P* value** Surgery vs. RT
		Surgery (*n* = 39)	RT (*n* = 25)		Surgery (*n* = 31)	RT (*n* = 24)	
Gender	Male	26 (67)	15 (60)	.588[a]	19 (61)	14 (58)	.824[a]
	Female	13 (33)	10 (40)		12 (39)	10 (41)	
Age at diagnosis (years) Mean (SD)		60 (11)	61 (7)	.696[b]	61 (12)	61 (7)	.849[b]
Deprivation index	1 (most deprived)	9 (24)	4 (17)	.933[a]	7 (23)	4 (17)	.974[a]
	2	11 (29)	8 (33)		9 (30)	8 (35)	
	3	7 (18)	4 (17)		4 (13)	4 (17)	
	4	7 (18)	6 (25)		7 (23)	5 (22)	
	5 (most affluent)	4 (11)	2 (8)		3 (10)	2 (9)	
	Unknown	1	1		7 (23)	4 (17)	
Smoking	Never used	2 (7)	3 (53)	.160[a]	2 (9)	2 (14)	.501[a]
	Former user	15 (56)	4 (27)		11 (48)	4 (29)	
	Current user	10 (37)	8 (20)		10 (44)	8 (57)	
	Unknown	12	10		8	10	
Alcohol	Non-drinker	7 (26)	3 (18)	.645[a]	7 (30)	3 (19)	.692[a]
	Moderate	6 (22)	2 (12)		3 (13)	1 (6)	
	Hazardous	9 (33)	7 (41)		8 (35)	7 (44)	
	Harmful	5 (19)	5 (29)		5 (22)	5 (31)	
	Unknown	12	8		8	8	
ACE-27	None	12 (33)	9 (36)	.325[a]	10 (35)	8 (33)	.308[a]
	Mild	16 (44)	13 (52)		12 (41)	13 (54)	
	Moderate	8 (22)	2 (8)		7 (24)	2 (8)	
	Severe	0 (0)	1 (4)		0 (0)	1 (4)	
	Unknown	3	0		2	0	
Oropharyngeal tumour site	Base of tongue	1 (3)	0 (0)	.411[a]	1 (3)	0 (0)	.363[a]
	Tonsil	9 (23)	9 (36)		6 (19)	8 (33)	
	Other	29 (74)	16 (64)		24 (77)	16 (67)	
HPV status	Negative	20 (77)	17 (77)	.977[a]	18 (86)	17 (81)	.679[a]
	Positive	6 (23)	5 (23)		3 (14)	4 (19)	
	Unknown	13	3		10	3	
Received treatment	Surgery	31 (80)	0 (0)	NA	31 (100)	0 (0)	NA
	RT	1 (3)	24 (96)		0 (0)	24 (100)	
	CRT	0 (0)	0 (0)		0 (0)	0 (0)	
	Surgery + (C)RT	7 (18)	1 (4)		0 (0)	0 (0)	
	No treatment	0 (0)	0 (0)		0 (0)	0 (0)	
Pre-treatment swallowing problems	No	18 (69)	15 (88)	.149[a]	16 (73)	14 (88)	.270[a]
	Yes	8 (31)	2 (12)		6 (27)	2 (13)	
	Unknown	13	8		9	8	

NB: Not all percentages sum up exactly to 100% due to rounding.

Abbreviations: ACE-27 = Adult Comorbidity Evaluation-27, HPV = human papilloma virus, SD = standard deviation.

Appendix 9 Self-reported swallowing outcomes and secondary functional outcomes of participants with T1N0 OPC at 4- and 12-month follow-up grouped by intended surgery and RT only.

		4-month follow-up		12-month follow-up	
		Number of participants (%)		Number of participants (%)	
		Surgery (n = 39)	RT (n = 25)	Surgery (n = 39)	RT (n = 25)
Self-reported swallowing outcomes (from EORTC-QLQ-H&N35)					
Problems swallowing liquids, pureed or solid food	No	19 (91)	11 (58)	18 (90)	15 (88)
	Yes	2 (10)	8 (42)	2 (10)	2 (12)
	Unknown	18	6	19	8
Problems swallowing liquids	No	20 (100)	19 (100)	20 (100)	17 (100)
	Yes	0 (0)	0 (0)	0 (0)	0 (0)
	Unknown	19	6	19	8
Problems swallowing pureed food	No	20 (95)	16 (89)	20 (100)	17 (100)
	Yes	1 (5)	2 (11)	0 (0)	0 (0)
	Unknown	18	7	19	8
Problems swallowing solid food	No	19 (91)	11 (58)	18 (90)	15 (8)
	Yes	2 (10)	8 (42)	2 (10)	2 (12)
	Unknown	18	6	19	8
Secondary functional outcomes (from EORTC-QLQ-H&N35)					
Weight loss	No	17 (77)	10 (53)	16 (80)	12 (80)
	Yes	5 (23)	9 (47)	4 (20)	3 (20)
	Unknown	17	6	19	10
Tube feeding	No	22 (100)	19 (100)	20 (100)	17 (100)
	Yes	0 (0)	0 (0)	0 (0)	0 (0)
	Unknown	17	6	19	8
Pain mouth, jaw or throat	No	16 (76)	12 (63)	18 (95)	13 (77)
	Yes	5 (24)	7 (37)	1 (5)	4 (24)
	Unknown	18	6	20	8
Coughing	No	20 (100)	19 (100)	19 (95)	15 (94)
	Yes	0 (0)	0 (0)	1 (5)	1 (6)
	Unknown	19	6	19	9
Trouble opening mouth	No	15 (71)	16 (84)	20 (100)	16 (94)
	Yes	6 (29)	3 (16)	0 (0)	14 (6)
	Unknown	18	6	19	8
Dry mouth	No	15 (71)	2 (11)	14 (70)	5 (29)
	Yes	6 (29)	17 (90)	6 (30)	12 (71)
	Unknown	18	6	19	8
Bothersome appearance	No	18 (86)	15 (79)	18 (90)	16 (94)
	Yes	3 (14)	4 (21)	2 (10)	1 (6)
	Unknown	18	6	19	8
Altered taste	No	16 (76)	7 (37)	16 (80)	9 (53)
	Yes	5 (24)	12 (63)	4 (20)	8 (47)
	Unknown	18	6	19	8

Appendix 9 Continued

		4-month follow-up		12-month follow-up	
		Number of participants (%)		Number of participants (%)	
		Surgery (*n* = 39)	RT (*n* = 25)	Surgery (*n* = 39)	RT (*n* = 25)
Study specific outcomes					
PEG tube in situ	No	36 (95)	22 (88)	38 (100)	23 (92)
	Yes	2 (5)	3 (12)	0 (0)	2 (8)
	Unknown	1	0	1	0
Tracheostomy in situ	No	38 (97)	25 (100)	37 (97)	24 (100)
	Yes	1 (3)	0 (0)	1 (3)	0 (0)
	Unknown	0	0	1	1

NB: Not all percentages sum up exactly to 100% due to rounding.

Appendix 10 Baseline characteristics of participants with early-stage OPC offered surgery or RT only grouped by HPV status. P values shown for comparisons between groups. Percentages and statistical tests for available cases only. aChi-square test, bindependent samples t-test.

		HPV-negative Number of participants (%)		***P* value**	**HPV-positive** Number of participants (%)		***P* value**
		Surgery (*n* = 55)	RT (*n* = 59)		Surgery (*n* = 69)	RT (*n* = 66)	
Gender	Male	39 (71)	38 (64)	.459[a]	56 (81)	54 (82)	.922[a]
	Female	16 (29)	21 (36)		13 (19)	12 (18)	
Age at diagnosis (years) Mean (SD)		62 (10)	64 (7)	.422[b]	56 (9)	62 (11)	< .001[b]
Deprivation index	1 (most deprived)	13 (27)	16 (29)	.425[a]	11 (17)	10 (16)	.038[a]
	2	12 (25)	16 (29)		16 (25)	10 (16)	
	3	12 (25)	9 (16)		11 (17)	22 (35)	
	4	6 (12)	12 (21)		8 (13)	13 (21)	
	5 (most affluent)	6 (12)	3 (5)		18 (28)	8 (13)	
	Unknown	6	3		5	3	
Smoking	Never used	5 (13)	4 (11)	.586[a]	15 (32)	16 (31)	.307[a]
	Former user	19 (50)	15 (41)		28 (60)	35 (67)	
	Current user	14 (37)	18 (49)		4 (9)	1 (2)	
	Unknown	17	22		22	14	
Alcohol	Non-drinker	7 (19)	7 (18)	.356[a]	12 (24)	18 (27)	.706[a]
	Moderate	7 (19)	8 (21)		16 (32)	16 (24)	
	Hazardous	16 (43)	10 (26)		21 (42)	19 (29)	
	Harmful	7 (19)	13 (34)		1 (2)	2 (3)	
	Unknown	18	21		19	11	
ACE-27	None	20 (38)	12 (21)	.138[a]	36 (54)	25 (39)	.006[a]
	Mild	17 (32)	25 (44)		24 (36)	19 (29)	
	Moderate	13 (25)	19 (33)		4 (6)	19 (29)	
	Severe	3 (6)	1 (2)		3 (5)	2 (3)	
	Unknown	2	2		2	1	

Appendix 10 Continued

		HPV-negative Number of participants (%)		***P* value**	**HPV-positive** Number of participants (%)		***P* value**
		Surgery (*n* = 55)	RT (*n* = 59)		Surgery (*n* = 69)	RT (*n* = 66)	
Oropharyngeal tumour site	Base of tongue	10 (18)	9 (15)	.435[a]	7 (10)	16 (24)	.072[a]
	Tonsil	11 (20)	18 (31)		53 (77)	45 (68)	
	Other	34 (62)	32 (54)		9 (13)	5 (8)	
T classification	T1	21 (38)	20 (34)	.634[a]	29 (42)	14 (21)	.009[a]
	T2	34 (62)	39 (66)		40 (58)	52 (78)	
N classification	N0	41 (75)	46 (78)	.974[a]	20 (29)	33 (50)	.087[a]
	N1	7 (13)	6 (10)		15 (22)	8 (12)	
	N2 (not bilateral)	0 (0)	0 (0)		2 (3)	3 (5)	
	N2a	1 (2)	1 (2)		6 (9)	6 (9)	
	N2b	6 (11)	6 (10)		26 (38)	16 (24)	
TNM stage	I	20 (36)	17 (29)	.691[a]	6 (9)	5 (8)	.042[a]
	II	21 (38)	29 (49)		14 (20)	28 (42)	
	III	7 (13)	6 (10)		15 (22)	8 (12)	
	IV	7 (13)	7 (12)		34 (49)	25 (38)	
Received treatment	Surgery	33 (60)	5 (9)	NA	19 (28)	0 (0)	NA
	RT	1 (2)	54 (92)		0 (0)	52 (79)	
	CRT	0 (0)	0 (0)		2 (3)	8 (12)	
	Surgery + (C)RT	21 (38)	0 (0)		48 (70)	6 (9)	
Pre-treatment swallowing problems	No	25 (66)	25 (37)	.870	42 (61)	45 (80)	.791
	Yes	13 (34)	12 (63)		9 (13)	11 (20)	
	Unknown	17	22		18	10	

NB: Not all percentages sum up exactly to 100% due to rounding.

Abbreviations: ACE-27 = Adult Comorbidity Evaluation-27, HPV = human papilloma virus.

Appendix 11 Self-reported swallowing outcomes and secondary functional outcomes at 12-month follow-up of participants who were offered surgery and RT only grouped by HPV status. Adjusted Poisson regression analysis (adjusted for age, gender, ACE-27, smoking status, tumour site, TNM-stage, HPV-status and pre-treatment swallowing problems) comparing RT to surgery (reference).

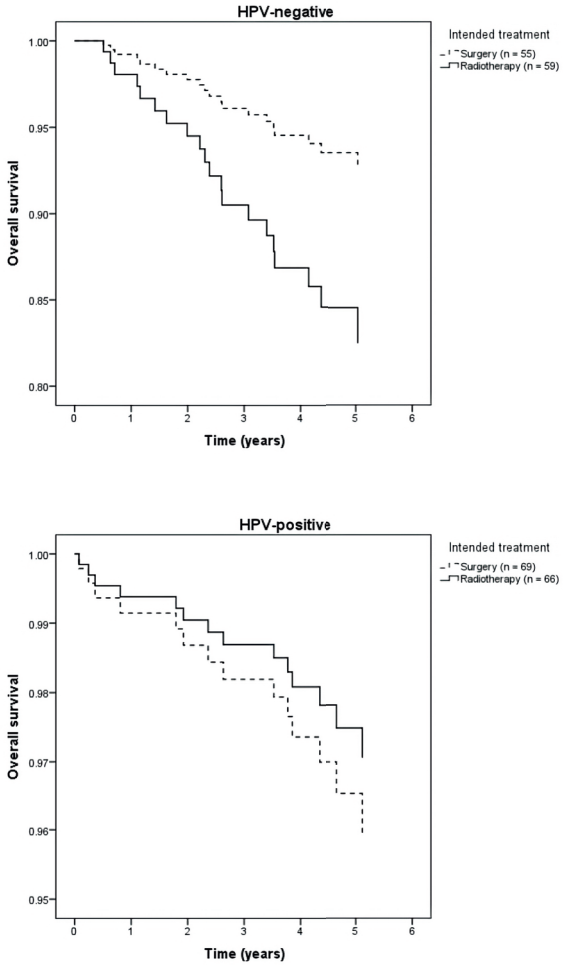
		HPV negative				HPV positive			
		Number of participants (%)		Regression analysis		Number of participants (%)		Regression analysis	
		Surgery ($n = 55$)	RT ($n = 59$)	Adjusted RR (95% CI)	*P* value	Surgery ($n = 69$)	RT ($n = 66$)	Adjusted RR (95% CI)	*P* value
Self-reported swallowing outcomes (from EORTC-QLQ-H&N35) 12-month follow-up									
Problems swallowing liquids, pureed or solid food	No	28 (76)	15 (60)	1.5 (0.6–3.7)	.344	31 (76)	29 (67)	1.3 (0.6–2.8)	.490
	Yes	9 (24)	10 (40)			10 (24)	14 (33)		
	Unknown	18	34			28	23		
Problems swallowing liquids	No	36 (97)	23 (89)	2.1 (0.3–13.6)	.405	38 (93)	40 (93)	0.4 (0.1–3.2)	.421
	Yes	1 (3)	3 (12)			3 (7)	3 (7)		
	Unknown	18	33			28	23		
Problems swallowing pureed food	No	36 (97)	23 (92)	2.7 (0.5–13.4)	.229	39 (95)	38 (88)	2.1 (0.4–10.3)	.374
	Yes	1 (3)	2 (8)			2 (5)	5 (12)		
	Unknown	18	34			28	23		
Problems swallowing solid food	No	28 (76)	16 (62)	1.5 (0.6–3.5)	.401	32 (78)	29 (67)	1.3 (0.6–2.8)	.490
	Yes	9 (24)	10 (39)			9 (22)	14 (33)		
	Unknown	18	33			28	23		
Secondary functional outcomes (from EORTC-QLQ-H&N35) 12-month follow-up									
Weight loss	No	27 (77)	12 (50)	2.1 (0.9–4.9)	.074	36 (88)	30 (71)	1.4 (0.5–4.2)	.509
	Yes	8 (23)	12 (50)			5 (12)	12 (29)		
	Unknown	20	35			28	24		
Tube feeding	No	36 (97)	23 (92)	NA		39 (95)	43 (100)	NA	
	Yes	1 (3)	2 (8)			2 (5)	0 (0)		
	Unknown	18	34			28	23		
Pain mouth, jaw or throat	No	25 (71)	18 (69)	1.1 (0.3–4.0)	.850	32 (82)	34 (81)	2.3 (0.6–8.5)	.198
	Yes	10 (29)	8 (31)			7 (18)	8 (19)		
	Unknown	20	33			30	24		
Coughing	No	34 (92)	23 (92)	0.8 (0.2–4.2)	.781	40 (98)	35 (81)	8.5 (3.2–23.0)	<.001
	Yes	3 (8)	2 (8)			1 (2)	8 (19)		
	Unknown	18	34			28	23		
Trouble opening mouth	No	33 (89)	20 (80)	1.7 (0.4–6.7)	.460	33 (81)	38 (88)	0.6 (0.2–2.2)	.420
	Yes	4 (11)	5 (20)			8 (20)	5 (12)		
	Unknown	18	34			28	23		
Dry mouth	No	26 (70)	3 (12)	4.5 (1.9–10.6)	.001	17 (42)	10 (23)	1.2 (0.8–1.9)	.327
	Yes	11 (30)	23 (89)			24 (59)	33 (77)		
	Unknown	18	33			28	23		

Appendix 11 Continued

		HPV negative				HPV positive			
		Number of participants (%)		Regression analysis		Number of participants (%)		Regression analysis	
		Surgery ($n = 55$)	RT ($n = 59$)	Adjusted RR (95% CI)	*P* value	Surgery ($n = 69$)	RT ($n = 66$)	Adjusted RR (95% CI)	*P* value
Bothersome appearance	No	32 (87)	22 (88)	0.9 (0.2–4.3)	.933	36 (88)	37 (86)	0.9 (0.3–2.2)	.744
	Yes	5 (14)	3 (12)			5 (12)	6 (14)		
	Unknown	18	34			28	23		
Altered taste	No	27 (73)	14 (54)	2.3 (0.8–6.2)	.103	26 (63)	21 (49)	1.5 (0.7–3.0)	.269
	Yes	10 (27)	12 (46)			15 (37)	22 (51)		
	Unknown	18	33			28	23		
Study specific outcomes									
PEG tube in situ	No	49 (91)	50 (88)	NA		63 (96)	62 (95)	NA	
	Yes	5 (9)	7 (12)			3 (5)	3 (5)		
	Unknown	1	2			3	1		
Tracheostomy in situ	No	52 (96)	57 (100)	NA		65 (99)	65 (100)	NA	
	Yes	2 (4)	0 (0)			1 (2)	0 (0)		
	Unknown	1	2			3	1		

NB: Not all percentages sum up exactly to 100% due to rounding.

Abbreviations: CI = confidence interval, RR = risk ratio.



Appendix 12 Kaplan Meier Curves. Top: HPV negative participants by intended treatment. Bottom: HPV positive participants by intended treatment.

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Chapter 3

The timed Swallowing Proficiency for Eating And Drinking (SPEAD) test to objectify (impaired) swallowing capacity in head and neck cancer patients and healthy controls

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ABSTRACT

Objective: Objective swallowing outcomes measure the physical swallowing function while subjective outcomes measure swallowing perception. A test for swallowing capacity, measuring the ingestion of all consistencies is currently not available. Therefore, the Swallowing Proficiency for Eating And Drinking (SPEAD)-test was developed. It entails the timed ingestion of thin liquid, thick liquid and solid. In this study, its feasibility, reliability and validity were evaluated in patients with dysphagia after treatment for head and neck cancer (HNC) and healthy participants.

Methods: Thirty-eight HNC patients and forty healthy participants were enrolled in this study and performed the SPEAD-test three times. Video recordings of the test were evaluated three times by one observer, and once by three additional observers, to assess test-retest, intra-rater and inter-rater reliability. Validity was assessed by calculating effect sizes for the difference between results of patients and healthy participants and by evaluating correlations with objective (e.g., videofluoroscopy and functional oral intake scale) and subjective (e.g., SWAL-QOL) swallowing outcomes.

Results: Test-retest, intra-rater and interrater reliability of ingestion duration was good to excellent. All hypotheses with regard to magnitude and direction of correlations were confirmed, supporting construct validity of the test.

Conclusion: Our initial results suggest that the SPEAD-test reliably measures the transport capacity of the upper digestive tract (in grams per second) and that this test can be useful to objectively evaluate and monitor the (safe) swallowing capacity in HNC patients, in both research as well as daily clinical practice.

INTRODUCTION

Swallowing impairment, impaired passage of a bolus from mouth to stomach or dysphagia, is a frequently occurring and disabling consequence of head and neck cancer (HNC) treatment, with different phases of the swallow affected including mastication, oral and oropharyngeal transport and opening of the upper esophageal sphincter (1-3). Dysphagia leads to a deteriorated quality of life and can increase the risk of developing serious health problems such as malnutrition and aspiration pneumonia (4, 5). The importance of attention to the swallowing function for patients with HNC has been recognized by the World Health Organization (WHO), who have included eating and drinking in the head and neck core set of the International Classification of Functioning, Disability and Health (ICF) (6).

Numerous methods for evaluation of swallowing function are currently available (7). Frequently used objective assessment methods include the Videofluoroscopy of Swallowing (VFS), also known as Modified Barium Swallow (MBS), Fiberoptic Endoscopic Examination of Swallowing (FEES), and pharyngeal manometry (8-10). Furthermore, tools to quantify physical examination results are available, such as the MASA-C which scores parameters including current diet, mouth opening, oral preparation and bolus clearance (11). Also, several evaluation methods or grading systems of these objective outcomes have been developed, such as the Oropharyngeal Swallow Efficiency (OPSE), the Modified Barium Swallow Impairment Profile (MBSImP), and the Dynamic Imaging Grade of Swallowing Toxicity (DIGEST) (12-14). In addition to these objective measurements, subjective instruments are available including self-reported assessment methods which are being used to evaluate swallowing function as experienced by patients themselves. This includes, for example, the Swallowing Quality of Life Questionnaire (SWAL-QOL) and MD Anderson Dysphagia Inventory (MDADI) (15).

Despite the wide range of available assessment methods, the correlation between the objective and subjective assessment methods appears to be poor (16, 17). The objective methods mainly measure the physical function needed for swallowing, and thus for eating and drinking. Patient-reported or subjective measures, on the other hand, measure the perceived swallowing ability and the impact on daily functioning. This perception is an expression of performance in daily life and of the impact of any disability. The relationship between these two expressions of human functioning is not necessarily a linear one, as recognized by the ICF model (6, 18). To capture relevant facets of an individual's swallowing problem, assessment of swallowing *capacity* in addition to function and perception is important. Swallowing capacity is defined as the time a person needs to swallow a predetermined amount/volume of liquids/solids under standardized circumstances (18). Therefore, the speed with which a person can eat and drink reflects the swallowing capacity, and is also likely to reflect the impact of swallowing dis(ability) on subjective experience and functioning in daily life to a larger extent than measures of swallowing function. Identifying discrepancies and/or interactions between an individual's physical functions, capacity, and performance can help guide the choice of rehabilitation interventions (6). Moreover, the assessment of capacity, in addition to function

and perception, can help to evaluate the effectiveness of swallowing rehabilitation. However, few tests are available for this purpose.

One currently available test is the timed 100- or 150-mL water swallow test (WST), developed to identify the patients at risk for dysphagia associated aspiration and also was evaluated in HNC patients (19, 20, 21). Another test that measures the capacity of eating is the recently developed Test Of Masticating And Swallowing Solids (TOMASS), which measures the eating function by evaluating the number of bites, chews, and swallows and amount of time a patient needs to eat a cracker (22, 23). This test has not yet been validated in a HNC population. By focusing on a single substance, both (bedside) tests have limited bandwidth to assess a patient's swallowing capacity along the continuum of swallowing ability. Because poor swallowing capacity in one texture might not mean that swallowing capacity for other textures is also poor, testing one texture might limit the clinical usefulness, prohibit full insight in the swallowing function, and possibly restrict the reliability and validity for assessing swallowing problems. A test that comprises all elements of the eating process is hypothesized more likely to be a good representation of patients' capacity of eating and drinking in daily life.

Therefore, we developed a test which evaluates an individual's (safe) swallowing capacity for eating as well as drinking; the Swallowing Proficiency for Eating And Drinking (SPEAD)-test. The SPEAD-test was based on WST and TOMASS, completing the spectrum of consistencies with tick liquid. The test entails the measurement of time needed to ingest three boluses of different consistencies (i.e., thin liquid, thick liquid and solid) and therefore measures the transport capacity of the upper digestive tract (in grams per second), a construct comparable to other physiological measures, e.g., to the forced vital lung capacity (in liters). The objective of this study was to evaluate the test's feasibility, reliability and validity in patients treated for HNC and in healthy participants.

METHODS

Design

This was a cross-sectional study on feasibility, validity and reliability of the SPEAD-test. The Medical Ethical Committee of the Netherlands Cancer Institute granted approval for the study (METC19.1262/N17SPE).

Participant selection

Eighty participants, composed of forty healthy individuals and forty individuals treated for HNC, were included in the study. With eighty participants, the expected ICC of the test-retest reliability of 0.8 can be estimated with a confidence interval of 0.1. Two included patients were later excluded from this analysis because one concerned a benign tumor of the tongue and the other concerned a distal esophageal carcinoma. The healthy participants were above age 40 (because 98% of HNC patients are above age 40 (24)) and had no history of or currently present dysphagia according to self-report. They were recruited from acquaintances of the researchers. The patients were a convenience sample, recruited from all patients with HNC (except skin cancer) who received a VFS as part of standard care in The Netherlands Cancer Institute between July 2018 and December 2019. Written informed consent was obtained from all participants.

Participant characteristics

Characteristics of all 78 participants are shown in Table 1. Compared to the healthy subjects, patients were older (median 65 vs. 54 years, $p < .001$), had a lower BMI (median 22 vs. 27, $p < .001$) and had a dental prosthesis more often (45% vs. 8%, $p < .001$). Also, healthy participants were female more often (26% vs 48%, $p = .064$).

Data collection

The following characteristics were collected from all participants, via a form completed prior to the SPEAD-test: gender, age, length, weight, body mass index (BMI), and the use of a (partial) dental prosthesis. For the patient group, the following additional characteristics were collected from their medical chart: tumor site, T- and N-stage (AJCC 7th edition), AJCC-stage, received treatment and time since treatment. In case a patient was treated for more than one tumor, characteristics of the tumor with the highest stage was recorded.

Table 1 Participant characteristics of HNC patient's (patient group) and healthy participants (healthy group). *P* values of either Mann-Whitney U test[a], Fisher's exact test[b] or linear-by-linear approximation of the Chi-square test[c].

		Patient group (N = 38) N (%)	**Healthy group (N = 40)** N (%)	***P* value**
Gender	Male	28 (74)	21 (53)	.064[b]
	Female	10 (26)	19 (48)	
Age Median (range)		65 (35-85)	54 (40-77)	<.001[a]
Length in m Median (range)		1.8 (1.5-1.9)	1.8 (1.5-1.9)	.928[a]
Weight in kg Median (range)		70 (47-103)	82 (60-110)	.003[a]
BMI Median (range)		22 (17-35)	27 (21-36)	<.001[a]
Dental prosthesis	Complete	13 (34)	0 (0)	<.001[c]
	Partial	4 (11)	3 (8)	
	None	21 (55)	37 (93)	
Tumor site	Oral cavity	5 (13)	NA	
	Oropharynx	13 (34)		
	Larynx	5 (13)		
	Hypopharynx	7 (18)		
	Nasopharynx	5 (13)		
	Submandibular gland	1 (3)		
	Unknown primary	2 (5)		
T-stage	T0	2 (5)	NA	
	T1	3 (8)		
	T2	8 (22)		
	T3	11 (30)		
	T4	13 (35)		
	Unknown	1		
N-stage	N0	7 (19)	NA	
	N1	5 (14)		
	N2	20 (54)		
	N3	5 (14)		
	Unknown	2		
AJCC-stage	I	1 (3)	NA	
	II	3 (8)		
	III	5 (15)		
	IV	28 (76)		
	Unknown	2		
Received treatment	Surgery	2 (5)	NA	
	RT	2 (5)		
	RT +	26 (68)		
	Surgery and RT (+)	7 (18)		
	Immunotherapy and surgery	1 (3)		
Months since treatment	Median (range)	3 (1-335)		

Abbreviations: NA = not applicable, RT = radiotherapy, RT + = radiotherapy with cisplatin/cetuximab/olaparib/immunotherapy, surgery included partial glossectomy (n = 4), total laryngectomy (n = 2), composite resection (n = 2), chordectomy (n = 1), extirpation of the submandibular gland (n = 1), esophageal resection (n = 1) or debulking of the tumor (n = 1).

The SPEAD-test

The SPEAD-test contains three subtasks covering the full range of food consistencies including texture levels 0, 3 and 7, respectively, according to the International Dysphagia Diet Standardization Initiative (IDDSI) framework, all at room temperature (Figure 1) (25). These three textures were selected given the frequent use of these in daily life. The level 0 texture consists of 100 g of water. The level 3 texture consists of 100 g of lemonade (15 g of strawberry flavored syrup added to 85 mL of water), thickened with two 4 g spoons of the thickening agent Nestlé ThickenUp© Clear (Nestlé Health Science, Oosterhout, The Netherlands). The level 7 texture consists of a cream cracker (3.125 grams).

The participant is comfortably seated upright in a chair at a table. The observer is seated opposite to the subject. The subject is instructed to ingest the three substances in order of increasing consistency, as quick as comfortably possible, with at least a one-minute break in between consistencies, as timed by the observer. The subject is asked to cough or stop whenever necessary and eat or drink like he or she is used to (e.g., with or without prosthesis, with or without spoon). All consistencies that the participant ingested in daily life at the time of the test were offered. Naturally, the patient was informed about the outcome of the VFS and was advised to skip a consistency in case of (silent) aspiration (penetration-aspiration score (PAS) of 7 or 8) on VFS for safety. The use of water during the ingestion of the solid is only allowed in case the person tested is completely unable to ingest the solid without it. For the purposes of the current study, we used a camera to videotape the subject from the viewpoint of the observer during the test.

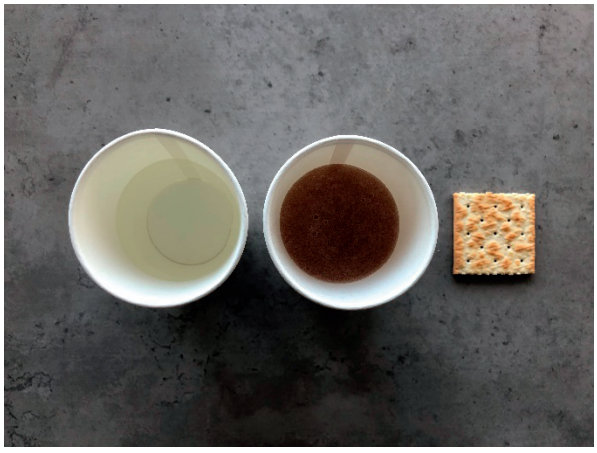

Figure 1 Consistencies of the SPEAD-test. Left: 100 g water (International Dysphagia Diet Standardization Initiative (IDDSI) level 0). Middle: 100 g thickened lemonade (IDDSI level 3). Right: 3.125 g cream cracker (IDDSI level 7).

The following outcomes are recorded and registered per consistency separately: total duration (time between substance touching lips until the end of the last swallow), grams swallowed (for thin and thick liquid measured with a measuring cup and for solid estimated as a percentage of leftover outside the mouth of 3.125 g), number of swallows (based on facial and laryngeal movement) , number of chews (based on mandibular movement), and whether the participant coughed at any time during or directly after ingestion of the consistency. The following outcomes are calculated: speed of ingestion per consistency (g/s) and average swallow volume (g/swallow). The primary outcome of the SPEAD-test is the SPEAD-rate (g/s), which is the mean ingestion speed of the three consistencies.

SPEAD-rate (g/s) = (speed thin liquid + speed thick liquid + speed solid) / 3

A higher SPEAD-rate thus represents better swallowing capacity. In case a participant is not able or not allowed (based on earlier videofluoroscopy studies) to ingest one or more of the consistencies, a speed of 0 g/s is used for that consistency. An instruction form for clinical use is presented in Appendix 1. Other outcomes, including number of swallows and chews and coughing, can be monitored when compared after repeating the SPEAD-test.

Safety, feasibility, and costs

To assess safety, we recorded whether any unsafe situations (e.g., noticeable aspiration or choking) occurred. To evaluate feasibility, after completion of one trial of the test, the participants were asked whether the test was uncomfortable in any way, and if this was the case to elaborate what was uncomfortable and how this could be avoided. Also, they were asked whether they had any other comments or suggestions after taking the test. Also, the time needed to perform the entire SPEAD-test, including preparation and cleaning time was assessed, and the costs for the products used for the test were calculated.

Reliability

Reliability of the assessment of duration, number of swallows and number of chews was assessed. To assess test-retest reliability, the SPEAD-test was performed three times by each participant, with at least fifteen minutes in between trials, timed by the observer. In order to determine intra-rater reliability, one observer evaluated the videotaped records of each test undertaken by all participants in random order three times. The interval between the evaluations was at least two weeks, to avoid the influence of recall. In order to assess inter-rater reliability, three different observers evaluated the videos of the first trial of all participants.

Validity

In order to assess validity of the SPEAD-test, several subjective as well as objective swallowing related outcomes were collected in all participants, except for VFS to avoid unacceptable radiation of the healthy participants. SPEAD-test and validity measures were collected on the same day, except for VFS. Median time between VFS and the other assessments was 9 days (range 0-41 days).

VFSs were performed only in the patient group as part of usual care either because of symptomatic dysphagia or according to clinical protocols. VFS was recorded in an upright position in lateral view with 25 frames per second. The subjects swallowed 3 and 10 cc thin liquid (IDDSI level 0), 5 cc thick liquid (level 3), and a piece of gingerbread (level 7) coated in Omnipaque consecutively from a spoon (Omnipaque contrast agent, GE Healthcare, Chicago, Illinois, United States). Pharyngeal swallowing safety (penetration/aspiration) and efficiency (residue) was graded by means of the validated **Dynamic Imaging Grade for Swallowing Toxicity (DIGEST)** (14, 26, 27). A higher score indicates more severe pharyngeal dysphagia. In case one of the consistencies was not tested, the DIGEST score was assessed based on the assessed consistencies. Also, aspiration on VFS (yes/no) was assessed.

The **Functional Oral Intake Scale (FOIS)** was assessed reflecting functional oral intake of food and liquid. It was filled in by the clinician by asking the participant about his/her diet. The FOIS ranges from 1 to 7 with 1 meaning nothing by mouth to 7 meaning no oral restrictions (28, 29).

Maximal inter-incisor (mouth) opening (MIO) was measured between the central incisors, using a disposable TheraBite range of motion scale (Atos Medical, Sweden) (30). Two measurements were performed, with the highest value recorded as the maximum mouth opening.

Also, a **study-specific questionnaire** was used with questions based on earlier published study specific questionnaires (27, 30). First, participants were asked to rate their swallowing function as a percentage, with 100% representing the swallowing function they had before cancer treatment (self-rated percentage swallowing function). The same question was asked regarding the speed of eating and drinking (self-rated percentage eating and drinking speed). Experienced maximal mouth opening (good, fair, moderate, or bad), taste and olfaction (normal, limited or absent), xerostomia (none, moderate, or bad) and dental prosthesis use (none, partial, or complete) were also included in the questionnaire as well as patient-reported degree of dyspnea, pain, and fatigue (not at all, a little, quite a bit and very much) were assessed.

The **Swallowing Quality of Life Questionnaire (SWAL-QOL)**, a validated 44-item questionnaire, was used to assess swallowing function and its influence on daily life (15, 31). It includes ten domains: burden*, food selection*, eating duration*, eating desire*, fear*, sleep, fatigue, communication, mental health*, social functioning*, and symptom frequency of which subscores can be calculated. The total SWAL-QOL score is calculated from the subscales marked with an asterisk. All scores range from 0 to 100 with higher scores indicating more dysphagia-related problems.

The two speech language pathologists (SLPs) who performed the VFS of patient, were asked to independently rate the degree of dysphagia (no, mild, moderate or severe). This rating was therefore based on patients' performance on VFS as well as the swallowing related complaints discussed prior to the VFS. The highest degree of the two ratings was used.

Statistical analysis

Analyses were performed using IBM® SPSS® Statistics 25.0. Participant characteristics, swallowing outcomes and results of the (first attempt of the) SPEAD-test were compared between the patients and healthy participants using the Mann-Whitney U test for continuous variables, the Fisher's exact test for categorical outcomes or the linear-by-linear approximation of the Chi-square test for ordinal outcomes. The correlation between SPEAD-rate and age, gender, length, dental prosthesis and spoon use was evaluated by means of the Spearman correlation coefficient (ρ).

The single measures Intraclass Correlation Coefficient (ICC) from a two-way random model using a consistency definition was used to evaluate intra-rater and inter-rater reliability. A two-way mixed model was used to evaluate test-retest reliability. If the ICC was below 0.50, reliability was considered poor, between 0.50 and 0.75 moderate, between 0.75 and 0.90 good and above 0.90 excellent (32). If the ICC was > 0.75, the test was considered sufficiently reliable. Since no gold standard is available, construct validity was assessed using known groups validity, convergent validity and discriminant validity. Known groups validity was evaluated by assessing the difference in SPEAD-rate between patients and healthy participants. SPEAD-rate was expected to be lower in patients compared to healthy participants. The Mann-Whitney U test for continuous variables or chi-square test for categorical outcomes was used to test the difference. Also, r-type effect sizes were calculated ($r = Z/\sqrt{N}$). According to the guidelines of Cohen (33), the effect sizes (r) of 0.1 to 0.3 were considered small, 0.3 to 0.5 moderate, and above 0.5 large. All effect sizes were expected to be large (> 0.5). In addition, an effect size for healthy participants versus patients, adjusted for age, dental prosthesis, and spoon use, was calculated by means of a linear regression model. For this analysis, all variables were standardized by subtracting the mean and dividing by the standard deviation. Also, the difference in SPEAD-rate between participants with no, mild, moderate and severe SLP graded dysphagia was tested by means of the Kruskal-Wallis test as well as the difference in SPEAD-rate between participants with different DIGEST scores.

The construct validity of the test was assessed based on a number of hypotheses. First, a number of hypotheses were tested with regard to SPEAD-test correlations with subjective outcomes: we expected the SPEAD-rate to be lower with decreasing self-rated percentage of eating and drinking speed, decreasing self-rated percentage of swallow function, increasing SWAL-QOL total score, increasing SWAL-QOL eating duration subscore, and increasing degree of dysphagia rated by the SLP. Second, the following hypotheses were tested to evaluate correlations with objective outcomes: we expected the SPEAD-rate to be lower with decreasing FOIS, increasing DIGEST grade and decreasing maximal mouth opening. These hypotheses were tested by calculating the Spearman correlation coefficient. Correlation coefficients (ρ) < 0.3 were indicative of a weak correlation, from 0.3 to 0.6 of a fair correlation, from 0.6 to 0.8 of a moderately strong and ≥ 0.8 of a strong correlation (34). The SPEAD-rate was expected to be strongly related to perceived swallowing performance than to physical swallowing functions,

and we therefore hypothesized better correlation with subjective outcomes (moderately strong to strong) than objective outcomes (fair to moderately strong).

To test divergent validity, the following hypotheses were tested: we expected the SPEAD-rate to be weakly correlated ($\rho < 0.3$) with the patient-reported dyspnea, pain, and fatigue.

The ability of the SPEAD-rate to discriminate between patients and healthy participants was further assessed by means of calculating the area under the Receiver Operating Characteristic (ROC) curve. The cut-off value of the SPEAD-rate with optimal sensitivity and specificity was determined.

RESULTS

Swallowing outcomes

Swallowing outcomes are presented in Table 2. Patients rated their eating and drinking speed and their overall swallowing function lower than healthy participants. Also, all SWAL-QOL scores were higher in patients, indicating worse swallowing related quality of life, and more patients experienced deteriorated taste and olfaction. Moreover, patients more often had a modified diet (FOIS below 7) and their median maximal mouth opening was smaller. The two SLPs rated the degree of dysphagia the same in 32 of the patients, with the other six only differing one degree.

Table 2 Swallowing outcomes. *P* values of either Mann-Whitney U test[a], linear-by-linear approximation of the Chi-square test[b].

	Patient group (*n* = 38) N (%)	**Healthy group (*n* = 40)** N (%)	***P* value**
Subjective swallowing outcomes			
Rated percentage eating and drinking speed Median (range)	50 (0-100)	100 (70-100)	<.001[a]
Rated percentage swallowing function Median (range)	58 (3-100)	100 (80-100)	<.001[a]
SWAL-QOL (0–100) Median (range) Higher score = more problems			
General burden	50 (0-100)	0 (0-100)	<.001[a]
Food selection	50 (0-100)	0 (0-38)	<.001[a]
Eating duration	69 (0-100)	0 (0-50)	<.001[a]
Eating desire	42 (0-100)	0 (0-75)	<.001[a]
Fear of eating	44 (0-100)	0 (0-38)	<.001[a]
Sleep	50 (0-100)	25 (0-100)	.011[a]
Fatigue	50 (0-83)	21 (0-75)	<.001[a]
Communication	44 (0-100)	0 (0-25)	<.001[a]
Mental health	38 (0-100)	0 (0-25)	<.001[a]
Social function	30 (0-80)	0 (0-25)	<.001[a]
Symptom score	44 (11-80)	7 (0-29)	<.001[a]
Total score	44 (3-91)	2 (0-42)	<.001[a]

Table 2 Continued

		Patient group (*n* = 38) N (%)	Healthy group (*n* = 40) N (%)	*P* value
Degree of dysphagia by SLP	None	6 (16)	NA	NA
	Mild	13 (34)		
	Moderate	14 (37)		
	Severe	5 (13)		
Experienced mouth opening	Poor	1 (3)	0 (0)	<.001[b]
	Moderate	9 (24)	0 (0)	
	Fair	5 (13)	1 (3)	
	Good	23 (61)	39 (98)	
Xerostomia	Severe	18 (47)	1 (3)	<.001[b]
	Moderate	14 (37)	2 (5)	
	No	6 (16)	37 (3)	
Taste	Absent	3 (8)	0 (0)	<.001[b]
	Limited	18 (47)	0 (0)	
	Normal	17 (45)	40 (100)	
Olfaction	Absent	0 (0)	0 (0)	.010[b]
	Limited	10 (26)	2 (5)	
	Normal	28 (74)	38 (95)	
Objective swallowing outcomes				
FOIS	1 (no oral intake)	0 (0)	0 (0)	<.001[b]
	2	2 (5)	0 (0)	
	3	6 (16)	0 (0)	
	4	0 (0)	0 (0)	
	5	6 (16)	0 (0)	
	6	10 (26)	0 (0)	
	7 (normal diet)	14 (37)	40 (100)	
DIGEST	0 (no aspiration/residue)	6 (17)	NA	NA
	1	14 (39)		
	2	6 (17)		
	3	10 (28)		
	4 (aspiration and residue)	0 (0)	NA	NA
Aspiration on VFS	No	15 (40)		
	Yes	23 (60)		
Maximal mouth opening in mm Median (range)		43 (10-56)	54 (36-70)	<.001[a]

Abbreviations: DIGEST = Dynamic Imaging Grade for Toxicity, FOIS = functional oral intake scale, NA = not applicable, N = number of participants, SLP = speech language pathologist, SWAL-QOL = Swallowing Quality of Life Questionnaire, VFS = videofluoroscopy.

SPEAD-test

All healthy participants ingested all three consistencies. Based on (silent) aspiration on VFS and daily ingestion of the consistencies, thin liquid was excluded from the test in eight patients (21%), thick liquid in one patient (3%) and solid in ten patients (26%). Fourteen patients were advised not to take thin liquid, of who one patient also was advised not to take thick liquid. Five

patients (36%) took the bolus anyways. None of the patients had (silent) aspiration on solids. All healthy participants performed the test three times, while all HNC patients performed the test twice and 21 out of 40 patients could perform the test three times. This was because some patients did not want to participate anymore after two trials, mainly because the amount to be ingested when performing the SPEAD-test three times was too much.

Results of the first trial of the SPEAD-test are summarized in Table 3. Eleven patients (29%) used a spoon to ingest the thick liquid compared to none of the healthy participants. Within the patients, using a spoon was not correlated to degree of dysphagia scored by the SLP (correlation coefficient 0.04, $p = .824$). Three patients (8%) needed water to eat the cracker while none of the healthy participants did.

Association of SPEAD-rate with participant characteristics

A higher SPEAD-rate is fairly correlated with younger age ($\rho = 0.44$, $p < .001$), as well as a greater body height ($\rho = 0.36$, $p = .001$), not having a dental prosthesis ($\rho = 0.42$, $p < .001$), and not using a spoon during the test ($\rho = 0.25$, $p = .026$). Gender was weakly correlated ($\rho = 0.18$, $p = .124$), with males having a higher SPEAD-rate in this sample.

Safety, feasibility, and costs

No unsafe situations occurred. Also, none of the healthy participants found the test uncomfortable or had remarks about it. Of the HNC patients, six had remarks about the test. Three disliked the taste of the tick liquid, two thought the quantity of the thick liquid was too much, and three thought the cracker was too dry or tasteless.

Taking the three consistencies including the two one-minute breaks in between took 188 s ranging from 148 s to a maximum of 373 s or six minutes. The time needed to prepare the test and clean up afterwards was approximately two minutes. In case only SPEAD-rate is calculated, which takes approximately two minutes, maximal time needed to take the test is estimated to be maximally eleven minutes in participants with the slowest eating and drinking speed. In case recordings are evaluated on number of swallows and chews an additional seven minutes should be added to the assessment time.

The total costs of the products needed was approximately €2 per test (i.e., one trial of thin liquid, thick liquid and solid).

Reliability

Results of reliability analyses including all 78 participants are presented in Table 4. Both test-retest, intra-rater and inter-rater reliability of duration measurements were good to excellent. Reliability on the assessment of the number of swallows was moderate to excellent and good to excellent for the number of chews. A small learning effect was noticeable, because the median duration for thin liquid in the first, second and third trial was 11 s (range 4-150 s), 10 s (range 4-81 s) and 10 s (4-60 s), respectively. For thick liquid, this was 24 s (range 7-89 s), 19 s (range 7-91 s) and 19 s (7-105 s) and for solid this was 38 s (range 13-156 s), 37 s (range 14-129 s) and 34 s (14-160 s).

Table 3 Outcomes of the SPEAD-test by degree of dysphagia according to speech language pathologist.

		Patient group (N = 38) Median (range)	**Healthy group (N = 40)** Median (range)	**Mann-Whitney U test[a] or Chi-square test[b]** P value	**|Effect size|**
Thin liquid (N performed)		N = 30	N = 40		
Ingestion speed (g/s)		6 (1-25)	11 (3-20)	< .001[a]	0.44
Duration (s)		16 (4-150)	9 (5-35)	< .001[a]	0.42
Grams swallowed		100 (10-100)	100 (100-100)	.018[a]	0.28
Number of swallows		6 (1-31)	5 (2-9)	.003[a]	0.36
Average swallow volume (g/swallow)		14 (3-50)	20 (11-50)	<.001[a]	0.45
Coughed N (%)	Yes	11 (37)	0 (0)	<.001[b]	
	No	19 (63)	40 (100)		
Thick liquid (N performed)		N = 37	N = 40		
Ingestion speed (g/s)		2 (0-11)	6 (2-14)	<.001[a]	0.57
Duration (s)		35 (9-89)	17 (7-50)	<.001[a]	0.54
Grams swallowed		100 (25-100)	100 (100-100)	<.001[a]	0.40
Number of swallows		6 (3-16)	6 (3-11)	.477[a]	0.08
Average swallow volume (g/swallow)		13 (4-25)	17 (9-33)	.004[a]	0.33
Coughed N (%)	Yes	10 (27)	0 (0)	<.001[b]	
	No	27 (73)	40 (100)		
Used spoon N (%)	Yes	10 (26)	0 (0)	<.001[b]	
	No	28 (74)	40 (100)		
Solid (N performed)		N = 28	N = 40		
Ingestion speed (g/s)		0.04 (0.01-0.15)	0.11 (0.05-0.24)	< .001[a]	0.65
Duration (s)		75 (21-156)	29 (13-63)	< .001[a]	0.65
Percentage swallowed		100 (20-100)	100 (100-100)	.042[a]	0.25
Number of swallows		4 (1-7)	2 (1-4)	< .001[a]	0.44
Average swallow volume (g/swallow)		1 (0-3)	2 (1-3)	< .001[a]	0.50
Number of chews		69 (28-194)	32 (15-69)	< .001[a]	0.64
Coughed N (%)	Yes	7 (25)	0 (0)	.001[b]	
	No	21 (75)	40 (100)		
Used water N (%)	Yes	3 (11)	0 (0)	.036[b]	
	No	25 (89)	40 (100)		
All consistencies					
SPEAD-rate (g/s)		2 (0-10)	6 (2-11)	<.001[a]	0.56

Abbreviations: N = number of participants.

No relevant differences in reliability were observed between male and female participants and participants with a BMI below or higher than 25.

Table 4 Intra-class Correlation Coefficients for test-retest, intra-rater and inter-rater reliability.

	Test-retest reliability (ICC with 95%CI)	Intra-rater reliability (ICC with 95%CI)	Inter-rater reliability (ICC with 95%CI)
Thin liquid			
Duration	0.90 (0.86-0.94)	1.00 (1.00-1.00)	0.98 (0.97-0.99)
Number of swallows	0.84 (0.77-0.90)	0.99 (0.99-1.00)	0.93 (0.90-0.95)
Thick liquid			
Duration	0.88 (0.83-0.92)	0.98 (0.97-0.99)	0.97 (0.96-0.98)
Number of swallows	0.68 (0.56-0.78)	0.96 (0.95-0.97)	0.74 (0.65-0.81)
Solid			
Duration	0.89 (0.83-0.93)	0.98 (0.96-0.98)	0.95 (0.93-0.97)
Number of swallows	0.60 (0.46-0.73)	0.96 (0.94-0.97)	0.75 (0.65-0.82)
Number of chews	0.89 (0.83-0.93)	1.00 (0.99-1.00)	0.98 (0.98-0.99)

Abbreviations: CI = confidence interval, ICC = intraclass correlation coefficient.

Known groups validity

Patients had a significantly lower SPEAD-rate as well as a lower speed on the individual consistencies, compared to healthy participants (see Table 3). As hypothesized, patients had a median SPEAD-rate of 2 g/s (range 0-10), compared to 6 g/s (range 2-11) for healthy participants corresponding to a large effect size of 0.56 (see also Figure 2). Adjusted for age, dental prosthesis, and spoon use, the effect size was moderate (0.33) with an estimated difference between patients and healthy participants of 3 g/s. For thin liquid, median ingestion speed in the patient group was 6 g/s (range 1-25 g/s) versus 11 g/s (range 3-20 g/s) in the healthy group which corresponds to a moderate effect size of 0.44. For thick liquid, this was 2 g/s (range 0-11 g/s) versus 6 g/s (range 2-14 g/s) corresponding to a large effect size of 0.57 and for solid 0.04 g/s (range 0.01-0.15 g/s) versus 0.11 g/s (range 0.05-0.24 g/s) corresponding to a large effect size of 0.65. Moreover, patients were unable to finish the consistency more often, their average swallow volume was lower, and they had to cough more often compared to healthy participants.

When dividing participants into four groups based on degree of dysphagia rated by the SLP (no, mild, moderate and severe, with the healthy participants rated as no), SPEAD-rate decreases with increasing degree of dysphagia ($p < .001$) (see Figure 3). Also, although not statistically significant, SPEAD-rate decreased with increasing median DIGEST-scores ($p = .054$). However, SPEAD-rates of patients with DIGEST scores of 1 and 2 largely overlapped.

The difference in ingestion speed of thin-liquid only between patients and healthy participants, as comparable to the outcome of the WST, had an effect size of 0.44. The difference in ingestion speed of only solids, as comparable to the outcome of the TOMASS, had an effect size of 0.65. Both were somewhat comparable to the effect size of the SPEAD-test with all consistencies combined of 0.56.

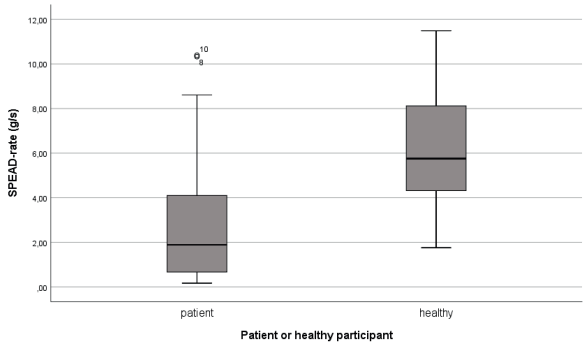

Figure 2 Boxplot of the SPEAD-rate for HNC patients and healthy participants.

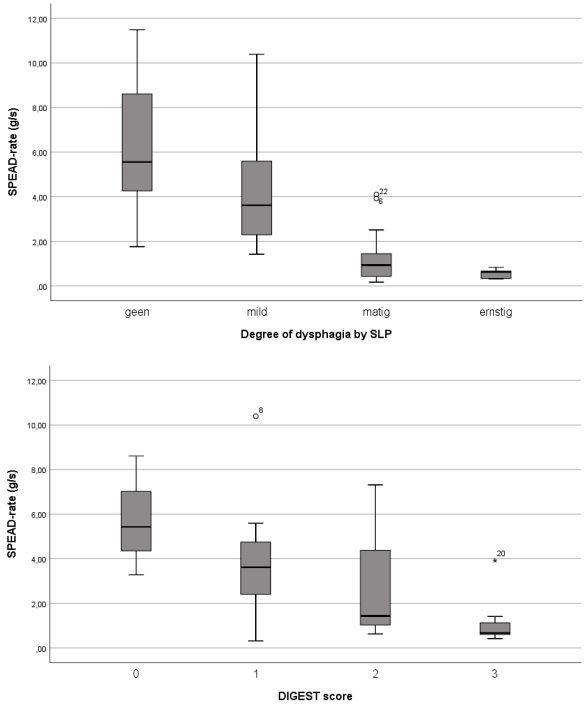

Figure 3 Boxplot of the SPEAD-rate for participants with different degrees of dysphagia according to the SLP (upper) and different DIGEST-scores (lower).

Convergent validity

The Spearman correlation coefficients between swallowing outcomes and the SPEAD-rate and speed of individual consistencies are listed in Table 5. The correlation between the SPEAD-rate and subjective outcomes was moderately strong (ρ ranging from 0.68 to 0.72). The correlation between objective outcomes was fair to moderately strong (ρ ranging from 0.49 to 0.70). The drinking speed of thin liquid was less correlated to subjective as well as objective outcomes than thick liquid and solid.

Correlation coefficients of the SPEAD-rate were higher compared to those of the ingestion speed of thin liquid, comparable to the outcome of the WST, or solid, comparable to the outcome of the TOMASS, for both subjective and objective swallowing outcomes.

Divergent validity

Correlations of the SPEAD-rate with participant-reported dyspnea, pain and fatigue was weak (ρ between 0.25 and 0.28) (Table 5).

Table 5 Spearman's correlation coefficients (ρ) of swallowing outcomes with results of the SPEAD-test.

		Spearman's ρ with *p* value			
		SPEAD-rate	**Ingestion speed thin liquid**	**Ingestion speed thick liquid**	**Ingestion speed solid**
Expected convergent correlation	**Subjective swallowing outcomes**				
	Self-rated percentage eating and drinking speed	0.71, p < .001	0.61, p < .001	0.74, p < .001	0.64, p < .001
	Self-rated percentage swallow function	0.72, p < .001	0.61, p < .001	0.71, p < .001	0.65, p < .001
	SWAL-QOL total score	-0.68, p < .001	-0.53, p < .001	-0.67, p < .001	-0.67, p < .001
	SWAL-QOL eating duration subscore	-0.69, p < .001	-0.57, p < .001	-0.70, p < .001	-0.66, p < .001
	Degree of dysphagia by SLP	-0.70, p < .001	-0.56, p < .001	-0.68, p < .001	-0.62, p < .001
	Objective swallowing outcomes				
	FOIS	0.70, p < .001	0.55, p < .001	0.67, p < .001	0.64, p < .001
	DIGEST grade	-0.51, p = .001	-0.35, p = .066	-0.44, p = .009	-0.32, p = .110
	Aspiration on VFS	-0.50, p = .001	-0.34, p = .067	-0.32, p = .344	-0.19, p .344
	Maximal mouth opening	0.49, p < .001	0.36, p = .002	0.50, p < .001	0.45, p < .001
Expected divergent correlation	**Other outcomes**				
	Participant-reported dyspnea	-0.28, p = .015	-0.18, p = .132	-0.29, p = .011	-0.41, p = .001
	Participant-reported pain	-0.25, p = .033	-0.16, p = .192	-0.32, p = .005	-0.22, p = .078
	Participant-reported fatigue	-0.28, p = .014	-0.19, p = .118	-0.37, p = .001	-0.34, p = .005

Abbreviations: DIGEST = Dynamic Imaging Grade for Toxicity, FOIS = functional oral intake scale, SLP = speech language pathologist, SWAL-QOL = Swallowing Quality of Life Questionnaire.

Reliability and validity without spoon

When only including participants, who did not use a spoon during ingestion, results were comparable to results with all participants included. Reliability of duration measurements were good to excellent. The median SPEAD-rate was 2 g/s (range 0-10) for patients and 6 g/s (range 2-11) for healthy participants which corresponds to an effect size of 0.51. Correlation coefficients, only including participants without a spoon, with subjective swallowing outcomes ranged from 0.64 to 0.72 and from 0.44 to 0.64 for objective swallowing outcomes. Correlation coefficients with patient-reported dyspnea, pain and fatigue ranged from 0.20 to 0.29.

Cut-off value

The area under the ROC-curve when the SPEAD-rate was used to discriminate between patients and healthy participants was 0.82 (see Figure 4). The cut-off value with an optimal sensitivity and specificity ratio is 4.2 g/s (sensitivity 80% and specificity 79%). The area under the ROC-curve when the SPEAD-rate was used to discriminate between aspirating and not aspirating patients was 0.79 (see Figure 5). The optimal cut-off value is 1.2 g/s (sensitivity 100% and specificity 57%).

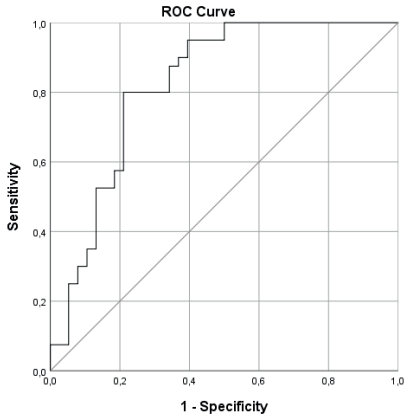

Figure 4 Ability of the SPEAD-rate to discriminate between HNC patients and healthy participants visualized in an ROC-curve. Area under the ROC-curve is 0.82.

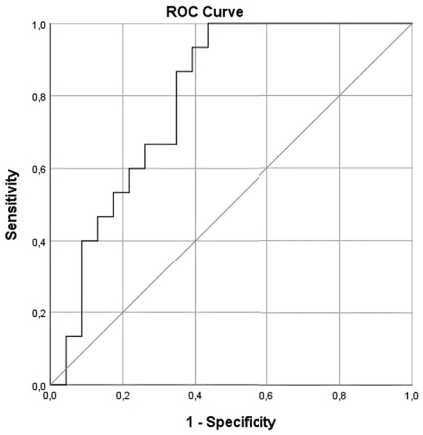

Figure 5 Ability of the SPEAD-rate to discriminate between patients aspiration on videofluoroscopy and not aspirating visualized in an ROC-curve. Area under the ROC-curve is 0.79.

DISCUSSION

The SPEAD-test is a new timed test that evaluates an individual's (safe) swallowing capacity for eating as well as drinking, by measuring the mean ingestion speed of three different consistencies (i.e., 100 g thin liquid, 100 g thick liquid, and a solid cream cracker). Results of this study support its safety and feasibility, with little time and money needed to perform the test. Also, assessment based on videos of the participant have proven to be reliable, enabling remote assessment in the era of telehealth. Test-retest, intra-rater and inter-rater reliability on duration measurement are good to excellent. Validity is supported by a significant difference in SPEAD-rate between HNC patients and healthy participants as well as correlations with subjective and objective swallowing outcomes. All three of the hypotheses tested to evaluate construct validity can be retained (i.e., a moderately strong to strong correlation with subjective measures, a fair to moderately strong correlation with objective measures, and a weak correlation with dyspnea, pain and fatigue).

Although two other swallowing capacity tests are currently available – the water swallow test (WST) and Test Of Masticating And Swallowing Solids (TOMASS) (19, 22) – the findings of our study indicate that the SPEAD adds clinical value. The WST was developed as a tool to screen for risk of aspiration (19). Later studies, however, have investigated the value of the WST for gaining quantitative information regarding the swallowing function (20, 21, 35). Patterson et al. (21) evaluated this test in 167 patients with HNC and found deterioration in WST outcomes (swallowing volume in mL/swallow and capacity in mL/s) from before treatment to three months after (chemo)radiotherapy and improvement afterwards. These results suggest a correlation with the degree of dysphagia, implying that the WST could indeed be used for monitoring swallowing function. After that, the TOMASS was developed as a second method of quantitative swallowing assessment by measuring the duration of solid bolus ingestion (22). The added value of the TOMASS test is that it assesses the oral preparation phase and the pressure build-up in the pharynx which is accompanied with solid bolus ingestion in contrast to thick liquid ingestion.

Yet, because they include only a single substance, both the TOMASS and the WST provide a limited assessment of overall swallowing capacity as needed in daily life. Depending on the etiology of the swallowing impairment, influenced by factors such as tumor localization, ingestion of one consistency can go without problems, while ingesting another consistency might reveal quality of life deteriorating impairment. This study showed that the SPEAD-rate better correlates with measures subjective and objective outcomes than the ingestion speed of thin liquid only and solid only. This suggests that by including the three main consistencies as ingested in daily life, the SPEAD-test provides a better bandwidth for obtaining quantitative information regarding swallowing capacity, and therefore better reflects daily functioning.

Objective swallowing measures that measure the physical function needed for swallowing, such as the VFS, do not always correlate well with the patients-reported subjective swallowing measures, which assess perceived swallowing ability and impact on functioning (16, 17). This might be, in part, because the objective measures available to date do not always include those aspects of swallowing that matters most to patients' functioning. For example, aspiration – a

very important parameter in most objective measures – does not always induce decreased swallowing performance in daily life. In contrast, the SPEAD-rate is an objective outcome measure that correlates well with the objective measures of function, and even better with subjective measures of perception. This is evidence that the SPEAD-test meets its intended purpose of measuring those aspects of swallowing capacity that are important for patients' functioning. Moreover, the SPEAD-rate correlates well with the degree of dysphagia as rated by experienced SLPs at our institute. This suggests the SPEAD-rate contains most elements that SLPs take into account by assessing the degree of swallowing problems in clinical practice. As such, the SPEAD-rate can complement currently available measures for quantifying swallowing capacity and monitoring the effect of certain swallowing rehabilitation strategies, both in research as well as in daily clinical practice.

In the development of the SPEAD-test we made choices related to the amount and manner of intake and the primary outcome of the test. The amount of the consistencies to be ingested by the participants was based on the WST and TOMASS. In our experience, the chosen amounts, 100 mL thin and thick liquid and the cracker is easy for participants with no swallowing impairment and can be difficult for patients with swallowing impairment, influencing the SPEAD-rate. Thus, we expected these amounts to provide sufficient variation for reliably assessing swallowing capacity.

Secondly, because initially we expected that participants would need a spoon to ingest thick liquid, we offered them this option. However, as the study progressed, it appeared that thick liquid could be ingested without a spoon, regardless degree of dysphagia. Therefore, we expect that in fact the vast majority of people will be able to perform the test without a spoon. As such, offering the option to use a spoon may introduce unnecessary variation in test administration. In a post-hoc analysis, we evaluated reliability and validity when participants who used a spoon were excluded. These results were comparable to those of the complete sample. Therefore, we recommend to perform the test without a spoon in clinical practice.

Thirdly, in the current study, all participants were observed from the front while measuring the results of the SPEAD-test. Although reliability results were good to excellent, observing the participants from the side might make it even easier to observe laryngeal movement.

Fourthly, the mean ingestion speed of all three consistencies (SPEAD-rate), was selected as the primary outcome of the SPEAD-test. This was chosen because ingestion speed is expected to better reflect swallowing capacity than swallow volume of number of chews alone. Also, it is not feasible to measure both duration and number of swallows or chews simultaneously when measuring the duration with a stopwatch. However, in clinical practice, video recording the participant taking the test is advised, partly because in case aspiration occurs or a patient needs assistance for other reasons the test is recorded and assessment of SPEAD-rate can be performed afterwards.

Fifth, participants unable to finish the solid without water were allowed to ingest water with it. The grams of water ingested were not added to the total amount because this would unwantedly increase the SPEAD-rate while taking water with the solid indicates worse swallowing capacity. For this reason, the SPEAD-rate should be considered an ordinal scale rather than an interval scale.

The SPEAD-test may have value in assessing swallowing capacity in dysphagia of other etiologies as well. Several swallowing tests have been developed for neurological patients, mainly focused on screening for dysphagia or aspiration after stroke (36, 37). Some also include the ingestion of a particular amount of water (38-40), or all three consistencies (41). During these tests, the patients ingests a small amount of the consistency and the observer checks whether signs of aspiration (e.g., coughing and voice change) occur. These tests, however, focus on safety rather than capacity. We therefore would like to encourage the evaluation of the reliability and validity of the SPEAD-test in populations with dysphagia due to other causes than HNC.

Limitations

This study has a few limitations. First, the study included a selected group of HNC patients who received a VFS as part of usual care. Therefore, the more severe cases of dysphagia might be overrepresented in this sample. However, since all HNC patients treated with chemoradiotherapy receive a post-treatment VFS at our institute, also patients with no to mild dysphagia were represented. In addition, the used patient population for this study is also the target population of the SPEAD-test, since the SPEAD-test will most likely be used in patients who will also receive a VFS. Given that, in this study, all patients received a VFS prior to the SPEAD-test does not imply that performing a VFS prior to the SPEAD-test is deemed mandatory, because when only the consistencies the patient also takes at home are tested no additional risk is created by performing the SPEAD-test.

Second, the intended use of the SPEAD-test is to measure the safe swallowing capacity. Therefore, similar to the advice patients receive for their daily situation, patients with (silent) aspiration on VFS (PAS 7 or 8) were advised to avoid the specific consistency during the SPEAD-test. Fourteen patients had (silent) aspiration (PAS of 7 or 8) on VFS, of who five (36%) did take the consistencies anyways. Therefore, in this study, not only safe swallows were analyzed.

Third, the observer was aware of the VFS result in this study, again, to ensure a safe swallow. We do not think that this led to any significant influence on the patients' performance on the SPEAD-test because the patient was not spoken to during ingestion of the boluses. Analyses of the videos were only performed several weeks/months after the SPEAD-test, and we believe it is unlikely the observer at that point would recall specifics of the VFS results.

Fourth, the study was not powered to determine normal values or cut-off values, as this was beyond the scope of the study. Therefore, future studies including larger samples of healthy participants and dysphagia patients are needed to establish such values.

Fifth, as thick liquid, we did not use a texture from daily life, such as yoghurt for example, because that might reduce reproducibility given the variability of the consistency between types, brands, and production day.

Sixth, patients were merely asked to provide feedback on how they experienced performing the SPEAD-test. In order to further clarify patients' experience and suggestions for development of the test, future studies could use more elaborate and formal methods, such as focus groups. Seventh, during the SPEAD-test, the patient is observed during swallowing and, as with any observer administered test, this may impact on performance to a certain extent.

CONCLUSION

The SPEAD-test measured (safe) swallowing capacity (in grams per second) by means of a timed bolus ingestion of three consistencies (i.e., thin liquid, thick liquid and solid) and has proven to be safe and feasible with good reliability and validity. It is an easily accessible test, requiring minimal equipment, time, and money. The test can be used to objectify, evaluate and monitor swallowing capacity in HNC patients, in both research as well as daily clinical practice. Future studies should be performed to further validate the SPEAD-test, and determine normal values and cut-off values in larger populations.

ACKNOWLEDGEMENTS

Michelle Hagemeijer is acknowledged for her support in performing the SPEAD-test in a significant proportion of the healthy participants.

APPENDICES

Appendix 1 SPEAD-test assessment form for clinical use.

SPEAD-test assessment form

Name _____
Date of birth _____
Date _____

Requirements

Thin liquid	100 g water in cup (IDDSI level 0)
Thick liquid	100 g lemonade thickened with two spoons of Nestlé ThickenUp© Clear in cup (IDDSI level 3)
Solid	1 cream cracker (IDDSI level 7)

Measuring cup
Video recording device
Stopwatch

Instructions

Only include consistencies that are safe to ingest or the patient also takes at home. Seat participant comfortably upright in chair and instruct participant the following: eat/drink from cup as quick as comfortably possibly, stop/cough when necessary, open mouth when finished. Record in the following order with at least a one-minute break in between: thin liquid > thick liquid > solid.

	Think liquid	Thick liquid	Solid
Leftover	_____g	_____g	_____%
Duration	_____	_____	_____
Swallows	_____	_____	_____
Chews	_____	_____	_____
Cough	+ / -	+ / -	+ / -

Calculate SPEAT-rate (mL = g)

Speed thin liquid = (100 g – leftover)/duration = _____
Speed thick liquid = (100 g – leftover)/duration = _____
Speed solid = (%leftover * 3.125 g)/duration = _____

SPEAT-rate = (speed thin liquid+speed thick liquid+speed solid) / 3

= _____ g/s

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Chapter 4

Long-term swallowing, trismus and speech outcomes after combined chemoradiotherapy and preventive rehabilitation for head and neck cancer; a ten-year plus update

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ABSTRACT

Background: The objective of this study was to explore the ten-year plus outcomes of Intensity Modulated Radiotherapy with concomitant chemotherapy (CRT) combined with preventive swallowing rehabilitation (CRT+) for head and neck cancer (HNC).

Methods: Subjective and objective swallowing, trismus and speech related outcomes were assessed at ten-year plus after CRT+. Outcomes were compared to previously published six-year results of the same cohort.

Results: Fourteen of the 22 patients at six-year follow-up were evaluable. Although objective swallowing related outcomes showed no deterioration (e.g., no feeding tube dependency and no pneumonia), swallowing related quality of life slightly deteriorated over time. No patients had or perceived trismus. Voice and speech questionnaires showed little problems in daily life. Overall quality of life (QOL) was good.

Conclusions: After CRT with preventive rehabilitation exercises for advanced HNC, swallowing, trismus and speech related outcomes moderately deteriorated from six- to ten-years, with an on average good overall QOL after.

INTRODUCTION

Advanced stage head and neck cancer (HNC) is commonly treated with chemoradiotherapy (CRT) (1). Although CRT is an organ preserving treatment modality, it is associated with substantial toxicities (2). Despite efforts to reduce radiotherapy dose on swallowing related structures (i.e., with intensity modulated radiotherapy (IMRT)), toxicities such as dysphagia are still a serious burden for survivors of advanced HNC (3).

Currently, strategies to preserve or strengthen swallowing musculature before, during or after treatment are making their way into regular care. Although the evidence is limited, some studies with good patient compliance have suggested benefit of preventive rehabilitation (4-16). At our institute, a randomized controlled trial (RCT) was performed, comparing preventive rehabilitation with and without the TheraBite Jaw Motion Rehabilitation System™ (Atos Medical, Sweden, Malmö)(6). Functional outcomes and quality of life after treatment up until six-year follow-up were comparable in both groups, besides less trismus in the TheraBite arm (6, 10, 17). A cost-effectiveness study using data of this study suggested that preventive rehabilitation, with or without TheraBite, is more cost-effective than usual care (18).

Due to increased survival of patients treated for HNC because of changing etiology and continuously improving treatment strategies, knowledge on long-term functional outcomes is essential (19). Functional outcomes of our preventive rehabilitation cohort have been described up until six years post treatment (6, 10, 17). Up until that time, functional outcomes were comparable between the two exercise groups. In both groups functional impairments were limited and more or less stable with no patients being feeding tube dependent at both two- and six-year follow-up. At two- and six-year follow-up 3 (10%) and 0 (0%) patients had a modified diet, respectively, and 2 (7%) and 1 (5%) patient(s) had trismus. Data from earlier studies on toxicities beyond this period have suggested that functional impairment after (C)RT may develop or worsen during the years after the end of treatment, possibly due to continued fibrosis of swallowing structures (20-22). Since preventive rehabilitation strategies are now applied more broadly, long-term outcomes may have improved, which could be relevant to medical decision making. Data on long-term functional outcomes after CRT with preventive swallowing rehabilitation are, however, currently lacking.

The objective of this study was to explore the functional outcomes and quality of life of the patients now more than ten years after CRT with preventive rehabilitation (with and without TheraBite), whose one-, two- and six-year data were assessed earlier (17). Functional outcomes at ten year- plus follow-up will be compared to those at six-year follow-up.

METHODS

Approval and consent

This study was approved by the medical research ethics committee of the Netherlands Cancer Institute (METC17.1906/N17SSF).Written informed consent was obtained from all patients.

Patient selection

All evaluable, disease-free patients who participated in the previously published RCT comparing preventive rehabilitation with and without the TheraBite Jaw Motion Rehabilitation System during CRT for HNC in the Netherlands Cancer Institute (NKI-AVL) were included in the analysis (6, 10, 17, 23). Initially, 55 patients treated with cisplatin-based CRT between September 2006 and April 2008 with curative intent for stage III-IV cancer of the oral cavity, nasopharynx, oropharynx, hypopharynx, and larynx were included. All patients received 70 Gy of Intensity Modulated RT (IMRT) in 35 fractions over seven weeks with concomitant cisplatin (100 mg/m^2) on days 1, 22, and 43. All 55 included patients received preventive exercises (randomized for exercises with or without the TheraBite) which included jaw range of motion and swallowing exercises. They were instructed to perform the exercises daily from the start of treatment up until one year afterwards, as described by van der Molen et al. (6). In summary, the experimental exercises consisted of a stretch exercise (i.e., passive and slow opening of the mouth using the TheraBite) and a strengthening exercise (i.e., swallow with tongue elevated to the palate at 50% of the maximal mouth opening using the Therabite). The standard rehabilitation consisted of five range of motion exercises and three strengthening exercises (i.e., Masako maneuver, effortful swallow and super-supraglottic swallow).

Data collection

The selection of outcomes measures collected in the present study were based on the data collected 6 years after CRT (17). Baseline characteristics included gender, age at start CRT, tumor site, T and N classification (AJCC 7th edition), AJCC stage, and preventive rehabilitation type (with or without TheraBite).

Swallowing related outcomes

The following swallowing outcomes and adverse events that might be related to swallowing impairment were assessed: history of pneumonia since six-year follow-up (according to patient and notes in medical chart), feeding tube dependency, and body weight. Videofluoroscopy was recorded in an upright position in lateral view with 25 frames per second. The subject was asked to swallow 3 and 10 cc thin liquid, 5 cc thick liquid, and a piece of gingerbread coated in Omnipaque consecutively from a spoon (Omnipaque contrast agent, GE Healthcare, Chicago, Illinois, United States). The validated Dynamic Imaging Grade for Toxicity (DIGEST) grading system was used to rate pharyngeal swallowing safety (penetration/aspiration) and efficiency (residue) (see Appendix 1) (24, 25). Videofluoroscopy studies were scored blinded for follow-up moment. The safety grade is assessed by means of the Penetration Aspiration Scale (PAS) over all bolus trials (26). Efficiency is assessed by estimating the maximum percentage of

pharyngeal residue over all bolus trials (either < 10%, 10-49%, 50-90%, or > 90%). The DIGEST grade combines both safety and efficiency in a 5-point ordinal scale ranging from grade 0 (no pharyngeal dysphagia) to grade 1 (mild), grade 2 (moderate), grade 3 (severe) and grade 4 (life threatening). All videofluoroscopy studies were assessed by two of the researchers who came to a consensus afterwards. Oral diet was assessed by means of the Functional Oral Intake Scale (FOIS), which reflects the oral intake on a seven-point ordinal scale with scores below 7 indicating a modified diet (27). A visual analog scale (VAS) of 0–100 mm was used to assess pain with scores greater than 4 mm indicating pain (28).

Also, subjective swallowing related outcomes were assessed by means of a study specific questionnaire as described earlier (29). The questionnaire included questions on whether the patient perceived xerostomia, difficulty swallowing and masticating, and problems with oral transport or swallowing of solids, thick liquids and/or thin liquids (outcome was dichotomized into no meaning not at all, and yes meaning a little, quite a bit or very much). Also, patients were asked whether they have been continuing performing the rehabilitation exercises after the one-year training period post CRT.

Trismus related outcomes

To assess trismus, we measured the maximal inter-incisal opening (MIO) by means of the TheraBite Jaw Range of Motion Scale (Atos Medical AB, Malmo, Sweden), and used a mouth opening of 35 mm or smaller as a criterion for trismus (30). The MIO was measured by two different raters at timepoints which might cause inter-rater variability. However, the inter-rater reliability of mouth opening measurement is very high (intraclass correlation coefficient of 0.98) (31). To increase reliability of the measurements in our study, two measurements were taken at each timepoint with the highest value as maximal MIO. Also, subjects were asked if they perceived their mouth opening as deteriorated.

Voice and speech related outcomes

Speech recordings consisted of an excerpt from a standard, balanced 189 word long Dutch text called 'De vijvervrouw' and a sustained /a/. The recordings were automatically analyzed by the program Automatic Speech analysis In Speech Therapy for Oncology (ASISTO) (32, 33). This program determined the intelligibility based on Alignment-free phonological and phonemic features (ALF-PPFs) with scores ranging from 0 to 100%. Voice quality was determined with the Acoustic Voice Quality Index (AVQI, version 2.03) (1 (normal)–8 (least normal); a value <2.92 reflects normal voice quality) using 4 seconds of the running speech and 3 seconds of the sustained /a/ (34, 35). Speech recordings from the six-year follow-up were unavailable for re-evaluation. Therefore, results from the analyses performed for the earlier published paper by Kraaijenga et al. on voice quality at six-year follow-up were reported, which were analysed using an earlier version of the ASISTO software.

As subjective outcome, patients were asked whether they perceived their voice as different.

Quality of life related outcomes

Symptom related quality of life questionnaires were used. The Dutch version of the SWAL-QOL, a validated 44-item questionnaire on dysphagia and its influence on daily life, was assessed. All scores range from 0 to 100 with higher scores indicating more dysphagia-related problems, and scores ≥ 14 points indicating swallowing problems in daily life (36-38). Subjective speech and voice function were assessed by means of the validated Dutch versions of the Voice Handicap Index (VHI) and Speech Handicap Index (SHI), respectively. These are both 30-item voice/speech-related quality of life questionnaires with higher scores indicating more speech/voice-related problems (39-42). A VHI score of 15 or higher, and a SHI score of 6 or higher indicate voice, respectively speech problems in daily life (38, 43).

Also, overall quality of life was assessed by means of the EQ-5D-5L. The EQ-5D-5L includes the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has five levels of severity ranging from no to extreme burden. We dichotomized outcomes in to any burden (slight, moderate, severe, unable to perform) and no burden. The five dimensions are completed by the EQ-VAS, which records the patient's self-rated health on a visual analogue scale ranging from worst (0) to best (100) health.

Statistical analysis

Analyses were performed using IBM® SPSS® Statistics 23.0 and R 3.6.2. Baseline characteristics and outcomes at both six and ten years after treatment were presented using descriptive statistics. Medians and ranges were used for numerical and ordinal variables. For proportions, the Wilson score 95% confidence intervals were calculated. For medians, bootstrapping was used to estimate 95% confidence intervals. For comparison, outcomes at six-year follow-up are described only of the 14 patients evaluable at ten-year plus follow-up. With the small sample size of this study, which was inevitable for the given patient population, only very large changes will be statistically significant using the traditional cut-off of $p = .05$ for statistical significance. Also, absence of statistically significant changes cannot be interpreted as evidence for no change. We therefore consider these results to be descriptive, rather than inferential, and accordingly we refrained from hypothesis testing. Instead, we interpret the measurements based on their clinical meaning for the individuals in the sample.

RESULTS

Baseline characteristics

Of the 22 patients evaluable six years after CRT with preventive rehabilitation (17), 14 patients were evaluable for participation at ten-year plus (see Figure 1 for the study flow chart). Of the eight unevaluable patients, three refused participation (one had lost his wife recently and two had other priorities). One patient could not be evaluated because she had a second primary esophageal carcinoma. Four patients had died in the meantime. Three died of unrelated causes (one died from injuries after a fall off stairs, one from heart failure, and one from a status epilepticus caused by a glioblastoma). The fourth patient died at home at the age of 76 from respiratory insufficiency caused by a pneumonia of unknown etiology. The median follow-up of the 14 evaluable patients was 128 months (range 120–139 months) after the start of CRT. None of the patients continued with the (preventive) exercises after one-year post CRT. Baseline characteristics are presented in Table 1.

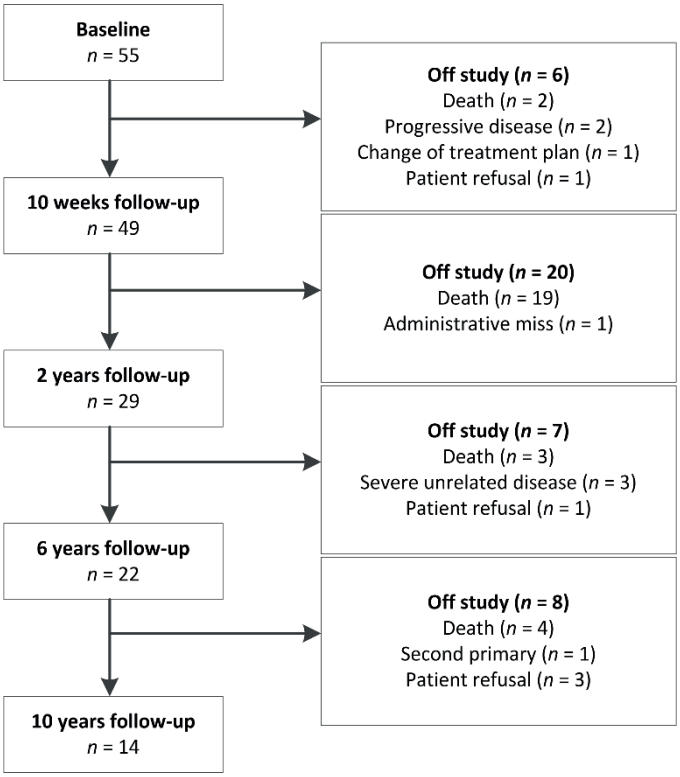

Figure 1 Flow chart with patient numbers at all follow-up moments and reasons for exclusion.

Table 1 Baseline characteristics of patients evaluable at ten-year plus follow-up ($n = 14$).

		Number of patients (%)
Gender	Male	11 (79)
	Female	3 (21)
Age at baseline Median (range)		58 (39–66)
Tumor site	Oral cavity/oropharynx	8 (57)
	Larynx/hypopharynx	4 (29)
	Nasopharynx	2 (14)
T classification	T1	3 (21)
	T2	7 (50)
	T3	4 (29)
	T4	0 (0)
N classification	N0	1 (7)
	N1	5 (36)
	N2	5 (36)
	N3	3 (21)
AJCC stage	II	0 (0)
	III	6 (43)
	IV	8 (57)
Rehabilitation	Without TheraBite	5 (36)
	With TheraBite	9 (64)

Abbreviations: AJCC stage= American Joint Committee on Cancer stage 7th edition, RT = radiotherapy

Swallowing related outcomes

Swallowing related outcomes at six- and ten-year plus follow-up, respectively, are presented in Table 2. Pharyngeal dysphagia based on DIGEST grades increased in 5 out of 10 patients with videofluoroscopy available, due to a decreased efficiency ($n = 3$), decreased safety ($n = 1$), or both ($n = 1$). Similar to the last follow-up, none of the currently evaluable patients were feeding tube dependent, or required a modified diet (FOIS < 7). None of the patients had had a pneumonia since last follow-up, but, as mentioned above, one of the currently non-evaluable patients, a 76-year old male, had died of pneumonia of unknown etiology after the last follow-up at six years, in which case aspiration as etiology obviously cannot be excluded. This patient had no penetration or aspiration on videofluoroscopy at six-year follow-up. The number of patients who perceived difficulty with oral transport of solids increased between six- and ten-year plus follow-up from 2 to 7 patients. For thick liquids this increased from 1 to 3 patients, and for thin liquids from 0 to 2 patients.

Table 2 Swallowing related outcomes at six- and ten-year plus follow-up of patients evaluable at ten-year plus follow-up ($n = 14$).

	Number of patients (%)			
	Six-year follow-up	**95%CI**	**Ten-year plus follow-up**	**95%CI**
Objective outcomes				
DIGEST grade based on VFS ($n = 10$)				
Safety grade 0	8 (80)	49-94%	7 (70)	40-89%
Safety grade 1	2 (20)	6-51%	1 (10)	2-40%
Safety grade 2	0 (0)	0-28%	1 (10)	2-40%
Safety grade 3	0 (0)	0-28%	1 (10)	2-40%
Safety grade 4	0 (0)	0-28%	0 (0)	0-28%
Efficiency grade 0	1 (10)	2-40%	0 (0)	0-28%
Efficiency grade 1	6 (60)	31-83%	4 (40)	17-69%
Efficiency grade 2	1 (10)	2-40%	1 (10)	2-40%
Efficiency grade 3	2 (20)	6-51%	5 (50)	24-76%
Efficiency grade 4	0 (0)	0-28%	0 (0)	0-28%
DIGEST grade 0	1 (10)	2-40%	0 (0)	0-28%
DIGEST grade 1	7 (70)	40-89%	5 (50)	24-76%
DIGEST grade 2	2 (20)	6-51%	3 (30)	11-60%
DIGEST grade 3	0 (0)	0-28%	2 (20)	6-51%
DIGEST grade 4	0 (0)	0-28%	0 (0)	0-28%
Pneumonia since six-year follow-up	0 (0)	0-22%	0 (0)	0-22%
Feeding tube dependent	0 (0)	0-22%	0 (0)	0-22%
Modified diet (FOIS < 7)	0 (0)	0-22%	0 (0)	0-22%
Weight in kg Median (range)	76 (68–103)	69-89	77 (70–103)	72-85
Pain (VAS) Median (range)	0 (0–25)	0-12	0 (0–30)	0-4
Subjective outcomes				
Perceived:				
Xerostomia	10 (71)	45-88%	10 (71)	45-88%
Difficulty swallowing	7 (50)	27-73%	10 (71)	45-88%
Difficulty masticating	1 (7)	1-31%	3 (21)	8-48%
Problems with:				
Oral transport with solids	2 (14)	4-40%	6 (43)	21-67%
Oral transport with thick liquids	1 (7)	1-31%	2 (14)	4-40%
Oral transport with thin liquids	0 (0)	0-22%	0 (0)	0-22%
Swallowing problems with solids	7 (50)	27-73%	9 (64)	39-84%
Swallowing problems with thick liquids	1 (7)	1-31%	3 (21)	8-48%
Swallowing problems with thin liquids	0 (0)	0-22%	2 (14)	4-40%

Abbreviations: CI = confidence interval, DIGEST = Dynamic Imaging Grade of Swallowing Toxicity, FOIS = functional oral intake scale, MIO = maximal inter-incisal opening, VAS = visual analog scale, VFS = videofluoroscopy.

Trismus related outcomes

Trismus related outcomes are presented in Table 3. Median mouth opening deteriorated from 51 (range 36–70) to 45 (range 36–86), but no patients had a mouth opening at or below the cut-off value of 35 mm indicating trismus (30). Also, none of the patients at ten-year plus follow-up perceived their mouth opening as deteriorated, including the four patients who had perceived their mouth opening as deteriorated at six-year follow-up.

Table 3 Trismus related outcomes at six- and ten-year plus follow-up of patients evaluable at ten-year plus follow-up ($n = 14$).

	Number of patients (%)			
	Six-year follow-up	**95% CI**	**Ten-year plus follow-up**	**95% CI**
Objective outcomes				
Mouth opening in mm Median (range)	51 (36–70)	39-65	45 (36–68)	38-60
Trismus (MIO < 36 mm)	0 (0)	0-22%	0 (0)	0-22%
Subjective outcomes				
Perceived deteriorated mouth opening	4 (29)	12-55%	0 (0)	0-22%

Abbreviations: CI = confidence interval, FOIS = functional oral intake scale, MIO = maximal inter-incisal opening, VAS = visual analog scale.

Voice and speech related outcomes

Voice and speech related outcomes are presented in Table 4. The objective voice quality (based on the AVQI) worsened from 4.7 (range 3.7–6.1) to 3.9 (1.6–8.0). The objective intelligibility (based on the ALF-PPFs) deteriorated slightly between six- and ten-year plus follow-up from 85 (range 67–92) to 75 (69–87). Less patients perceived their voice as different at ten-year plus follow-up (50%) compared to six-year follow-up (57%).

Table 4 Voice and speech related outcomes at six- and ten-year plus follow-up of patients evaluable at ten-year plus follow-up ($n = 14$).

	Number of patients (%)			
	Six-year follow-up	**95% CI**	**Ten-year plus follow-up**	**95% CI**
Objective outcomes				
AVQI (1-8) Median (range)	4.7 (3.7–6.1)*	NA*	3.9 (1.6–8.0)	2.4-5.3
ALF-PPFs (0-100) Median (range)	85 (67–92)*	NA*	75 (69–87)	69-86
Subjective outcomes				
Perceived different voice	8 (57)	33-79%	7 (50)	27-73%

VHI and SHI scores of respectively 13 and 12 subjects were available at six-year follow-up.
* Values from earlier publication of Kraaijenga et al. Analyses on speech recordings could not be repeated.
Abbreviations: ALF-PPFs = Alignment-free phonological and phonemic features with higher values indicating better intelligibility, AVQI = Acoustic Voice Quality Index with lower values indicating better voice quality, CI = confidence interval, CRT = chemoradiotherapy.

Quality of life related outcomes

See Table 5 for all quality of life related outcomes. Scores increased moderately on all of the Dutch SWAL-QOL subscales, except for 'food selection' and 'fear of eating', indicating a deteriorated swallowing-related quality of life. Also, the median total SWAL-QOL score deteriorated from 12 (range 0–58) to 22 (range 0–41), which is above the cut-off value of 14, indicating swallowing problems in daily life. At six-year follow-up, 5 of the 13 patients (39%) who filled in the SWAL-QOL had a score above the cut-off value. At-ten-year plus follow-up, this was the case for 8 of the 14 patients (57%).

Overall, the results suggest that at ten-year plus follow-up, patients have only minor problems in voice/speech-related quality of life. Median VHI scores slightly worsened from 2 to 5, indicating a little more voice related problems in daily life, while maximum scores improved from 91 to 47, indicating voice related quality of life of patients with the worst VHI scores improved. Also, at both six-year and ten-year plus follow-up four patients had a VHI score above the cut-off value (of whom three were the same patients). The patients with a VHI score above the cut-off had tumors of mixed localizations (hypopharynx ($n = 2$), oropharynx ($n = 1$), and nasopharynx ($n = 1$)). Subjective speech (based on the median SHI) remained stable, while maximum SHI scores also improved from 92 to 47. Of the six patients that currently had an SHI above the cut-off value indicating speech problems in daily life, only four had an SHI above cut-off value at last follow-up. Of the six patients with SHI scores above the cut-off value, three had an hypopharyngeal tumor, two an oropharyngeal tumor, and one had a nasopharyngeal tumor.
EQ-5D-5L scores slightly increased from six- to ten-year plus follow-up, indicating a lower quality of life, although the median EQ-VAS scores were more or less equal (85 (range 60–100) and 88 (range 50–100), respectively). At six-year follow-up 2 (14%), 0 (0%), 2 (14%), 5 (36%) and 4 (29%) patients reported problems with mobility, self-care, usual activities, pain/discomfort and anxiety/depression respectively. At ten-year plus follow-up this was the case in 4 (29%), 1 (7%), 6 (43%), 4 (29%) and 4 (29%) patients, respectively.

Table 5 Quality of life related outcomes at six- and ten-year plus follow-up of patients evaluable at ten-year plus follow-up ($n = 14$).

	Number of patients (%)			
	Six-year follow-up	**95% CI**	**Ten-year plus follow-up**	**95% CI**
SWAL-QOL (0–100) Median (range)				
General burden	0 (0–88)	0-25	25 (0–63)	0-50
Food selection	0 (0–75)	0-25	7 (0–38)	0-25
Eating duration	38 (0–75)	0-50	38 (0–63)	13-50
Eating desire	8 (0–75)	0-33	21 (0–58)	0-33
Fear of eating	8 (0–75)	0-33	25 (0–69)	6-44
Sleep	25 (0–75)	0-50	38 (0–75)	25-63
Fatigue	17 (0–67)	0-42	38 (0–58)	8-50
Communication	0 (0–100)	0-50	25 (0–50)	0-50
Mental health	0 (0–70)	0-25	10 (0–50)	0-35
Social function	0 (0–50)	0-25	10 (0–40)	0-25
Symptom score	21 (0–59)	5-45	21 (0–41)	4-36
Total score	12 (0–58)	0-28	22 (0–41)	2-34
Swallowing problems in daily life based on SWAL-QOL ≥ 14	5 (38)	18-64%	8 (57)	33-79%
VHI Median (range)				
Voice domain (0–56)	2 (0–42)	0-22	5 (0–32)	0-25
Psychosocial domain (0–56)	0 (0–47)	0-5	0 (0–13)	0-10
Total score (0–120)	2 (0–91)	0-31	5 (0–47)	0-30
Voice problems in daily life based on VHI ≥ 15 N (%)	4 (31)	13-58%	4 (29)	12-55%
SHI Median (range)				
Speech domain (0–56)	3 (0–45)	0-27	3 (0–34)	0-20
Psychosocial domain (0–56)	0 (0–44)	0-11	0 (0–11)	0-10
Total score (0–120)	3 (0–92)	0-44	3 (0–47)	0-29
Speech problems in daily life based on SHI ≥ 6 N (%)	4 (33)	14-61%	6 (43)	21-67%
EQ-5D-5L dimension; problems with:				
Mobility	2 (14)	4-40%	4 (29)	12-55%
Self-care	0 (0)	0-22%	1 (7)	1-31%
Usual activity	2 (14)	4-40%	6 (43)	21-67%
Pain/discomfort	5 (36)	16-61%	4 (29)	12-55%
Anxiety/depression	4 (29)	12-55%	4 (29)	12-55%
EQ-VAS (0–100) Median (range)	85 (60–100)		88 (50–100)	

SWAL-QOL scores of respectively 13 and 14 subjects were available at six- and ten-year follow-up.

Abbreviations: CI = confidence interval, EQ-5D-5L = EuroQol-5D-5L, EQ-VAS = EuroQoL Visual Analog Scale, SHI = speech handicap index, VHI = voice handicap index.

DISCUSSION

Given the increasing survival rates of patients treated for HNC, due to changing etiology and continuously improving treatment strategies, knowledge of long-term functional outcomes had gained importance (19). This is the first study to report on functional outcomes and quality of life of patients more than ten years after IMRT with concurrent chemotherapy for HNC combined with preventive rehabilitation exercises, which is quickly becoming current practice at a rising number of institutes. In our cohort, objective swallowing problems were minimal, with slight deterioration compared to the results at six-year follow-up assessment. None of the evaluable patients at ten-year plus follow-up were feeding tube dependent, consumed a modified diet (FOIS < 7) or had suffered from pneumonia since the six-year follow-up. However, subjective swallowing related quality of life moderately worsened according to SWAL-QOL scores. None of the patients had or perceived trismus. Subjective and objective voice and speech related outcomes stayed more or less stable from six- to ten-year follow-up. Overall quality of life remained at a high level, according the EQ-VAS assessment, although a third of the patients experienced at least some pain or discomfort. The results suggest that with current practice, including IMRT and preventive rehabilitation exercises, the functional outcomes and quality of life of patients surviving more than ten are reasonably well-maintained.

The worsening observed in, predominantly subjective, functional outcomes might be caused by multiple factors. Firstly, ageing likely plays a role in the deterioration of swallowing (efficiency), and speech, function over time (44). Multiple studies have shown that older individuals have less effective swallowing function compared to younger adults (45). Secondly, late treatment effects such as neuropathy and continuing fibrosis of swallowing muscles are a known cause of late functional problems after radiotherapy for HNC (21, 22). The mechanism of this continuing fibrosis is probably based on a continuous (over)production of factors activating wound healing, which continues until long after the initial radiotherapy (22). Also, since the resolution of the videofluoroscopy studies was better at ten-year follow up, minimal aspiration might have been missed at six-year follow-up. There were some discrepancies between subjective and objective outcomes. For example, the median MIO decreased with 6 mm between six- and ten-year plus follow-up which did not result in any of the patients with either clinical trismus or perceived trismus. The four patients with perceived trismus at the six-year mark, did not perceive their mouth opening as decreased while either mouth opening was stable ($n = 2$) or decreased ($n = 2$). This might be due to a very gradual decrease in median MIO which enables habituating to and coping with the new situation. This was not true, however, for swallowing; the moderately deteriorated swallowing related quality of life as measured by the SWAL-QOL was not accompanied by worsened objective measures, which stayed stable or even improved. This might be because subjective measures are more sensitive to small deteriorations in swallowing function than objective measures.

Some earlier studies have investigated long-term functional outcomes after CRT. Kraaijenga et al. published ten-year results of a historical cohort treated with CRT for HNC at our institute

between December 1999 and November 2004 (29, 46, 47). During this time period IMRT was applied less often (50% vs. 100%) and no preventive rehabilitation interventions were offered. When our results are compared to that cohort, aspiration was observed less often (30% in our study vs. 68% in the study of Kraaijenga et al.), as well as contrast residue (70% vs. 100%). Also, less patients were feeding tube dependent (0% vs. 14%), had pneumonia the past six months (0% vs. 14%) and had an FOIS below 7 indicating a modified diet (0% vs. 55%). To properly appreciate the difference in functional outcomes, one should keep in mind that the patients of the historical cohort were somewhat older (median 63 (range 42–74) vs. 58 (range 39–66) in our study), and had more stage IV tumors (68% vs. 57%). Yet, the differences likely also reflect the improvement resulting from more advanced radiotherapy in combination with preventive rehabilitation.

Besides this historical cohort treated at our institute, other studies have also reported on long-term swallowing related outcomes after CRT for HNC without preventive rehabilitation (48-50). All of these studies report that severe late toxicity is common after CRT for HNC. Machtay et al. found that 99 of the 230 patients (34%) at a median follow-up of 3 years after CRT (no IMRT) for HNC experienced late toxicity (48). Rutten et al. concluded that 57% of the 77 analyzed CRT for HNC patients (of whom 17% received IMRT) had impaired swallowing and 23% had silent aspiration at a median follow-up of 3.7 years after CRT for HNC (49). Only 15.6% reported to have a normal diet. Frowen et al. analyzed 39 patients after CRT (no IMRT) for HNC and found that at 5 years after treatment, 2 patients (5%) were PEG tube dependent (50). Hutcheson et al. published results from the longest follow-up on swallowing function after CRT (7% IMRT) for HNC (21). They also reported a high prevalence of impaired swallowing at nine years post (C)RT, with 66% being gastrostomy dependent (21), although, this result might not be representative for all HNC patients receiving CRT, because the patients included in their analysis were complaining about dysphagia and specifically referred for a modified barium swallow.

Long-term speech related outcomes after CRT for HNC are scarce in literature (51). Results suggest that speech problems are common after CRT, but extensive long-term (10-year) evaluations are lacking (52, 53). Kraaijenga et al. published voice and speech related outcomes of the previously mentioned historical cohort ten-years after CRT (54). Voice and speech problems were common in that cohort, with 68% and 77% of the 22 evaluated patients reporting voice and speech problems in daily life, based on VHI and SHI scores above the cut-off values. In the present cohort, there were less patients with scores above the cut-off value (29% and 43% for VHI and SHI). Again, comparisons between these two different cohorts of the NKI-AVL should be interpreted with caution since differences might be caused by preventive rehabilitation strategies, but might also be due to differences in patient and tumor characteristics. The median intelligibility deteriorated from 85% to 75% in this cohort. This might be, just as the deterioration of swallowing function, caused by continuing fibrosis or the effects of ageing which both affect structures of the upper aerodigestive tract.

While the benefit of IMRT over conventional RT is not disputed, it has been challenging to substantiate the benefit of preventive rehabilitation in clinical research. Recently, a Cochrane review by Perry et al. on preventive exercises was published (13). They concluded that the evidence supporting the effectiveness of preventive exercises on functional outcomes post treatment was not yet convincing. The lack of convincing evidence is not necessarily due to the lack of observed effectiveness, but is caused by the limited sample sizes of the included studies, resulting in limited power and therefore imprecise estimates of effect, and the impossibility of meta-analysis due to the dissimilarities in outcome measures used. An important issue with this review is that it did not consider the relevance of patient compliance to the exercises. Individual studies do suggest positive effects of preventive exercises with superior swallowing function when compared to (historical) controls (6-9, 11, 14). Moreover, patients who maintain their oral intake during CRT have favorable outcomes compared to patients who become tube dependent (55, 56). These findings support the preposition that both the exercises and the maintenance of oral intake prevent decreased use, and thereby they may prevent non-use atrophy of swallowing muscles, which is the rationale behind preventive strategies.

Limitations

The main limitation of this study is the small sample size, with only 14 of the 22 patients at the six-year follow-up still alive and evaluable at ten-year plus. It is, however, not an uncommon sample size given the survival rate in advanced HNC. Also, DIGEST grades were assessed on the videofluoroscopy studies including only four bolus trials instead of ten bolus trials on which the grading system was validated.

CONCLUSION

Functional status and quality of life of patients treated for advanced HNC with state-of-the-art CRT and preventive rehabilitation exercises who have survived ten or more years is reasonably well-maintained. Swallowing, trismus and speech related outcomes only moderately deteriorated from six- to ten-years, with a perceived excellent overall quality of life.

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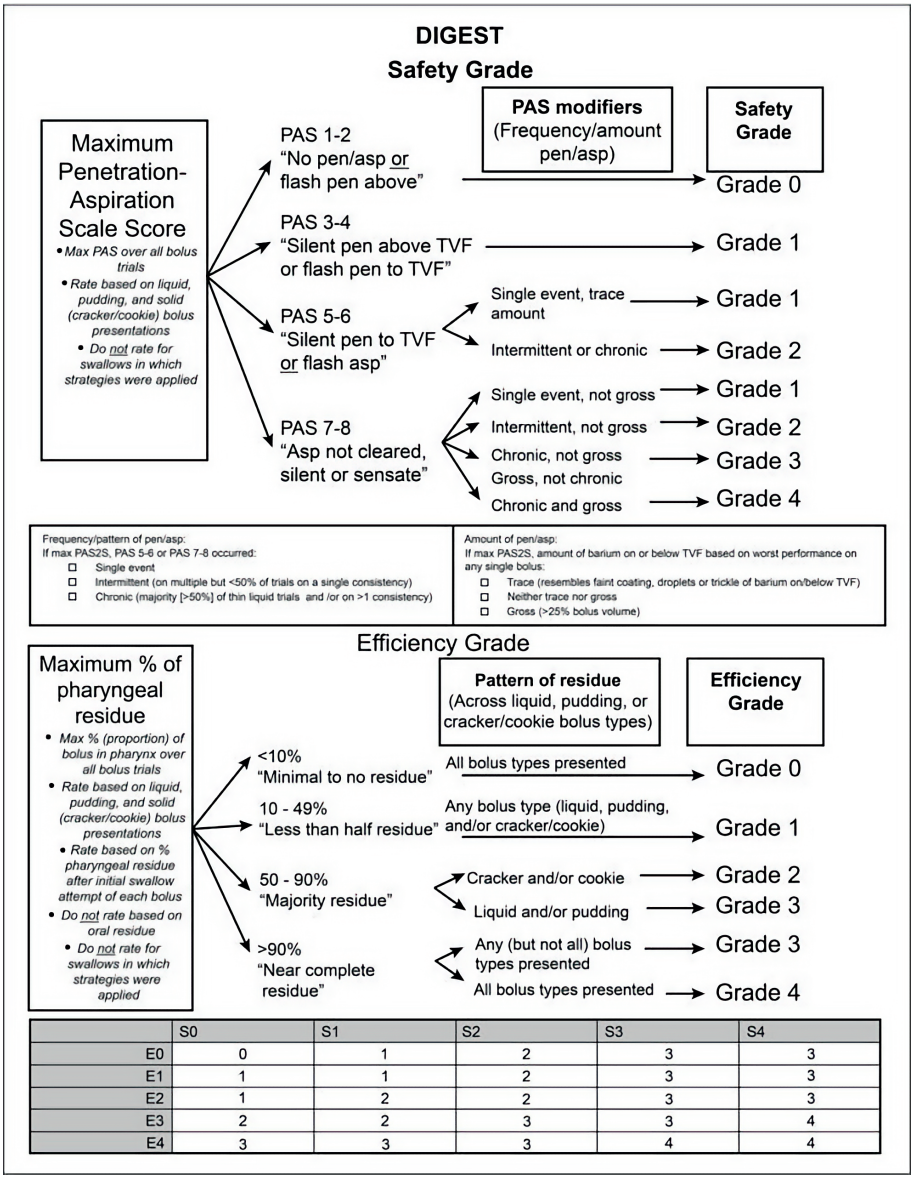
APPENDICES

Appendix 1 Dynamic Imaging Grade of Swallowing Toxicity (DIGEST) scoring system.



	S0	S1	S2	S3	S4
E0	0	1	2	3	3
E1	1	1	2	3	3
E2	1	2	2	3	3
E3	2	2	3	3	4
E4	3	3	3	4	4

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Chapter 5

Dysphagia, trismus and speech impairment following (chemo) radiation for oropharyngeal carcinoma: a one-year course

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ABSTRACT

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

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

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

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

INTRODUCTION

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

Despite advancement in treatment, e.g., Intensity Modulated RT (IMRT) and Volumetric Modulated Arc Therapy (VMAT), and rehabilitation, e.g., the addition of prophylactic swallowing exercises to ameliorate functional sequelae related to the tumor and its treatment, negative side effects still do occur. Multiple studies have shown that RT(+) for OPC, although organ preserving, is accompanied with serious functional impairment and a decreased quality of life in the short- and long-term (3-6). Apart from xerostomia, swallowing impairment (dysphagia), is the most important side effect, which can worsen over time or even develop years after treatment (4, 7-10). Impaired mouth opening (trismus), also commonly occurs after radiation-based treatment for OPC. Incidence rates of trismus vary across studies including patients with all head and neck cancer sites treated with surgery and/or RT(+), but oropharyngeal localization of the tumor consistently seems a significant risk factor (11-16). Besides, RT(+) of the oropharynx also may affect articulation and speech (17). Finally, a potential increased risk of carotid stenosis and cerebrovascular accidents has also been documented after RT(+) (18). These negative side effects and the prolonged survival achieved with the improved treatment technologies over the last decades demand an increased awareness of functionality and quality of life after OPC treatment.

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

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

METHODS

Ethical considerations

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

Patient selection

All patients diagnosed with head and neck cancer in the NKI-AVL, a tertiary cancer center, are followed up in ongoing prospective assessments by speech-language pathologists, who intensively monitor functional limitations before, during and after treatment and start (additional) targeted rehabilitation.

For this analysis, Dutch speaking patients were included who were curatively treated with primary RT or RT+ (RT with cisplatin or cetuximab) for a stage III-IV squamous cell carcinoma of the oropharynx between January 2013 and September 2018. Patients were excluded in case of distant metastases, a synchronous primary tumor elsewhere, prior treatment of the head and neck area (except neck dissection or skin lesions), missing pre-treatment assessment data or if only pretreatment assessment data were available. Patients were excluded from follow-up of this study when additional oncological treatment was given due to residual or recurrent disease.

Radiotherapy based treatment

According to protocol, the treatment consisted of radiotherapy given with 6 MV photons up to 70 Gy in 35 fractions in six weeks in case of RT alone and seven weeks in case of RT+ using sequential of simultaneous integrated boost (SIB) according to the IMRT technique (either step and shoot or VMAT). Patients receiving sequential integrated boost were given an elective dosage of 46 Gy (23 fractions of 2 Gy) with a total dosage of 70 Gy (35 fractions of 2 Gy). Patients receiving simultaneous integrated boost were given an elective dosage of 54.25 Gy (35 fractions of 1.55 Gy) with a total dosage of 70 Gy (35 fractions of 2 Gy).

Concurrent systemic treatment (which was indicated in case of stage N2b or higher or extranodal spread) consisted of cisplatin or cetuximab. Cisplatin was administered intravenously either in high-dose (100mg/m^2 at day 1, 22 and 43 of radiotherapy), intermediate-dose (40mg/m^2 every week), or low-dose (6mg/m^2 daily during the first 5 weeks of radiotherapy). Cetuximab was given when patients were unfit for cisplatin. One week before the start of RT, a loading dose of 400 mg/m^2 was administered, followed by 250 mg/m^2 weekly during 7 weeks.

Preventive rehabilitation protocol

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

Data collection

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

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

Swallowing outcomes

The primary observer-rated swallowing outcome was the functional oral intake scale (FOIS) which is a validated seven-point ordinal scale with lower scores indicating more intake problems (26). As primary patient-rated swallowing outcome, the SWAL-QOL was used. This is a validated 44-item questionnaire on dysphagia and its influence on daily life. It includes ten domains: burden*, food selection*, eating duration*, eating desire*, fear*, sleep, fatigue, communication, mental health*, social functioning*, and symptom frequency. The total SWAL-QOL score is calculated from the subscales marked with an asterisk. All scores range from 0 to 100 with higher scores indicating more dysphagia-related problems (27, 28).

Secondary swallowing outcomes included feeding tube dependence and pneumonia during the past six months.

Mouth opening outcomes

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

Voice and speech outcomes

In order to assess observer-rated voice and speech outcomes, audio recordings were made of patients performing a set of speech tasks which included respectively reading aloud a 149 word long Dutch reading text called 'Tachtig dappere fietsers' (Eighty brave cyclists), a word list, and sustained vowels (/a/, /i/, and /u/). All recordings were analyzes using the PRAAT program (30). The primary observer-rated speech outcome was the vowel space area, a measure of articulation, for which the read text was used, or the word list if the text was not available. It was calculated as a percentage of the maximum total area of the vowel triangle (31). In this study, values below 80% were used to indicate abnormal articulation.

The primary patient-rated speech outcome was the Speech Handicap Index (SHI). This is a thirty-item speech-related quality of life questionnaire on which a patient indicates the frequency of problems experienced on a five-point scale: never (= 0), almost never (= 1), sometimes (= 2), almost always (= 3), and always (= 4). The score can range from 0–120 with higher scores indicating more speech-related problems. A psychosocial and a speech function subscale can be calculated from these thirty questions. The SHI also includes one global question indication the overall speech quality (excellent (= 0), good (= 30), average (= 70), and bad (= 100)) (32, 33).

Secondary speech outcomes were the articulation rate in syllables per second, which was measured from the reading text using a script in PRAAT (34). The voice outcome measure was the acoustic voice quality index (AVQI), which was determined using a combination of 3 seconds of the sustained /a/ and 4 seconds of the read text (35, 36). If no 3 seconds of /a/ was available, a combination of the sustained vowel records was used. If the read text was not present, 4 seconds of the word list was used. This outcome ranges from 1 to 10, with 1 being most equal to normal and 10 least equal to normal. A value of the AVQI less than 2.95 was considered a good voice quality (37).

Statistical analysis

Analyses were performed using IBM® SPSS® Statistics 25.0. Baseline characteristics were presented using descriptive statistics. To test whether patient and tumor characteristics of the patients at *t*0, *t*1 and *t*2 were different, the Kruskal-Wallis test was used for continuous data and the linear-by-linear approximation of the Pearson's Chi-square test (exact two-sided *p* value) for dichotomous and ordinal data. To test differences in baseline characteristics of included patients and patients who were excluded because they either had only data at *t*0 available or did not have data at *t*0 available, the Mann Whitney U test for continuous data was used, the linear-by-linear approximation of the Pearson's Chi-square test (exact two-sided significance) for ordinal data and the Fisher's exact test for dichotomous data. Proportions and percentages were used to describe dichotomous outcomes and the median and range were used to describe all continuous outcomes. Differences between three timepoints were statistically analyzed by means of paired tests (i.e., Friedman test for continuous or ordinal data and a Cochran's Q for dichotomous data) as well as the differences between two timepoints (i.e., Wilcoxon signed rank test for continuous or ordinal data and the McNemar test for dichotomous data).

Univariable logistic regression analysis was used to explore factors related to dysphagia (FOIS < 7), trismus (mouth opening < 36 mm) and abnormal articulation (vowel space area > 80%) at *t*2. Differences in outcomes between HPV positive and negative patients and patients with and without pretreatment sarcopenia were assessed. Differences in baseline characteristics were assessed by means of the Mann-Whitney U test for continuous data, the linear-by-linear approximation of the Pearson's Chi-square test (exact two-sided *p* value) for ordinal data and the Fisher's exact test for dichotomous data. *P* values were adjusted for tumor and treatment characteristics (T and N classification, treatment and modified diet at t0 for differences in HPV classification and AJCC stage and modified diet at *t*0 for sarcopenia) by means of multivariable logistic or linear regression analyses. Results were considered statistically significant when the *p* value was less than .05. For all post-hoc pairwise comparisons, a *p* value less than .01 was considered statistically significant.

RESULTS

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

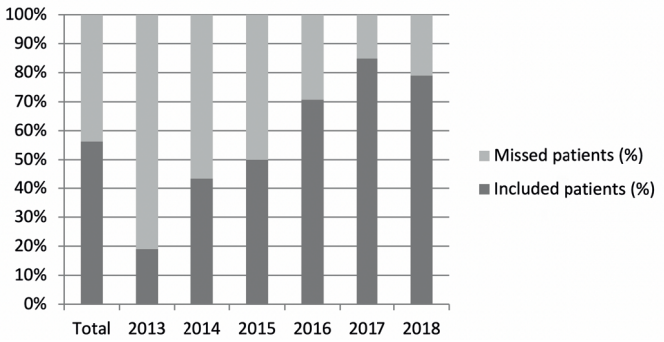

Figure 1 Percentages of 'missed' patients per accrual year. 'Missed' patients are defined as patients who were eligible and willing to participate but data at $t0$ was not collected.

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

This left 108 patients for inclusion in the current analysis. Ninety-nine patients (92%) were present at $t1$ and 71 patients (66%) at $t2$ with 62 patients (57%) present at all three assessments. In Figure 2 the reasons for loss to follow-up are presented. Median follow-up time at $t1$ was 6 months (range 2 months to 9 months) and 12 months (range 8 to 18 months) at $t2$.

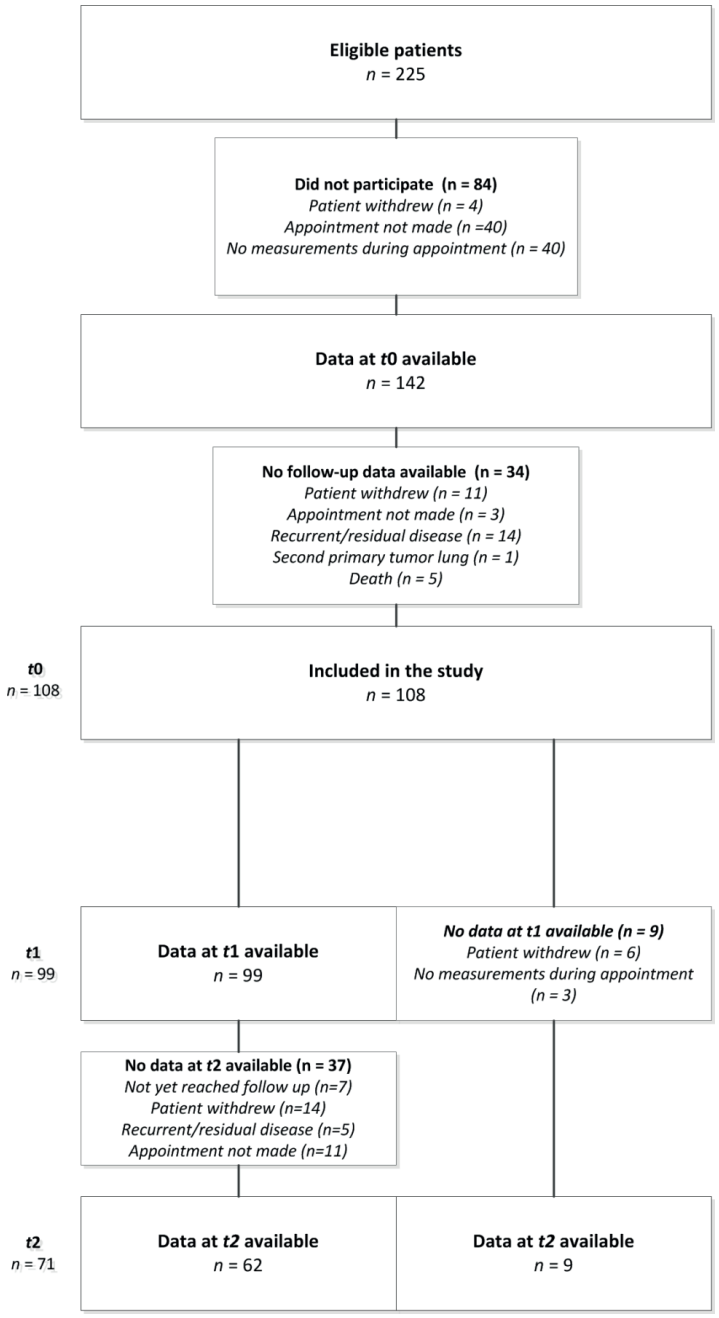

Figure 2 Follow-up flowchart

Baseline characteristics

Baseline characteristics are presented in Table 1. Of the 108 included patients, 73 (67%) were male, 53 patients (49%) had an ACE-27 score > 0 indicating comorbidity, 49 patients (45%) had sarcopenia, 35 patients (32%) had a tumor located in the base of tongue, 80 (74%) had stage IV disease and 70 (68%) were HPV positive. There were no significant differences regarding these characteristics between the patients present at the different assessments. Patients who were excluded because only t0 data was available ($n = 34$), had higher tumor stages, and had more often a modified diet pretreatment (FOIS < 7) and trismus. Patients who were eligible but not included in the study ($n = 84$) were comparable to the included patients with regard to patient, tumor and treatment characteristics. However, baseline BMI, SMM, presence of sarcopenia, FOIS and mouth opening were not available for these patients.

Of the 108 included patients, 42 were treated with RT only (39 by tumor indication and 3 because they were unfit for systemic therapy), and 66 with RT+ (49 with cisplatin and 17 with cetuximab). Patients treated with RT+ more often had pretreatment sarcopenia, obviously had higher tumor stages, and more often had HPV negative tumors. All baseline characteristics categorized by treatment modality are presented in Appendix 2.

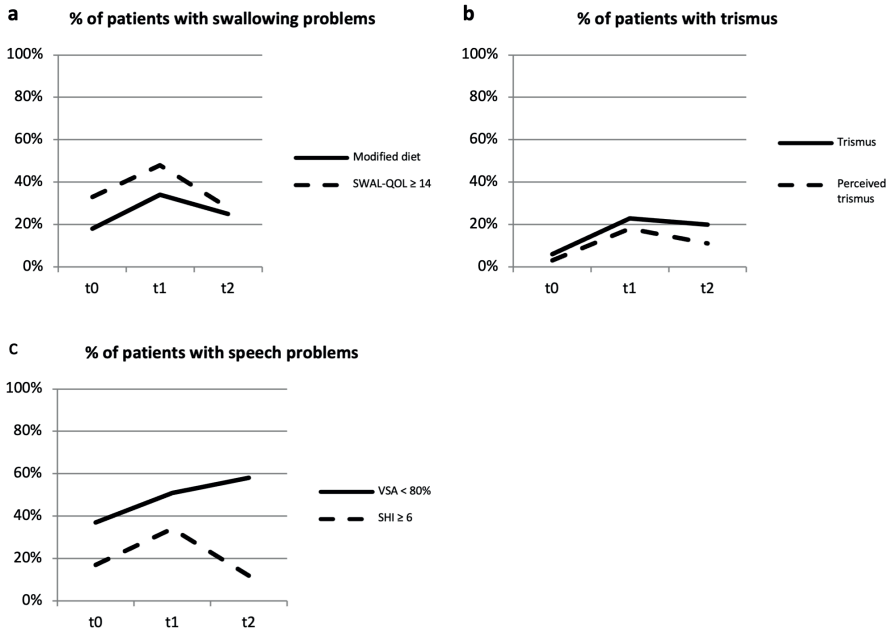

Figure 3 Percentage of patients with subjective and objective functional limitations at *t*0, *t*1 and *t*2.
Abbreviations: SHI = speech handicap index, VSA = vowel space area.

Table 1 Baseline characteristics of patients at *t*0, *t*1 and *t*2. *P* values shown for Kruskal-Wallis Test[a], linear-by-linear approximation of the Pearson's Chi-square Test[b], Mann Whitney U test[c] or Fisher's exact test[d].

		***t*0** *n* = 108	***t*1** *n* = 99	***t*2** *n* = 71	***P* value *t*0, *t*1, *t*2**	**Only *t*0 available** *n* = 34	***P* value *t*0, only *t*0**	**Not included no *t*0 available** *n* = 84	***P* value *t*0, no *t*0**
Gender	Male	73 (68)	68 (69)	52 (73)	.461[b]	24 (71)	.834[d]	54 (64)	.648[d]
	Female	35 (32)	31 (31)	19 (27)		10 (29)		30 (36)	
Age at baseline Median (range)		63 (39–81)	63 (39–81)	60 (39–77)	.499[a]	65 (49–78)	.316[c]	62 (47-83)	.530[c]
ACE-27	0	53 (49)	46 (47)	39 (55)	.357[b]	14 (41)	.248[b]	37 (44)	.442[b]
	1	37 (34)	35 (35)	26 (37)		10 (29)		30 (36)	
	2	14 (13)	14 (14)	3 (4)		9 (27)		13 (16)	
	3	4 (4)	4 (4)	3 (4)		1 (3)		4 (5)	
BMI Median (range)		25 (17-44)	25 (17-44)	26 (17-44)	.791[a]	24 (49-78)	.127[d]		
SMM Median (range)		44 (22-64)	44 (22-64)	45 (22-64)	.506[a]				
Sarcopenia	No	59 (55)	53 (54)	44 (62)	.402[b]				
	Yes	49 (45)	46 (47)	27 (38)					
Oropharyngeal tumor site	Base of tongue	35 (32)	33 (33)	25 (35)	.819[b]	13 (38)	.888[b]	31 (37)	.685[b]
	Tonsil	57 (53)	54 (55)	35 (49)		13 (38)		33 (39)	
	Other	16 (15)	12 (12)	11 (16)		8 (24)		20 (24)	
T classification	T1	27 (25)	23 (23)	19 (27)	.832[b]	4 (12)	.006[b]	22 (26)	.791[b]
	T2	30 (28)	30 (30)	19 (27)		8 (24)		28 (33)	
	T3	29 (27)	25 (25)	20 (28)		5 (15)		14 (17)	
	T4	22 (20)	21 (21)	13 (18)		17 (50)		20 (24)	
N classification	N0	12 (11)	11 (11)	8 (11)	.794[b]	3 (9)	.589[b]	6 (7)	.205[b]
	N1	24 (22)	22 (22)	13 (18)		7 (21)		14 (17)	
	N2	69 (64)	63 (64)	48 (68)		22 (65)		62 (74)	
	N3	3 (3)	3 (3)	2 (3)		2 (6)		2 (2)	
AJCC stage	III	28 (26)	25 (25)	18 (25)	.931[b]	4 (12)	.102[d]	17 (20)	.394[d]
	IV	80 (74)	74 (75)	53 (75)		30 (88)		67 (80)	
HPV status	Negative	33 (32)	31 (31)	18 (26)	.454[b]	14 (47)	.192[d]	29 (40)	.267[d]
	Positive	70 (68)	64 (67)	51 (74)		16 (53)		43 (60)	
	Unknown	5	4	2		4		12	
Treatment modality	RT	39 (36)	36 (36)	26 (37)	.973[b]	9 (27)	.384[b]	33 (39)	.481[b]
	RT unfit for RT+	3 (3)	3 (3)	2 (3)		2 (6)		6 (7)	
	RT + cetuximab	17 (16)	17 (17)	11 (16)		7 (21)		12 (14)	
	RT + cisplatin	49 (45)	43 (43)	32 (45)		16 (47)		33 (39)	
Modified diet at *t*0 (FOIS < 7)	No	89 (82)	81 (82)	66 (93)	.090[b]	23 (72)	.212[d]	NA	
	Yes	19 (18)	18 (18)	5 (7)		9 (28)			
	Unknown	0	0	0		2			

Table 1 Continued

		***t*0** *n* = 108	***t*1** *n* = 99	***t*2** *n* = 71	***P* value *t*0, *t*1, *t*2**	**Only *t*0 available** *n* = 34	***P* value *t*0, only *t*0**	**Not included no *t*0 available** *n* = 84	***P* value *t*0, no *t*0**
Trismus at *t*0	No	98 (94)	91 (96)	64 (94)	1.000[b]	21 (66)	<.001[d]	NA	
	Yes	6 (6)	4 (4)	4 (6)		11 (34)			
	Unknown	4	4	3		2			

NB: Not all percentages sum up exactly to 100% due to rounding.

Abbreviations: BMI = body mass index, HPV = human papilloma virus, FOIS = functional oral intake scale, other = soft palate, uvula, oropharyngeal wall, vallecula or pharyngeal arch, RT = radiotherapy, SMM = skeletal muscle mass, *t*0 = pretreatment, *t*1 = six months after treatment, *t*2 = twelve months after treatment, sarcopenia = SMM below 43.2 cm^2/m^2.

Swallowing outcomes

Swallowing outcomes are presented in Figure 3a and Table 2. Swallowing problems increased significantly from *t*0 to *t*1, and decreased afterwards although not returning to baseline. This was also true for the percentage of patients who needed a modified diet (FOIS < 7), the median total SWAL-QOL score, as well as for most subscales of the SWAL-QOL. Respectively 2 (2%), 6 (6%) and 0 patients (0%) were feeding tube dependent at *t*0, *t*1 and *t*2. At t0, 4 patients (4%) had suffered from a pneumonia in the six months prior to the assessment. At *t*1, this concerned 3 patients (3%), of whom one also had a pneumonia before *t*0. At *t*2, this concerned 3 patients (4%), none of whom had suffered from a pneumonia before *t*0 or *t*1.

Swallowing outcomes stratified by treatment modality are presented in Figure 4a and appendix 3. Patients treated with cisplatin-based RT+ more often had a modified diet (FOIS < 7) at t0, t1 and t2 compared to patients treated with RT only. In patients treated with RT+ (cisplatin and cetuximab), post-treatment SWAL-QOL scores were higher than in patients treated with RT only, indicating more swallowing related problems.

Trismus outcomes

Trismus outcomes are presented in Figure 3b and Table 3. The percentage of patients with trismus significantly worsened from *t*0 to *t*1 and improved from *t*1 to *t*2, however, not to baseline levels. Perceived trismus followed the same trend, however, not all patients with objective trismus (mouth opening < 36 mm) perceived their mouth opening as impaired (Figure 3b).

Trismus outcomes stratified by treatment modality are presented in Figure 4b and Appendix 4. Patients treated with RT+ had and perceived more post treatment trismus compared to patients treated with RT only.

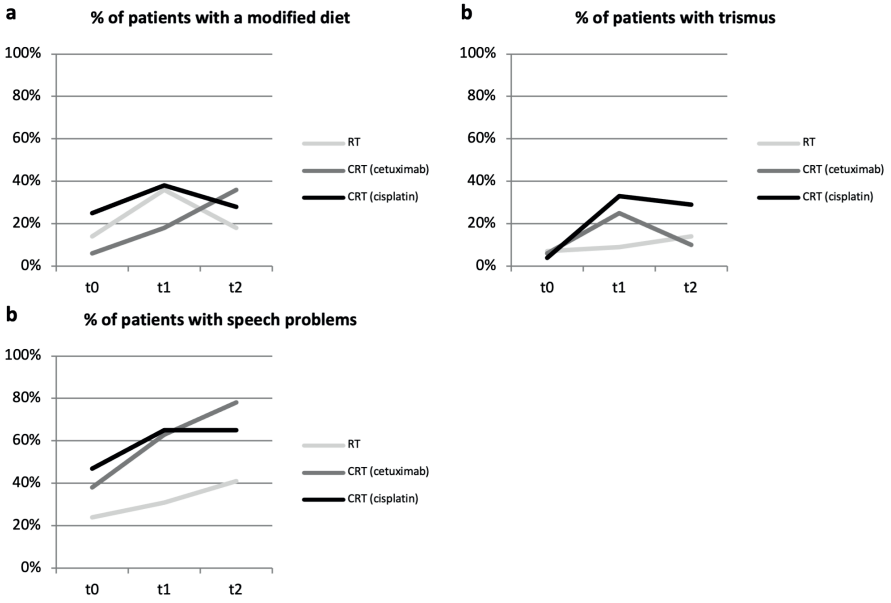

Figure 4 Percentage of patients with a modified diet (FOIS < 7) (a), trismus (b) or speech problems (vowel space area < 80%) (c) at *t*0, *t*1 and *t*2 stratified by treatment modality.

Table 2 Swallowing outcomes at *t*0, *t*1 and *t*2. *P* values shown for Friedman test[a], Cochran's Q test[b], Wilcoxon signed rank test[c] or McNemar test[d], ↑ indicating more problems and ↓ indicating less problems.

		Total			***P* value** *t*0, *t*1, *t*2	***P* value** *t*0 to *t*1	***P* value** *t*1 to *t*2	***P* value** *t*0 to *t*2
		***t*0** *n* = 108	***t*1** *n* = 99	***t*2** *n* = 71				
Observer-rated outcome								
FOIS	7	89 (82)	65 (66)	53 (75)	.012[a]	.195[c]	.499[c]	.043[c] ↑
	6	8 (7)	24 (25)	14 (20)				
	5	7 (7)	4 (4)	3 (4)				
	4	2 (2)	1 (1)	1 (1)				
	3	2 (2)	4 (4)	0 (0)				
	2	0 (0)	0 (0)	0 (0)				
	1	0 (0)	0 (0)	0 (0)				
	Unknown	0	1	0				
Modified diet (FOIS < 7)	No	89 (82)	65 (66)	53 (75)	.005[b]	.012[d] ↑	.832[d]	.004[d] ↑
	Yes	19 (18)	33 (34)	18 (25)				
	Unknown	0	1	0				

Table 2 Continued

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

NB: Not all percentages sum up exactly to 100% due to rounding.

Abbreviations: FOIS = functional oral intake scale, NGT = nasogastric tube, PRG = percutaneous radiological gastrostomy, *t*0 = pretreatment, *t*1 = six months after treatment, *t*2 = twelve months after treatment.

Speech and voice outcomes

Speech and voice outcomes are presented in Figure 3c and Table 4. Vowel space area decreased significantly from *t*0 to *t*1, and not significantly from *t*1 to *t*2, indicating worsening articulation. Articulation rate and voice quality (AVQI) did not change significantly over time. Significantly more patients had speech related problems in daily life, as assessed with the SHI, at *t*1 compared to *t*0.

Speech and voice outcomes stratified by treatment modality are presented in Figure 4c and Appendix 5. Patients treated with RT+ more often had a vowel space below 80%, indicating abnormal articulation, at *t*0, *t*1 and *t*2. SHI scores were comparable for patients treated with RT and RT+.

Table 3 Trismus outcomes at *t*0, *t*1 and *t*2. *P* values shown for Friedman test[a], Cochran's Q test[b], Wilcoxon signed rank test[c] or McNemar test[d]. ↑ indicating more problems and ↓ indicating less problems.

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

NB: Not all percentages sum up exactly to 100% due to rounding.

Abbreviations: FOIS = functional oral intake scale, NGT = nasogastric tube, PRG = percutaneous radiological gastrostomy, *t*0 = pretreatment, *t*1 = six months after treatment, *t*2 = twelve months after treatment

Table 4 Speech and voice outcomes at *t*0, *t*1 and *t*2. *P* values shown for Friedman test[a], Cochran's Q test[b], Wilcoxon signed rank test[c] or McNemar test[d]. ↑ indicating more problems and ↓ indicating less problems.

		Total			*P* value	*P* value	*P* value	*P* value
		***t*0** *n* = 108	***t*1** *n* = 99	***t*2** *n* = 71	*t*0, *t*1, *t*2	*t*0 to *t*1	*t*1 to *t*2	*t*0 to *t*2
Observer-rated outcomes								
Vowel Space Area (%) Median (range)		85 (51-129)	79 (49-107)	77 (51-112)	.014[a]	.015[c] ↑	.137[c]	.002[c] ↑
Vowel Space Area < 80%	No	59 (63)	37 (49)	24 (42)	.050[b]	.210[d]	.344[d]	.019[d] ↑
	Yes	35 (37)	39 (51)	33 (58)				
	Unknown	14	23	14				
Patient-rated outcomes								
SHI Median (range)								
Speech domain (0–56)		0 (0-42)	2 (0-32)	0 (0-31)	.076[a]	.005[c] ↑	.045[c] ↓	.580[c]
Psychosocial domain (0–56)		0 (0-39)	0 (0-34)	0 (0-15)	.326[a]	.476[c]	.236[c]	.281[c]
Total score (0–120)		0 (0-83)	3 (0-61)	0 (0-40)	.190[a]	.001[c] ↑	.073[c]	.640[c]
SHI ≥ 6	No	65 (83)	39 (66)	36 (88)	.074[b]	.006[d] ↑	.453[d]	.500[d]
	Yes	13 (17)	20 (34)	5 (12)				
	Unknown	30	40	30				
Secondary outcomes								
Articulation rate (syllables/s) Median (range)		2.3 (0.2-7.7)	2.6 (0.6-6.1)	2.7 (0.1-6.1)	.739[a]	.302[c]	.626[c]	.698[c]
AVQI Median (range)		4.5 (3.3-5.3)	4.5 (3.4-5.5)	4.5 (3.6-5.5)	.901[a]	.905[c]	.723[c]	.473[c]

NB: Not all percentages sum up exactly to 100% due to rounding.

Abbreviations: AVQI = acoustic voice quality index, FOIS = functional oral intake scale, NGT = nasogastric tube, PRG = percutaneous radiological gastrostomy, SHI = speech handicap index, *t*0 = pretreatment, *t*1 = six months after treatment, *t*2 = twelve months after treatment

Factors associated with functional limitations

Appendix 6 shows the baseline characteristics stratified by patients who did or did not have a modified diet (FOIS < 7) at *t*2. A modified diet at *t*2 was univariably associated with pretreatment lower BMI, lower SMI, sarcopenia, and a T4 tumor.

Appendix 7 shows the baseline characteristics stratified by patients who had trismus (mouth opening < 36 mm) at *t*2. Trismus at *t*2 was univariably associated with tumor site other than base of tongue and tonsil (i.e., soft palate, uvula, pharyngeal wall, vallecula, and pharyngeal arches).

Appendix 8 shows the baseline characteristics stratified by patients who had a vowel space below 80%, indicating abnormal articulation, at *t*2. A vowel space below 80% at *t*2 was univariably associated with a pretreatment vowel space area below 80% only.

HPV status

Appendix 9 shows the baseline characteristics stratified by HPV status. Compared to patients with an HPV negative tumor, patients with an HPV associated tumor had a higher BMI, higher SMI, lower T classifications, higher N classification, were more often treated with RT only, and had less often a modified diet at baseline.

Functional outcomes at *t*0, *t*1 and *t*2 stratified by HPV status are presented in Figure 5 and appendix 10. As presented in Figure 5a, at *t*1 and *t*2, patients with an HPV negative tumor more often had a modified diet compared to patients with an HPV positive tumor. Also, SWAL-QOL scores were higher in the HPV negative group at both *t*1 and *t*2. The prevalence of trismus was comparable between in het HPV negative and positive group at *t*1 and at *t*2 HPV negative patients had less often trismus compared to HPV positive patients. Patients with an HPV negative tumor had slightly worse speech and voice outcomes, especially at *t*1. After adjusting for T and N classification, treatment and pretreatment modified diet, none of the differences were statistically significant, except at *t*2, patients with an HPV positive tumor had a smaller mouth opening.

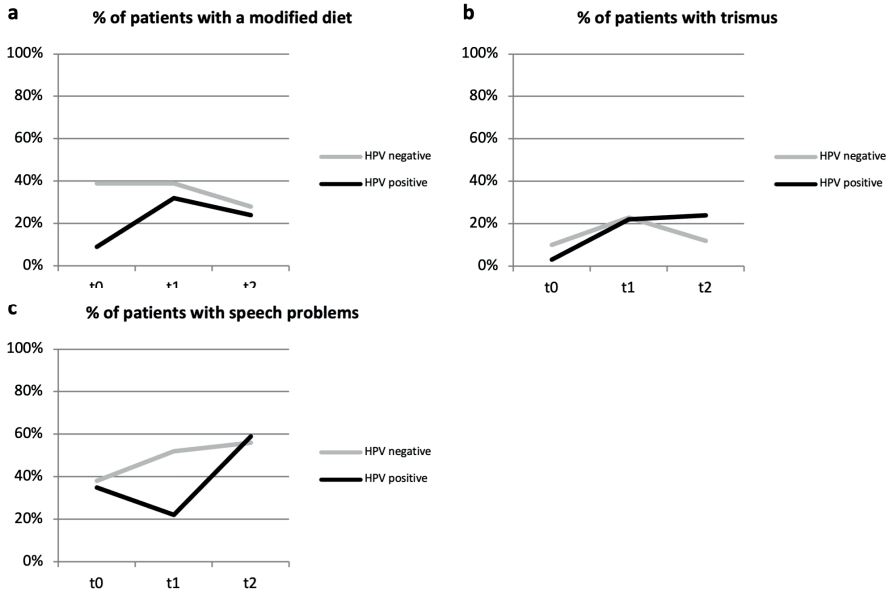

Figure 5 Percentage of patients with a modified diet (FOIS < 7) (a), trismus (b) or speech problems (vowel space area < 80%) (c) at *t*0, *t*1 and *t*2 stratified by HPV status.

Sarcopenia

Appendix 11 shows the baseline characteristics stratified by pretreatment sarcopenia. Patients with pretreatment sarcopenia were more often female, had a lower BMI, higher T-classifications, higher disease stages, more often an HPV negative tumor, and more often had a modified diet at baseline compared to patients without pretreatment sarcopenia.

All outcomes stratified by pretreatment sarcopenia are presented in Figure 6 and Appendix 12. As presented in Figure 6a, pretreatment sarcopenia was associated with more modified diet at all timepoints. Also, at *t*0 and *t*1, SWAL-QOL scores were higher in patients with sarcopenia, indicating more swallowing related problems. At *t*2, SWAL-QOL scores were comparable. Trismus outcomes were comparable between patients with and without sarcopenia at *t*0, *t*1 and *t*2. Prevalence of objective speech problems (vowel space area below 80%) was comparable at *t*0 and *t*1, but higher in patients with sarcopenia at *t*2. Patient reported speech problems, however, were more prevalent in patients with sarcopenia. After adjusting for AJCC stage and pretreatment modified diet, only modified diet and the total SWAL-QOL score at *t*1 were significantly higher in patients with pretreatment sarcopenia.

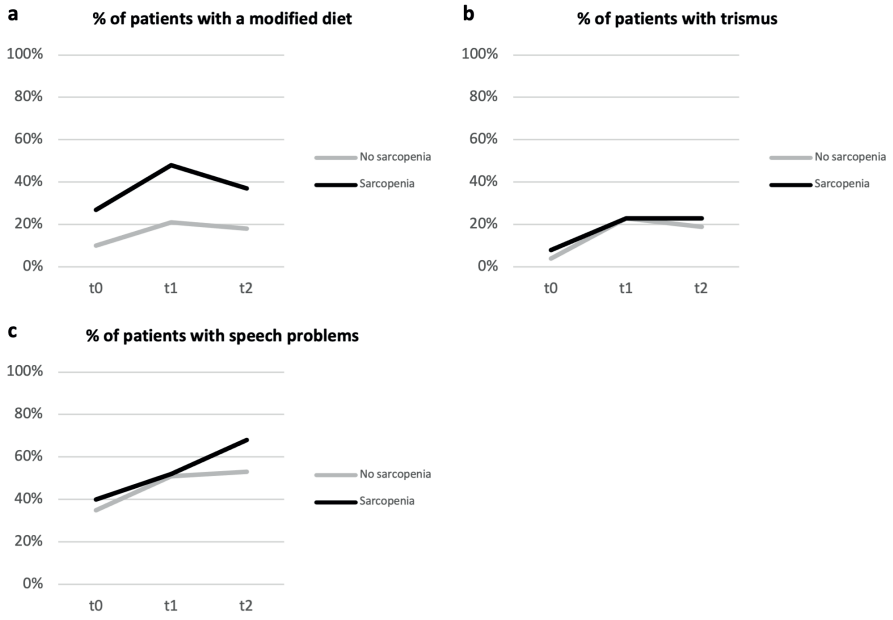

Figure 6 Percentage of patients with a modified diet (FOIS < 7) (a) trismus (b) or speech problems (vowel space area < 80%) (c) at *t*0, *t*1 and *t*2 stratified by pretreatment sarcopenia.

DISCUSSION

The objective of this study was to assess objective and subjective swallowing function, mouth opening and speech over a one-year period in a large cohort after RT(+) for advanced stage OPC treatment in conjunction with a dedicated preventive rehabilitation program, also focusing on the role of HPV status and pretreatment sarcopenia. These results are relevant for the optimization of current rehabilitation protocols. Patients were treated with IMRT with or without systemic therapy and a concurrent preventive rehabilitation program. Data collection was part of a systematic, intensive routine monitoring program at our institute. The study showed that the normalcy of oral intake and SWAL-QOL scores first deteriorated up to six months, and subsequently improved up until twelve months after treatment, but did not return to baseline levels. Rate of feeding tube dependency in this cohort was low, with none of the patients being feeding tube dependent at one year after treatment. Also, very few patients experienced pneumonia during the one-year follow-up. Trismus and speech problems showed the same trend as swallowing function, with increased prevalence of problems at six-month follow-up, and lower – but still above baseline – prevalence rates at one-year post-treatment. Patients treated with cisplatin-based RT+, HPV negative tumors, and patients with pretreatment sarcopenia were more likely to have functional limitations. Patients treated with RT+ had worse swallowing, trismus and speech and voice outcomes, compared to those treated with RT alone.

Most of the above summarized outcomes were in line with expectations and are comparable to those of other studies concluding that a substantial proportion of the patients have functional impairment after treatment. Although it is hard to compare the present results to other studies given the heterogeneity of cohorts and outcome measures currently used, some comparisons can be made. Starmer et al. evaluated 71 patients with OPC treated with IMRT with or without systemic therapy and preventive swallowing rehabilitation around 5 months post-treatment (9). Probably because 92% of the patients received RT+, prevalence of a modified diet according to FOIS scores was higher in that study (86% compared to 34% in our study). Hunter et al. evaluated the two-year period after RT+ without preventive swallowing rehabilitation for stage III-IV OPC in 72 patients (10). At six and twelve months after treatment respectively, 6% and 2% had grade 2 dysphagia (modified diet) and 6% and 1% had grade 3 dysphagia (feeding tube dependence) according to the Common Toxicity Criteria Adverse Effects (CTCAE) scale. The significantly lower percentage of patients with a modified diet in that study may, in part, be because another outcome measure was used (CTCAE scale versus FOIS). Congruent with our finding, other studies also found that functional limitations worsened the first months after therapy and improved through twelve months after treatment with minimal improvement in the year thereafter (10, 38).

Only few studies have investigated trismus within the first year after radiation-based treatment and a preventive rehabilitation protocol for advanced stage OPC. Kraaijenga et al. found that 9 of 24 patients (27%) after RT+ for OPC had trismus at a median follow-up of 13 weeks (16). In our study this concerned 23% at six-month follow-up and 20% at twelve-month follow-up.

Incidence rates of trismus in other studies including all head and neck cancer localizations treated with surgery and/or radiation vary, but oropharyngeal localization of the tumor consistently seems a risk factor (11-15, 39). This is probably because treatment of the oropharynx causes fibrosis in the mastication musculature (16). This hypothesis is also supported by our results showing that patients with tumor localizations within the oropharynx other than base of tongue have trismus more often.

Apparently, despite trismus preventing measures in our preventive rehabilitation program, trismus is still a prevalent problem in this cohort. Therefore, extra measures could be taken to prevent and treat trismus, for example, by selecting high risk patients for more intensive guidance, and emphasizing the need for trismus prevention stronger, prior to treatment. The consistent use of mouth opening exercises (e.g., with tongue blades or TheraBite®) in this patient group might have been advantageous (40). The lack of reimbursement for TheraBite® in the Netherlands, preventing regular use of this medical device in our patient population, is noteworthy in this respect.

With respect to speech and voice outcomes, according to our results, observer-rated intelligibility was deteriorated at six-month follow-up and stayed stable up until twelve-month follow-up. Subjective speech outcomes, however, deteriorated up until six months and returned to baseline levels at twelve-month follow-up. This is most likely because patients get used to the altered speech. Vainshtein et al. found the same trend in patient-reported voice quality, which decreased maximally at one month after treatment and recovered to baseline after twelve to eighteen months (41). In an earlier study from our institute, Jacobi et al. found comparable results. They reported that computer analyzed articulation and sound quality was impaired in head and neck cancer patients after RT+, especially with oral and oropharyngeal cancer sites (42).

Our results suggest that patients treated with concomitant systemic therapy have more functional limitations than patients treated with RT alone. This might be due to the toxicity of systemic therapy, but might also be because of the higher tumor stages, and therefore also larger radiotherapy fields. Only 17 (16%) of the 108 included patients were treated with cetuximab based RT+ and therefore there is a high risk of atypical sampling and conclusions on functional outcomes relative to RT only or cisplatin-based RT+ based on these analyses should be made with caution. A recently published randomized study concluded that the degree of toxicities, including dysphagia, between cisplatin and cetuximab in HPV positive OPC was comparable (5).

In our cohort, although HPV status was not associated with trismus and speech outcomes, patients with HPV positive tumors had less objective and subjective functional impairment. However, patients with HPV positive tumors also had more favorable baseline characteristics, including higher pretreatment SMI (as also reported by Chargi et al. (43)), lower T classification, were more often treated with RT only and less often had a modified diet before treatment.

When adjusting for baseline characteristics in multivariable analyses, HPV status was not significantly associated with functional limitations, except for a smaller mouth opening at one-year post-treatment. Although no definite conclusions can be drawn, it seems that HPV status itself does not influence post-treatment functional limitations.

Results in literature have contrasting results regarding the association of HPV status with functional limitations after RT(+). Vangelov et al. evaluated 100 patients with OPC treated with RT(+), and found that after adjusting for baseline characteristics (i.e., smoking, nodal stage, IMRT, and oropharyngeal RT dose), patients with an HPV positive tumor more often had tube feeding and weight loss, compared to patients with an HPV negative tumor (44). Again, adjusted for baseline characteristics (i.e., age, gender, stage, treatment modality, RT dose, neck node irradiation, and pretreatment weight loss), Vatca et al., on the other hand, evaluated 72 OPC patients treated with RT+ and found that patients with an HPV positive tumor had more mucositis and weight loss during treatment (45). Sharma et al. evaluated 228 OPC patients and found that quality of life in HPV positive patients was lower shortly after treatment but became comparable by one year after treatment, also adjusted for baseline differences (46), which is similar to our findings.

A low skeletal muscle mass, or sarcopenia, before treatment, was associated with an impaired diet before and after treatment. This is in line with results of a previous study performed at our institute which demonstrated that sarcopenia is a strong determinant for feeding tube use after RT+ for head and neck cancer (20). Skeletal muscle loss is thought to be related to swallowing muscle loss, causing swallowing difficulties which might result in a modified diet or eventually tube dependency. Moreover, swallowing problems itself may result in skeletal muscle loss due to insufficient nutritional intake. Therefore, these results support the hypothesis that sarcopenia might be a relevant target to optimize patients' condition before as well as after treatment to improve functional status. Apparently, our current preventive rehabilitation protocol does not target muscle mass sufficiently and/or not sufficiently long enough to close the gap between sarcopenic and non-sarcopenic patients with regard to swallowing impairment. In view of the association between pretreatment sarcopenia and functional outcomes, integrating SMI determination before treatment is warranted.

Limitations

A limitation of this study is the suboptimal accrual during the first years of the data collection. These analyses were performed on data collected as part of standard care. Collecting data in this way usually introduced a risk for suboptimal inclusion especially during startup. Although at first inclusion rates were low, they improved over time with current inclusion rates between 79-85%, making it likely that this cohort is representative for the entire cohort. In addition, because baseline characteristics between included patients and not included patients were similar, no selection bias due to (non-)inclusion seems present.

CONCLUSION

Objective and patient-perceived swallowing, mouth opening, and speech function of patients treated with IMRT with or without systemic therapy combined with a preventive rehabilitation program for OPC deteriorate up until six months and improve until twelve months after treatment, but do not return to baseline levels. Patients treated with cisplatin-based CRT, HPV negative tumors and patients with pretreatment sarcopenia were more likely to have functional limitations. HPV negative status itself is not likely to be a cause of functional limitations, but the associated unfavorable patient and tumor characteristics are. Pretreatment sarcopenia might be a relevant target for prehabilitation strategies. Although for most patients in this cohort organ preserving treatment resulted in function preservation, there is a proportion of patients with functional problems, suggesting room for improvement of the current rehabilitation program.

ACKNOWLEDGEMENTS

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APPENDICES

Appendix 1 Functional outcomes at *t*1 and *t*2 stratified by inclusion year. *P* values shown for multivariable regression adjusted for AJCC stage and modified diet at *t*0.

		*t*1		*t*2	
		2013/2014 *n* = 14	**2017/2018** *n* = 40	**2013/2014** *n* = 14	**2017/2018** *n* = 29
Swallowing outcomes					
Modified diet (FOIS < 7)	No	9 (64)	26 (67)	13 (93)	20 (69)
	Yes	5 (36)	13 (33)	1 (7)	9 (31)
	Unknown	0	1	0	0
SWAL-QOL total score (0–100) Median (range)		21 (0-37)	20 (0-77)	10 (0-26)	6 (0-37)
SWAL-QOL ≥ 14	No	3 (43)	10 (42)	9 (75)	17 (77)
	Yes	4 (57)	14 (58)	3 (25)	5 (23)
	Unknown	7	16	2	7
Trismus outcomes					
Mouth opening in mm Median (range)		46 (30-59)	44 (27-52)	44 (10-58)	43 (25-52)
Trismus	No	11 (85)	28 (76)	11 (79)	24 (83)
	Yes	2 (15)	9 (24)	3 (21)	5 (17)
	Unknown	1	3	0	1
Perceived trismus	No	9 (82)	28 (78)	11 (85)	27 (93)
	Yes	2 (18)	8 (22)	2 (15)	2 (7)
	Unknown	3	4	1	0
Speech and voice outcomes					
Vowel Space Area (%) Median (range)		81 (59-99)	75 (49-100)	86 (58-96)	71 (51-102)
Vowel Space Area < 80%	No	5 (50)	14 (39)	7 (58)	6 (24)
	Yes	5 (50)	22 (61)	5 (42)	19 (76)
	Unknown	4	4	2	4
SHI total score (0–120) Median (range)		0 (0-7)	4 (0-60)	0 (0-22)	0 (0-40)
SHI ≥ 6	No	6 (86)	9 (56)	9 (82)	12 (92)
	Yes	1 (14)	71 (44)	2 (18)	1 (8)
	Unknown	7	24	3	16

NB: Not all percentages sum up exactly to 100% due to rounding.

Abbreviations: FOIS = functional oral intake scale, HPV = human papillomavirus, SHI = speech handicap index, *t*1 = six months after treatment, *t*2 = twelve months after treatment.

Appendix 2 Baseline characteristics stratified by treatment modality.

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

NB: Not all percentages sum up exactly to 100% due to rounding.

Abbreviations: BMI = body mass index, FOIS = functional oral intake scale, HPV = human papilloma virus, other = soft palate, uvula, oropharyngeal wall, vallecula or pharyngeal arch, RT = radiotherapy, SMM = skeletal muscle mass.

Appendix 3 Swallowing outcomes at *t*0, *t*1 and *t*2 stratified by treatment modality. P values shown for Friedman test[a] or Cochran's Q test[b].

		RT			RT + cetuximab			RT + cisplatin		
		***t*0** *n* = 42	***t*1** *n* = 39	***t*2** *n* = 28	***t*0** *n* = 17	***t*1** *n* = 17	***t*2** *n* = 11	***t*0** *n* = 49	***t*1** *n* = 43	***t*2** *n* = 32
Observer-rated outcome										
FOIS	7	36 (86)	25 (64)	23 (82)	16 (94)	14 (82)	7 (64)	37 (76)	26 (62)	23 (72)
	6	2 (5)	12 (31)	5 (18)	1 (6)	1 (6)	3 (27)	6 (12)	11 (26)	6 (19)
	5	2 (5)	2 (5)	0 (0)	0 (0)	1 (6)	1 (9)	5 (10)	1 (2)	2 (6)
	4	1 (2)	0 (0)	0 (0)	0 (0)	1 (6)	0 (0)	1 (2)	1 (2)	1 (3)
	3	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (7)	0 (0)
	2	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	1	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Unknown	0	0	0	0	0	0	0	0	0
FOIS < 7	No	36 (86)	25 (64)	23 (82)	16 (94)	14 (82)	7 (64)	37 (76)	26 (62)	23 (72)
	Yes	6 (14)	14 (36)	5 (18)	1 (6)	3 (18)	4 (36)	12 (25)	16 (38)	9 (28)
	Unknown	0	0	0	0	0	0	0	1	0
Patient-rated outcome										
SWAL-QOL (0–100) Median (range)										
General burden		0 (0-88)	0 (0-50)	0 (0-38)	0 (0-50)	0 (0-100)	25 (0-50)	0 (0-75)	13 (0-63)	0 (0-50)
Food selection		0 (0-88)	0 (0-50)	0 (0-38)	0 (0-25)	25 (0-100)	25 (0-50)	7 (0-75)	19 (0-75)	0 (0-50)
Eating duration		0 (0-88)	32 (0-100)	13 (0-100)	0 (0-63)	38 (0-88)	38 (0-88)	19 (0-75)	50 (0-100)	38 (0-75)
Eating desire		0 (0-92)	17 (0-42)	8 (0-38)	9 (0-50)	25 (0-50)	34 (0-58)	13 (0-83)	25 (0-83)	17 (0-67)
Fear		0 (0-69)	0 (0-38)	0 (0-38)	0 (0-38)	25 (0-69)	16 (0-25)	0 (0-50)	19 (0-69)	16 (0-38)
Sleep		38 (0-100)	38 (0-75)	25 (0-88)	38 (0-88)	50 (0-75)	13 (0-63)	44 (0-88)	38 (0-75)	25 (0-50)
Fatigue		25 (0-67)	25 (0-58)	17 (0-83)	17 (0-50)	25 (0-75)	21 (0-50)	21 (0-67)	42 (0-75)	25 (0-83)
Communication		0 (0-50)	0 (0-38)	0 (0-25)	0 (0-50)	25 (0-75)	7 (0-25)	0 (0-75)	0 (0-63)	0 (0-63)
Mental health		0 (0-69)	0 (0-25)	0 (0-30)	0 (0-25)	25 (0-100)	20 (0-25)	0 (0-75)	3 (0-60)	0 (0-45)
Social functioning		0 (0-40)	0 (0-40)	0 (0-30)	0 (0-25)	25 (0-60)	0 (0-25)	0 (0-70)	0 (0-50)	0 (0-30)

Appendix 3 Continued

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

NB: Not all percentages sum up exactly to 100% due to rounding.

Abbreviations: FOIS = functional oral intake scale, *t*0 = pretreatment, *t*1 = six months after treatment, *t*2 = twelve months after treatment.

Appendix 4 Trismus outcomes at *t*0, *t*1 and *t*2 stratified by treatment modality.

		RT			RT + cetuximab			RT + cisplatin		
		***t*0**	***t*1**	***t*2**	***t*0**	***t*1**	***t*2**	***t*0**	***t*1**	***t*2**
		n = 42	*n* = 39	*n* = 28	*n* = 17	*n* = 17	*n* = 11	*n* = 49	*n* = 43	*n* = 32
Observer-rated outcomes										
Mouth opening in mm	Median (range)	49 (25-65)	47 (31-63)	48 (27-64)	48 (30-60)	42 (27-55)	43 (32-50)	47 (18-64)	40 (16-59)	41 (10-58)
Trismus	No	39 (93)	29 (91)	24 (86)	16 (94)	12 (75)	9 (90)	43 (96)	27 (68)	22 (71)
	Yes	3 (7)	3 (9)	4 (14)	1 (6)	4 (25)	1 (10)	2 (4)	13 (33)	9 (29)
	Unknown	0	7	0	0	1	1	4	3	1
Patient-rated outcomes										
Perceived trismus	No	34 (100)	26 (90)	25 (93)	16 (94)	13 (81)	8 (100)	37 (93)	28 (76)	23 (82)
	Yes	0 (0)	3 (10)	2 (7)	1 (6)	3 (19)	0 (0)	3 (8)	9 (24)	5 (18)
	Unknown	8	10	1	0	1	3	9	6	4

NB: Not all percentages sum up exactly to 100% due to rounding.

Abbreviations: FOIS = functional oral intake scale, NGT = nasogastric tube, PRG = percutaneous radiological gastrostomy, *t*0 = pretreatment, *t*1 = six months after treatment, *t*2 = twelve months after treatment

Appendix 5 Speech outcomes at *t*0, *t*1 and *t*2 stratified by treatment modality.

		RT			RT + cetuximab			RT + cisplatin		
		***t*0** *n* = 42	***t*1** *n* = 39	***t*2** *n* = 28	***t*0** *n* = 17	***t*1** *n* = 17	***t*2** *n* = 11	***t*0** *n* = 49	***t*1** *n* = 43	***t*2** *n* = 32
Observer-rated outcomes										
Vowel Space Area (%) Median (range)		92 (61-128)	86 (56-107)	83 (53-112)	86 (68-129)	74 (59-97)	69 (53-96)	81 (51-114)	76 (49-102)	76 (51-97)
Vowel Space Area < 80%	No	25 (76)	20 (69)	13 (59)	10 (63)	6 (38)	2 (22)	24 (53)	11 (36)	9 (35)
	Yes	8 (24)	9 (31)	9 (41)	6 (38)	10 (63)	7 (78)	21 (47)	20 (65)	17 (65)
	Unknown	9	10	6	1	1	2	4	12	6
Patient-rated outcomes										
SHI Median (range)										
Speech domain (0–56)		1 (0-18)	2 (0-21)	0 (0-14)	0 (0-25)	2 (0-27)	0 (0-6)	0 (0-42)	2 (0-32)	1 (0-31)
Psychosocial domain (0–56)		0 (0-5)	0 (0-10)	0 (0-7)	0 (0-32)	0 (0-34)	0 (0-1)	0 (0-39)	0 (0-19)	0 (0-15)
Total score (0–120)		1 (0-23)	2 (0-36)	0 (0-23)	0 (0-57)	2 (0-61)	0 (0-6)	0 (0-83)	3 (0-52)	1 (0-40)
SHI ≥ 6	No	23 (82)	13 (65)	16 (94)	12 (86)	10 (77)	6 (86)	30 (83)	16 (62)	14 (82)
	Yes	5 (18)	7 (35)	1 (6)	2 (14)	3 (23)	1 (14)	6 (17)	10 (39)	3 (18)
	Unknown	14	19	11	3	4	4	13	17	15
Secondary outcomes										
Articulation rate (syllables/s) Median (range)		2.2 (0.9-7.7)	2.8 (1.4-4.2)	2.9 (0.1-5.0)	2.7 (1.0-4.3)	2.6 (0.6-4.6)	2.7 (1.6-5.1)	2.2 (0.2-5.8)	2.6 (0.6-6.1)	2.4 (0.6-6.1)
AVQI Median (range)		4.7 (3.7-5.3)	4.5 (3.4-5.5)	4.7 (4.1-5.3)	4.4 (3.7-5.1)	4.4 (3.6-5.1)	4.5 (4.1-5.2)	4.5 (3.3-5.2)	4.5 (3.5-5.3)	4.5 (3.6-5.5)

NB: Not all percentages sum up exactly to 100% due to rounding.

Abbreviations: AVQI = acoustic voice quality index, FOIS = functional oral intake scale, SHI = speech handicap index, *t*0 = pretreatment, *t*1 = six months after treatment, *t*2 = twelve months after treatment

Appendix 6 Baseline characteristics by modified diet (FOIS < 7) at *t*2 and univariable analysis.

		Normal diet (FOIS 7) at *t*1 *n* = 53	Modified diet (FOIS < 7) at *t*1 *n* = 18	Univariable logistic regression analysis	
				OR (95%CI)	*P* value
Gender					
	Male	40 (76)	12 (67)	1.0	
	Female	13 (25)	6 (33)	1.5 (0.5-4.9)	.468
Age at baseline Median (range)		62 (39-81)	63 (47-75)	1.0 (1.0-1.1)	.477
ACE-27					.963
	0	28 (53)	11 (61)	1.0	
	1	20 (38)	6 (33)	0.8 (0.2-2.4)	.645
	2	2 (4)	1 (6)	1.3 (0.1-15.5)	.850
	3	3 (6)	0 (0)	NA	NA
BMI Median (range)		25 (17-44)	23 (18-30)	0.8 (0.7-1.0)	.020
SMM Median (range)		45 (27-64)	41 (30-54)	0.9 (0.8-1.0)	.034
Sarcopenia					
	No	36 (68)	8 (44)	1.0	
	Yes	17 (32)	10 (56)	2.6 (0.9-7.9)	.081
Tumor site					.588
	Base of tongue	20 (38)	5 (28)	1.0	
	Tonsil	26 (49)	9 (50)	1.4 (0.4-4.8)	.607
	Other	7 (13)	4 (22)	2.3 (0.5-11.0)	.303
T classification					.222
	T1	18 (34)	1 (6)	1.0	
	T2	13 (25)	6 (33)	8.3 (0.9-77.6)	.063
	T3	14 (26)	6 (33)	7.7 (0.8-71.7)	.072
	T4	8 (15)	5 (28)	11.3 (1.1-112.5)	.039
HPV status					
	Negative	13 (25)	5 (29)	1.0	
	Positive	39 (75)	12 (71)	0.8 (0.2-2.7)	.719
	Unknown	1	1		
Treatment modality					.444
	RT	23 (43)	5 (28)	1.0	
	RT + cetuximab	7 (13)	4 (22)	2.6 (0.6-12.6)	.226
	RT + cisplatin	23 (43)	9 (50)	1.8 (0.5-6.2)	.352
Pretreatment modified diet (FOIS < 7)					
	No	50 (94)	16 (89)	1.0	
	Yes	3 (6)	2 (11)	2.1 (0.3-13.6)	.443

NB: Not all percentages sum up exactly to 100% due to rounding.

Abbreviations: BMI = body mass index, CI = confidence interval, HPV = human papilloma virus, FOIS = functional oral intake scale, OR = odds ratio, other = soft palate, uvula, oropharyngeal wall, vallecula or pharyngeal arch,

RT = radiotherapy, sarcopenia = SMM below 43.2 cm^2/m^2, SMM = skeletal muscle mass.

Appendix 7 Baseline characteristics by trismus at *t2* and univariable analysis.

		No trismus at *t1* *n* = 55	Trismus at *t1* *n* = 14	Univariable logistic regression analysis	
				OR (95%CI)	*P* value
Gender					
	Male	39 (71)	12 (86)	1.0	
	Female	16 (29)	2 (14)	0.4 (0.1-2.0)	.272
Age at baseline Median (range)		60 (39-77)	64 (42-73)	1.1 (1.0-1.1)	.154
ACE-27					.886
	0	31 (56)	7 (50)	1.0	
	1	19 (35)	7 (50)	1.6 (0.5-5.4)	.421
	2	2 (4)	0 (0)	NA	NA
	3	3 (6)	0 (0)	NA	NA
BMI Median (range)		26 (17-44)	24 (18-30)	0.9 (0.7-1.0)	.073
SMM Median (range)		45 (22-64)	44 (34-50)	1.0 (0.9-1.1)	.617
Sarcopenia					
	No	35 (64)	8 (57)	1.0	
	Yes	20 (36)	6 (43)	1.3 (0.4-4.3)	.655
Tumor site					.142
	Base of tongue	23 (42)	2 (14)	1.0	
	Tonsil	25 (46)	8 (57)	3.7 (0.7-19.2)	.122
	Other	7 (13)	4 (29)	6.6 (1.0-43.8)	.052
T classification					.164
	T1	17 (31)	2 (14)	1.0	
	T2	17 (31)	2 (14)	1.0 (0.1-7.9)	1.000
	T3	12 (22)	7 (50)	5.0 (0.9-28.2)	.071
	T4	9 (16)	3 (21)	2.8 (0.4-10.2)	.298
HPV status					
	Negative	15 (28)	2 (14)	1.0	
	Positive	38 (72)	12 (86)	2.4 (0.5-11.9)	.294
	Unknown	2	0		
Treatment modality					.272
	RT	24 (44)	4 (29)	1.0	
	RT + cetuximab	9 (16)	1 (7)	0.7 (0.1-6.8)	.732
	RT + cisplatin	22 (40)	9 (64)	2.5 (0.7-9.1)	.180
Pretreatment trismus					
	No	52 (96)	10 (83)		
	Yes	2 (4)	2 (17)	5.2 (0.7-41.4)	.119
	Unknown	1	2		

NB: Not all percentages sum up exactly to 100% due to rounding.

Abbreviations: BMI = body mass index, CI = confidence interval, HPV = human papilloma virus, FOIS = functional oral intake scale, OR = odds ratio, other = soft palate, uvula, oropharyngeal wall, vallecula or pharyngeal arch,

RT = radiotherapy, sarcopenia = SMM below 43.2 cm^2/m^2, SMM = skeletal muscle mass.

Appendix 8 Baseline characteristics by vowel space area below 80% at *t*1 and univariable analysis.

		VSA > 80% at *t*1 *n* = 24	VSA < 80% *t*1 *n* = 33	Univariable logistic regression analysis	
				OR (95%CI)	*P* value
Gender					
	Male	20 (83)	24 (73)	1.0	
	Female	4 (17)	9 (27)	1.9 (0.5-7.0)	.350
Age at baseline Median (range)		61 (44-75)	60 (39-75)	1.0 (1.0-1.1)	.756
ACE-27					.501
	0	12 (50)	21 (64)	1.0	
	1	11 (46)	8 (24)	0.4 (0.1-1.3)	.136
	2	0 (0)	2 (6)	NA	
	3	1 (4)	2 (6)	1.1 (0.1-14.0)	.917
BMI Median (range)		26 (20-44)	25 (18-33)	1.0 (0.8-1.1)	.473
SMM Median (range)		46 (32-64)	45 (30-54)	1.0 (0.9-1.0)	.345
Sarcopenia					
	No	18 (75)	20 (61)	1.0	
	Yes	6 (25)	13 (39)	2.0 (0.6-6.2)	.258
Tumor site					.756
	Base of tongue	8 (33)	14 (42)	1.0	
	Tonsil	12 (50)	15 (46)	0.7 (0.2-2.3)	.568
	Other	4 (17)	4 (12)	0.6 (0.1-2.9)	.502
T classification					.963
	T1	7 (29)	8 (24)	1.0	
	T2	7 (29)	10 (30)	1.3 (0.3-5.1)	.755
	T3	6 (25)	8 (24)	1.2 (0.3-5.1)	.837
	T4	4 (17)	7 (21)	1.5 (0.3-7.5)	.600
HPV status					
	Negative	7 (30)	9 (28)	1.0	
	Positive	16 (70)	23 (72)	1.1 (0.3-3.6)	.852
	Unknown	1	1		
Treatment modality					.108
	RT	13 (54)	9 (27)	1.0	
	RT + cetuximab	2 (8)	7 (21)	5.1 (0.8-30.2)	.075
	RT + cisplatin	9 (38)	17 (52)	2.7 (0.8-8.8)	.093
Pretreatment VSA < 80%					
	No	17 (77)	14 (48)	1.0	
	Yes	4 (24)	15 (52)	4.6 (1.2-16.9)	.023
	Unknown	3	4		

NB: Not all percentages sum up exactly to 100% due to rounding.

Abbreviations: BMI = body mass index, CI = confidence interval, HPV = human papilloma virus, FOIS = functional oral intake scale, OR = odds ratio, other = soft palate, uvula, oropharyngeal wall, vallecula or pharyngeal arch, RT = radiotherapy, sarcopenia = SMM below 43.2 cm^2/m^2, SMM = skeletal muscle mass, VSA = vowel space area.

Appendix 9 Baseline characteristics stratified by HPV status. *P* values shown for Mann-Whitney U test[a], linear-by-linear approximation of the Pearson's Chi-square test[b] or Fisher's exact Test[c].

		HPV - *n* = 33	**HPV +** *n* = 70	***P* value**
Gender	Male	20 (61)	50 (71)	.366[c]
	Female	13 (39)	20 (29)	
Age at baseline Median (range)		62 (44-75)	62 (39-79)	.511[a]
ACE-27	0	14 (42)	38 (54)	.151[b]
	1	13 (39)	24 (34)	
	2	3 (9)	7 (10)	
	3	3 (9)	1 (1)	
BMI Median (range)		24 (17-33)	26 (17-44)	.001[a]
SMM Median (range)		41 (27-54)	45 (22-64)	.031[a]
Sarcopenia	No	14 (42)	43 (61)	.090[c]
	Yes	19 (58)	27 (39)	
Oropharyngeal tumor site	Base of tongue	10 (30)	24 (34)	.198[b]
	Tonsil	15 (46)	40 (57)	
	Other	8 (24)	6 (9)	
T classification	T1	1 (3)	26 (37)	<.001[b]
	T2	7 (21)	21 (30)	
	T3	15 (46)	11 (16)	
	T4	10 (30)	12 (17)	
N classification	N0	6 (18)	5 (7)	.026[b]
	N1	9 (27)	13 (19)	
	N2	18 (55)	49 (70)	
	N3	0 (0)	3 (4)	
AJCC stage	III	10 (30)	15 (21)	.336[c]
	IV	23 (70)	55 (79)	
Treatment modality	RT	6 (18)	32 (46)	.005[b]
	RT unfit for RT+	1 (3)	1 (1)	
	RT + cetuximab	18 (55)	30 (43)	
	RT + cisplatin	8 (24)	7 (10)	
Modified diet at *t*0 (FOIS < 7)	No	20 (61)	64 (91)	.001[c]
	Yes	13 (39)	6 (9)	
Trismus at *t*0	No	28 (90)	66 (97)	.175[c]
	Yes	3 (10)	2 (3)	
	Unknown	2	2	

NB: Not all percentages sum up exactly to 100% due to rounding.

Abbreviations: BMI = body mass index, HPV = human papilloma virus, other = soft palate, uvula, oropharyngeal wall, vallecula or pharyngeal arch, RT = radiotherapy, sarcopenia = SMM below 43.2 cm^2/m^2, SMM = skeletal muscle mass.

Appendix 10 Functional outcomes at *t*1 and *t*2 stratified by HPV status. *P* values shown for multivariable regression adjusted for T and N classification, treatment and modified diet at *t*0.

		***t*1**			***t*2**		
		HPV - n = 31	**HPV +** n = 64	**Adjusted *p* value**	**HPV -** n = 18	**HPV +** n = 51	**Adjusted *p* value**
Swallowing outcomes							
Modified diet (FOIS < 7)	No	19 (61)	43 (68)	.206	13 (72)	39 (77)	.460
	Yes	12 (39)	20 (32)		5 (28)	12 (24)	
	Unknown	0	1		0	0	
SWAL-QOL total score (0–100) Median (range)		21 (0-77)	8 (0-52)	.492	14 (0-32)	5 (0-43)	.652
SWAL-QOL ≥ 14	No	9 (38)	26 (65)	.868	8 (62)	29 (76)	.292
	Yes	15 (63)	14 (35)		5 (39)	9 (24)	
	Unknown	7	24		5	13	
Trismus outcomes							
Mouth opening in mm Median (range)		42 (18-54)	45 (16-63)	.627	45 (27-53)	43 (10-64)	.046
Trismus	No	23 (77)	43 (78)	.611	15 (88)	38 (76)	.086
	Yes	7 (23)	12 (22)		2 (12)	12 (24)	
	Unknown	1	9		1	1	
Perceived trismus	No	25 (86)	40 (80)	.074	15 (94)	39 (87)	.996
	Yes	4 (14)	10 (20)		1 (6)	6 (13)	
	Unknown	2	14		2	6	
Speech and voice outcomes							
Vowel Space Area (%) Median (range)		77 (58-100)	82 (49-107)	.913	77 (51-102)	76 (53-112)	.528
Vowel Space Area < 80%	No	13 (48)	43 (78)	.645	7 (44)	16 (41)	.463
	Yes	14 (52)	12 (22)		9 (56)	23 (59)	
	Unknown	4	9		2	12	
SHI total score (0–120) Median (range)		4 (0-61)	3 (0-52)	.896	1 (0-10)	0 (0-40)	.151
SHI ≥ 6	No	12 (60)	25 (69)	.995	11 (85)	24 (92)	.325
	Yes	8 (40)	11 (31)		2 (15)	2 (8)	
	Unknown	11	28		5	25	

NB: Not all percentages sum up exactly to 100% due to rounding.

Abbreviations: FOIS = functional oral intake scale, HPV = human papillomavirus, SHI = speech handicap index, *t*1 = six months after treatment, *t*2 = twelve months after treatment.

Appendix 11 Baseline characteristics stratified by pretreatment sarcopenia. *P* values shown for Mann-Whitney U test[a], linear-by-linear approximation of the Pearson's Chi-square test[b] or Fisher's exact Test[c].

		No sarcopenia N = 59	Sarcopenia N = 49	*P* value
Gender	Male	57 (97)	16 (33)	< .001[c]
	Female	2 (3)	33 (67)	
Age at baseline Median (range)		61 (39-81)	63 (47-79)	.095[a]
ACE-27	0	29 (49)	24 (49)	1.000[b]
	1	21 (36)	16 (33)	
	2	6 (10)	8 (16)	
	3	3 (5)	1 (2)	
BMI Median (range)		26 (18-44)	23 (17-35)	< .001[a]
Oropharyngeal tumor site	Base of tongue	22 (37)	13 (27)	.112[b]
	Tonsil	31 (53)	26 (53)	
	Other	6 (10)	10 (20)	
T classification	T1	19 (32)	8 (16)	.031[b]
	T2	16 (27)	14 (29)	
	T3	16 (27)	13 (27)	
	T4	8 (14)	14 (29)	
N classification	N0	8 (14)	4 (8)	.287[b]
	N1	15 (25)	9 (18)	
	N2	34 (58)	35 (71)	
	N3	2 (3)	1 (20	
AJCC stage	III	20 (34)	8 (16)	.048[c]
	IV	39 (66)	41 (84)	
HPV	Negative	14 (25)	19 (41)	.090[c]
	Positive	43 (75)	27 (59)	
	Unknown	2	3	
Treatment modality	RT	27 (46)	12 (24)	.090[b]
	RT unfit for RT+	0 (0)	3 (6)	
	RT + cetuximab	9 (15)	8 (16)	
	RT + cisplatin	23 (39)	26 (53)	
Modified diet at *t*0 (FOIS < 7)	No	53 (90)	36 (74)	.041[c]
	Yes	6 (10)	13 (27)	
Trismus at *t*0	No	54 (96)	44 (92)	.411[c]
	Yes	2 (4)	4 (8)	
	Unknown	3	1	

NB: Not all percentages sum up exactly to 100% due to rounding.

Abbreviations: BMI = body mass index, HPV = human papilloma virus, other = soft palate, uvula, oropharyngeal wall, vallecula or pharyngeal arch, RT = radiotherapy, sarcopenia = skeletal muscle mass below 43.2 cm^2/m^2.

Appendix 12 Functional outcomes at *t*1 and *t*2 stratified by pretreatment sarcopenia. *P* values shown for multivariable regression adjusted for AJCC stage and modified diet at *t*0.

		*t*1			*t*2		
		No sarcopenia n = 53	**Sarcopenia** n = 46	**Adjusted *p* value**	**No sarcopenia** n = 44	**Sarcopenia** n = 27	**Adjusted *p* value**
Swallowing outcomes							
Modified diet (FOIS < 7)	No	41 (79)	24 (52)	.013	36 (82)	17 (63)	.088
	Yes	11 (21)	22 (48)		8 (18)	10 (37)	
	Unknown	1	0		0	0	
SWAL-QOL total score (0–100) Median (range)		10 (0-41)	22 (0-77)	.031	9 (0-32)	8 (0-43)	.133
SWAL-QOL ≥ 14	No	23 (64)	12 (39)	.135	26 (70)	12 (75)	.783
	Yes	13 (36)	19 (61)		11 (30)	4 (25)	
	Unknown	17	15		7	11	
Trismus outcomes							
Mouth opening in mm Median (range)		45 (27-63)	44 (16-58)	.528	45 (27-64)	43 (10-52)	.143
Trismus	No	37 (77)	31 (78)	.662	35 (81)	20 (77)	.831
	Yes	11 (23)	9 (23)		8 (19)	6 (23)	
	Unknown	5	6		1	1	
Perceived trismus	No	37 (82)	30 (81)	.958	35 (90)	21 (88)	.892
	Yes	8 (18)	7 (19)		4 (10)	3 (13)	
	Unknown	8	9		5	3	
Speech and voice outcomes							
Vowel Space Area (%) Median (range)		80 (56-107)	79 (49-100)	.760	79 (51-112)	73 (53-102)	.731
Vowel Space Area < 80%	No	21 (49)	16 (49)	.085	18 (47)	6 (32)	.431
	Yes	22 (51)	17 (52)		20 (53)	13 (68)	
	Unknown	10	13		6	8	
SHI total score (0–120) Median (range)		0 (0-36)	3 (0-61)	.115	0 (0-23)	1 (0-40)	.210
SHI ≥ 6	No	24 (73)	15 (58)	.266	25 (89)	11 (85)	.563
	Yes	9 (27)	11 (42)		3 (11)	2 (15)	
	Unknown	20	20		16	14	

NB: Not all percentages sum up exactly to 100% due to rounding.

Abbreviations: FOIS = functional oral intake scale, HPV = human papillomavirus, SHI = speech handicap index, sarcopenia = skeletal muscle mass below 43.2 cm^2/m^2, *t*1 = six months after treatment, *t*2 = twelve months after treatment.

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Chapter 6

MRI assessment of swallow muscle activation with the Swallow Exercise Aid and with conventional exercises in healthy volunteers: an explorative biomechanical study

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ABSTRACT

Objectives: Swallowing muscle strength exercises are effective in restoring swallowing function. In order to perform the exercises with progressive load, the Swallow Exercise Aid (SEA) was developed. Precise knowledge on which muscles are activated with swallowing exercises, especially with the SEA, is lacking. This knowledge would aid in optimizing the training program to target the relevant swallowing muscles, if necessary.

Materials and Methods: Three healthy volunteers performed the three SEA exercises (chin tuck against resistance, jaw opening against resistance and effortful swallow) and three conventional exercises (conventional effortful swallow, Shaker and Masako) in supine position inside an MRI scanner. Fast muscle-functional MRI scans (generating quantitative T2-maps) were made immediately before and after the exercises. Median T2-values at rest and after exercise were compared to identify activated muscles.

Results: After the three SEA exercises, the suprahyoid, infrahyoid, sternocleidomastoid, and lateral pterygoid muscles showed significant T2-value increase. After the Shaker, the lateral pterygoid muscles did not show such an increase, but the three other muscle groups did. The conventional effortful swallow and Masako caused no significant increase in any of these muscle groups.

Conclusion: During conventional (Shaker) exercises, the suprahyoid, infrahyoid, and sternocleidomastoid muscles are activated. During the SEA exercises, the suprahyoid, infrahyoid, sternocleidomastoid, and lateral pterygoid muscles are activated. The findings of this explorative study further support the potential of the SEA to improve swallowing rehabilitation.

INTRODUCTION

Swallowing is a complex mechanism facilitated by over thirty muscles of the head and neck area (1, 2). Coordination of these muscles facilitate the four phases of swallowing (i.e., oral preparatory phase, oral phase, oropharyngeal phase, and esophageal phase) (2). Interruption of this mechanism, dysphagia, is a common problem after treatment for head and neck cancer (HNC) (3-6). This is frequently caused by impaired laryngeal elevation, mainly accomplished by the suprahyoid muscles, and/or pharyngeal constriction, accomplished by the pharyngeal muscles (7-10). Impairment of the pharyngeal constrictors results in impaired bolus transportation, and reduced laryngeal elevation results in both impaired laryngeal closure and reduced opening of the upper esophageal sphincter (7-9). This results in an increased risk for aspiration and pharyngeal residue. Also, tongue strength, which plays an important role in moving the food bolus from the oral cavity into the pharynx, can be reduced (11). Trismus is another highly prevalent effect of head and neck cancer treatment, which can negatively impact chew function (12).

Swallowing muscle strength exercises are known to be effective in restoring swallowing function (13-16). These exercises are designed to target the abovementioned causes of functional impairment (2). A weakness of these standard swallowing exercises is that exercise intensity can only be modified by changing the number of repetitions or the duration of the contraction whereas the optimal strengthening of muscles requires progressive overload (17). Therefore, we recently developed the Swallow Exercise Aid (SEA), a tool enabling three different muscle strength swallowing exercises with progressive load to activate the suprahyoid, tongue, pharyngeal and jaw opening musculature, with the objective to improve effectiveness of the strength training (18). The feasibility and effectiveness of the SEA have been studied with healthy individuals as well as with dysphagia patients, with positive results for exercise compliance and effectiveness (18, 19). However, precise knowledge on which muscles are activated while performing swallowing exercises, especially with the SEA, is still lacking.

Muscle activation causes an altered water distribution within the muscle, which can be detected as increased transverse relaxation time constant by means of Magnetic Resonance Imaging (MRI) (20, 21). Transverse relaxation time constants, also known as T2-values, are a measure of the life-time of the transverse magnetization of water protons within a voxel. T2 mapping of muscles, derived from muscle functional-MRI (mfMRI) scans, is a non-invasive quantitative technique which can be used to visualize muscle activation patterns during/at the end of an exercise session (22-24). The technique has been validated to demonstrate muscle activation in a variety of muscle exercises including those of the lower limb and core as well as those of the head and neck area (10, 20, 21, 24-34).

The objective of this explorative biomechanical study is to investigate which muscles are activated during swallowing muscle strength exercises with the SEA (chin tuck against resistance, jaw opening against resistance and effortful swallow) and without an exercise tool providing external load (conventional effortful swallow, Masako and Shaker) by means of mfMRI.

MATERIALS AND METHODS

Compliance with ethical standards

This study was approved by the medical research ethics committee of the Netherlands Cancer Institute (METC18.0768/N18SEA) and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

Sample size calculation

We expect an increase in T2-value from 45 ms (SD 3) to 50 ms (SD 3) based on previous research (10, 28). With three volunteers, and measuring both left and right side of the muscle (group), this provides six observations per muscle group. Although hypothesis testing was not the primary aim of the study, with this sample size, the study would have 95% power to detect this difference based on a significance level of 0.05 for each comparison, not accounting for multiple testing.

Subjects

Three healthy volunteers (one female and two males; aged 25, 26 and 29) with no known altered anatomy of the head and neck area, performed the exercises with the SEA. Likewise, three healthy volunteers performed the standard exercises (two females and one male, aged 25, 26 and 31).

SEA

The SEA, as extensively described before (18), is constructed by expanding the TheraBite Jaw Mobilization device with a chest bar (see Figure 1). By placing one or two elastic silicon 'ActiveBands' at various positions, external and progressive load can be obtained during the exercise regimen.

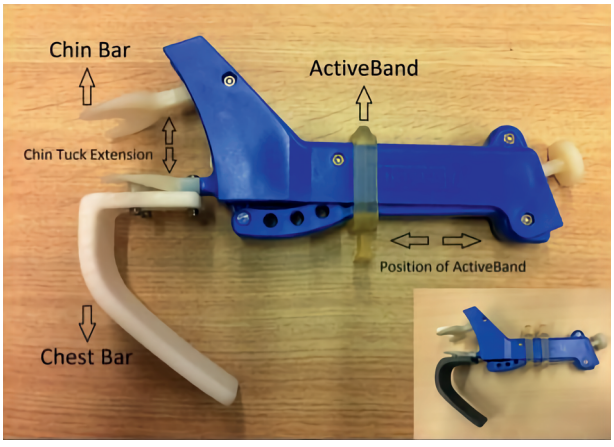

Figure 1 Swallow Exercise Aid (SEA).

SEA exercises

The three exercises performed with the SEA are presented in Figure 2 (18, 35). The chin tuck against resistance exercise (CTAR+) is performed by repetitively pressing the chin downwards against the chin bar of the SEA, while keeping the mouth closed, until the chin bar reaches the chest bar attachment (providing tactile feedback). It was hypothesized that mainly the suprahyoid muscles will be activated during this exercise.

The jaw opening against resistance exercise (JOAR+) is performed by repetitively pressing the mandible down while opening the mouth, again compressing the chin bar onto the chest bar. It was hypothesized that both the suprahyoid and jaw opening musculature will be activated during this exercise.

The effortful swallow exercise (ES+) is performed with the chin placed on the chin bar (pressed halfway down (50%)), whereby the subject effortful swallows voluntarily as if swallowing a large bolus with the mandible down and the lips/mouth closed. This exercise was hypothesized to not only stimulate the suprahyoid and jaw muscles involved in mouth opening, but also the tongue and pharyngeal musculature.

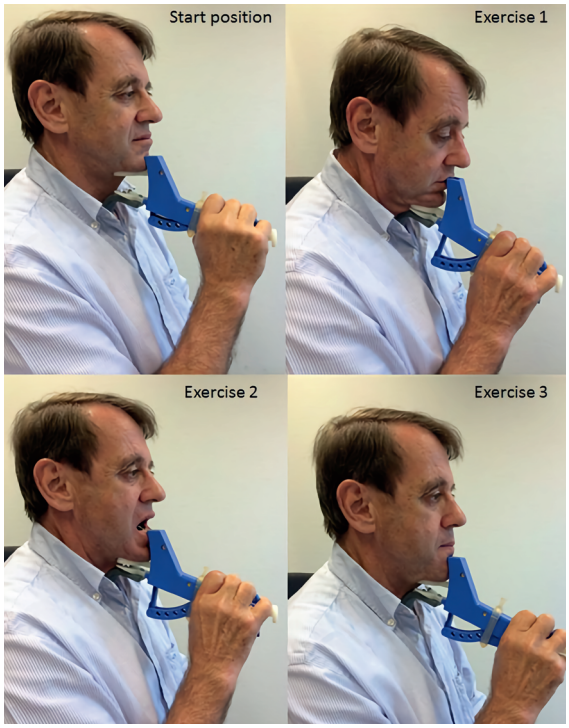

Figure 2 Exercises performed with the swallow exercise aid. Top left: start position; top right: chin tuck against resistance (CTAR) exercise; bottom left: jaw opening against resistance (JOAR) exercise; bottom right: effortful swallow (ES) exercise.

Standard exercises

The conventional effortful swallow (cES), Masako and Shaker exercise are commonly applied conventional swallowing exercises performed without an exercise tool providing external and progressive load. These exercises were used to compare the level of swallowing muscle activation during exercising with and without the SEA. Moreover, the SEA exercises were based on these exercises, and consequently we hypothesized that the same muscles would be activated.

During the cES exercise, the subject is instructed to forcefully swallow as if swallowing a large bolus. It is supposed to increase pharyngeal and tongue musculature strength and to improve the backward movement of the tongue base resulting in a better clearance of the vallecula (2).

During the Masako exercise, the subject has to stick out his/her tongue as far as possible and hold it in that position with their teeth or fingers while swallowing. The degree of tongue protrusion was not further standardized in this study. It is supposed to improve pharyngeal contraction by strengthening the glossopharyngeal muscle (36).

During the Shaker exercise, the subject lies in supine position and repetitively lifts his/her head for thirty times, followed by a period of rest of 30 seconds. Then the subject lifts his/her head for one minute, rests, and repeats the cycle (performing the head lift three times in total). The exercise is supposed to strengthen the suprahyoid muscles and therefore to improve opening of the upper esophageal sphincter (37), but also to activate the sternocleidomastoid muscles. Especially this exercises has shown to be effective in improving swallowing function (13, 14).

Procedure

Each subject performed the exercises in supine position in the MRI. The six exercises were performed on six separate days to avoid effects of the previous exercise disturbing the results of the next. The exercises were performed in a fixed order: CTAR+, JOAR+, ES+, cES, Masako and Shaker. First, the volunteers were asked to relax before the scan in order to get reliable resting-state T2 values for the swallow muscles. Then, an MRI-scan was made before the participant performed the exercise until exhaustion (i.e., the subject was not able to perform another repetition of the exercise). The second MRI-scan was made directly at completion of the exercise. To provide an indication of exercise duration, time between the pre and post exercise MRI was measured.

MRI acquisition

Regular T2-weighted images do not provide sufficient contrast to distinguish activated swallowing muscles after exercise. Image contrast is highly dependent on an optimal echo-time, which is muscle dependent, and very low for small T2 differences as observed in the swallowing muscles. We therefore chose the direct quantitative measurement of T2-values in milliseconds of the muscles by producing a T2-map. This map is a spatial distribution of voxel based T2-values associated with the anatomical features of the head and neck area.

All scans were performed on a 3T Ingenia scanner (Philips Healthcare, Best, The Netherlands) using a dStream head-spine coil for optimal signal to noise ratio and allowing sufficient space to perform the exercises with the SEA. T2-mapping requires in general a time-consuming multi-echo T2W acquisition. Given the direct decrease in T2-value after exercise, we used a k-t-T2 accelerated research software patch (38) to speed-up the acquisition to a little over 4 minutes per scan. The field of view of the multi-slice multi-echo T2-weighted turbo spin-echo sequence was 170 mm in the AP and RL direction and 129 mm in the FH direction. Acquired voxel size was 1.2 x 1.2 mm inplane with a reconstructed voxel size of 0.6 x 0.6 mm, using contiguous slices with a thickness of 3 mm. The 12 echo-times ranged between 16 ms up to 104 ms with increments of 8 ms. The repetition time was 4211 ms. Halfscan is 0.613 and SENSE acceleration factor is 2 in the LR direction. A voxel-wise fit to the T2-decay curve was based on those 12 echo-times, generating a quantitative 3D T2-map over the field of view.

T2-value measurements

The following muscles were included in the field of view: masseter muscles, lateral pterygoid muscles, medial pterygoid muscles, intrinsic tongue muscles, extrinsic tongue muscles (genioglossus muscle), suprahyoid muscles, infrahyoid muscles (thyrohyoid muscle), sternocleidomastoid muscles and superior pharyngeal constrictor muscle. The mean T2-values of these muscles were measured in PACS viewer by means of selecting one region of interest (ROI) per muscle (> 10 mm^2), on an axial image at a predetermined height where the muscle is the largest, blinded for exercise type and whether it concerned a scan before or after exercise (Figure 3). Homogeneous T2-values along the entire muscle were assumed, based on published results and our own measurement on a sample of the muscles in this study (39). Larger non-muscular tissues (e.g., blood vessels and fat) were excluded from the ROI as much as possible, although inclusion of non-muscular tissue within the ROI was inevitable since these are embedded within the muscle. Per subject, both the muscles on left and right side were measured. The measurements of the MRI scans before and after all exercise of all subjects were performed by two researchers (one medical doctor and one technical physician) independently. Both researchers received an example MRI scan indicating the anatomical height on which the measurements should be done for each muscle (see Figure 3). The average of the two measurements were used for analyses. Also, in order to compare T2-values in a (control) muscle not used during the exercises, the T2-values in the splenius capitis muscles before and after the cES exercise were measured. This exercise was selected because we expected only after the cES the field of view would contain non-activated muscles.

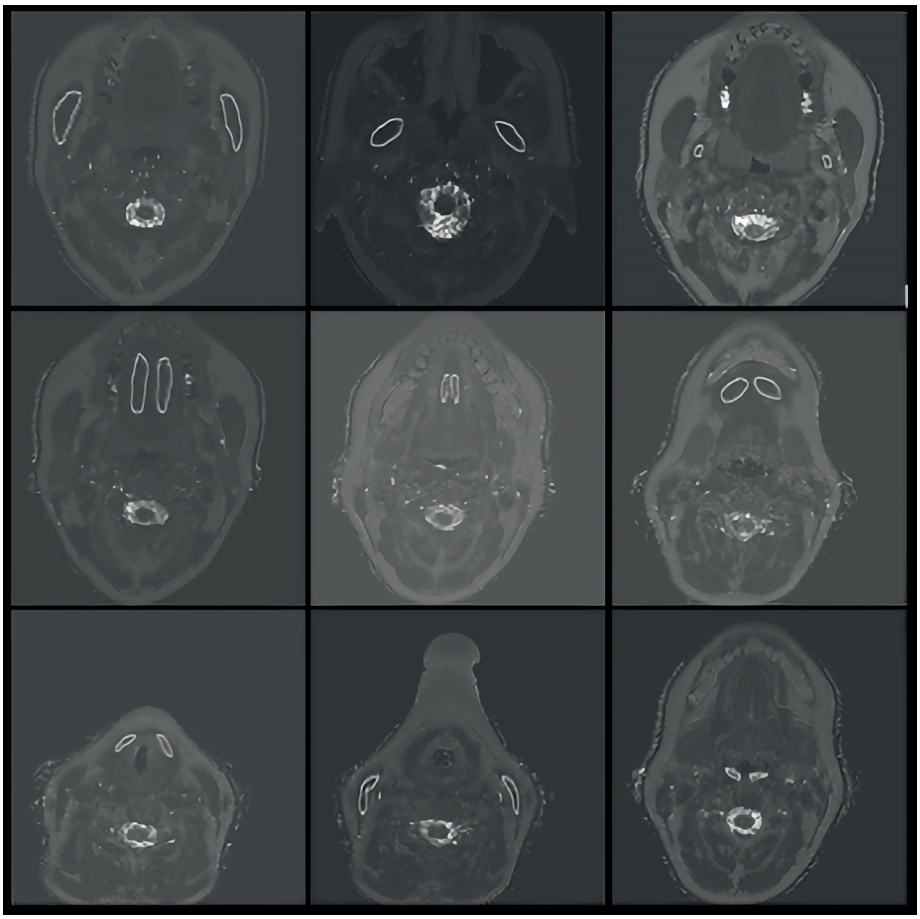

Figure 3 Examples of MRI slices with T2 measurements of (from top left to bottom right) the masseter, lateral pterygoid, medial pterygoid, intrinsic tongue, extrinsic tongue, suprahyoid, infrahyoid, sternocleidomastoid and superior pharyngeal constrictor muscles. White circles delineate the region of interests.

Statistical analysis

Analyses were performed using IBM® SPSS® Statistics 22.0 (40). Inter-rater reliability was assessed by means of the average measures Intra-Class Coefficient (ICC) from a two-way mixed model using a consistency definition. Median T2-values of the selected ROI of the included muscles at rest and after exercise (six measurements per muscle) were compared by means of the Wilcoxon signed rank test. Based on this test, an accompanying *r*-type effect size was calculated to provide a standardized measure of strength of the effect. Following the guidelines of Cohen (41), the *r*-type effect sizes of 0.1 were considered small, 0.3 moderate, and 0.5 large. Large effect sizes ($r > 0.5$) were considered indicative of meaningful observations.

RESULTS

There was a minimal interval of three days between the exercises. Time between pre and post exercise MRI are shown in Table 1. Estimated exercise duration ranged from approximately 4 to 6 minutes for SEA exercises and from approximately 5 to 9 minutes for conventional exercises. The inter-rater reliability was moderate to excellent (ICC per muscle group ranged from 0.65 to 0.93, see Table 2) (42). Median T2-values in the control muscle (splenius capitis muscles) before and after cES were 36 ms (range 34–38 ms) and 36 ms (35–37 ms) respectively (effect size 0.03) (Figure 4).

Table 1 Time between pre and post exercise MRI as indication of exercise duration. Of this time, calculation time of the T2-map (maximally 2 minutes) has to be subtracted to estimate exercise duration.

Subject nr.	CTAR+	JOAR+	ES+	cES	Masako	Shaker
1	8 min 21 s	6 min 51 s	6 min 9 s	7 min 32 s	7 min 28 s	7 min 17 s
2	6 min 9 s	6 min 58 s	7 min 56 s	-	-	-
3	8 min 46 s	6 min 35 s	6 min 42 s	-	-	-
4	-	-	-	7 min 2 s	7 min 42 s	10 min 12 s
5	-	-	-	10 min 55 s	8 min 20 s	9 min 28 s

Abbreviations: + = exercise performed with swallow exercise aid, cES = conventional effortful swallow, CTAR = chin tuck against resistance, ES = effortful swallow, JOAR = jaw opening against resistance

Table 2 Average measures Intra-Class Coefficient (ICC) from a two-way mixed model using an absolute agreement definition per measured muscle (group).

	ICC (95% CI)
Masseter muscle	0.87 (0.80-0.92)
Lateral pterygoid muscle	0.92 (0.87-0.95)
Medial pterygoid muscle	0.65 (0.44-0.78)
Intrinsic tongue muscle	0.90 (0.84-0.94)
Extrinsic tongue muscle	0.87 (0.79-0.92)
Suprahyoid muscles	0.91 (0.85-0.94)
Infrahyoid muscles	0.89 (0.83-0.93)
Sternocleidomastoid muscle	0.93 (0.89-0.96)
Superior pharyngeal constrictor muscles	0.68 (0.49-0.80)

Abbreviations: CI = confidence interval

Median T2-values before and after SEA exercises are presented in Table 3 and Figures 5-7. After CTAR+, JOAR+ as well as the ES+, T2-values of the suprahyoid muscles were significantly increased (all effect sizes of 0.64) (Figures 5a, 6a and 7a). The JOAR+ additionally caused a significant increased T2-value of the lateral pterygoid muscles (effect size 0.64) (Figure 6b). The ES+ additionally caused significant increased T2-values of infrahyoid muscles (effect size 0.64) and the lateral pterygoid muscle (effect size 0.64) (Figured 7b and 7c). After CTAR+, T2-values of the infrahyoid muscles (effect size 0.58) and the sternocleidomastoid muscles (effect size

0.64) were also significantly increased (figures 5b and 5c). Thus, the combination of the three SEA exercises activated three relevant muscle groups for swallowing and chewing (i.e., lateral pterygoid, suprahyoid and infrahyoid muscles) plus the sternocleidomastoid muscles.

Median T2-values before and after the conventional exercises without exercise tool are presented in Table 4 and Figure 8. The Shaker exercise significantly increased the suprahyoid muscles (effect size 0.64), infrahyoid muscles (effect size 0.58) and sternocleidomastoid muscles (effect size 0.64) (Figures 8a, 8b, and 8c). After cES and Masako, none of the muscles showed significantly increased T2-values in this set-up. Thus, the Shaker exercise activated two relevant muscle groups for swallowing (i.e., suprahyoid and infrahyoid muscles) plus the sternocleidomastoid muscles (effect sizes of 0.64 and 0.58), whereas the effortful swallow and Masako do not show significant muscle activation in this experiment.

The T2-values of the masseter, intrinsic and extrinsic tongue muscles and superior pharyngeal constrictor muscle were not significantly increased after any of the exercises. A schematic overview of the activated muscles after SEA and standard exercises is shown in Figure 9.

Table 3 Median T2 values (in milliseconds) per muscle (group) before and after SEA exercises. *P* values of Wilcoxon signed rank test are presented. Bold faced *p* values are below .05 and effect sizes are above 0.50.

	T2-value before exercise (ms) Median (min–max)	**T2-value after exercise (ms)** Median (min–max)	***p* value**	**|r|**
CTAR+				
Masseter muscle	44 (37–46)	44 (39–46)	.753	0.09
Lateral pterygoid muscle	48 (38–52)	48 (40–51)	.753	0.09
Medial pterygoid muscle	40 (36–43)	41 (38–44)	.249	0.33
Intrinsic tongue muscle	48 (45–54)	50 (47–54)	.753	0.09
Extrinsic tongue muscle	43 (40–45)	42 (40–48)	.345	0.27
Suprahyoid muscles	37 (37–38)	40 (39–42)	**.028**	**0.64**
Infrahyoid muscles	38 (33–44)	42 (34–49)	**.046**	**0.58**
Sternocleidomastoid muscle	36 (29–40)	40 (33–48)	**.028**	**0.64**
Superior pharyngeal constrictor muscles	45 (42–51)	44 (42–48)	.249	0.33
JOAR+				
Masseter muscle	42 (40–47)	43 (41–44)	.463	0.21
Lateral pterygoid muscle	48 (47–52)	56 (52–61)	**.028**	**0.64**
Medial pterygoid muscle	39 (36–41)	40 (34–41)	.917	0.03
Intrinsic tongue muscle	58 (53–61)	58 (54–62)	.917	0.03
Extrinsic tongue muscle	41 (40–43)	41 (39–47)	.753	0.09
Suprahyoid muscles	36 (36–39)	47 (42–52)	**.028**	**0.64**
Infrahyoid muscles	37 (34–40)	40 (35–42)	.116	0.45
Sternocleidomastoid muscle	40 (33–44)	39 (33–41)	.249	0.33
Superior pharyngeal constrictor muscles	44 (38–51)	44 (40–47)	.753	0.09

Table 3 Continued

	T2-value before exercise (ms) Median (min–max)	**T2-value after exercise (ms)** Median (min–max)	***p* value**	**|r|**
ES+				
Masseter muscle	43 (38–48)	43 (38–48)	.600	0.15
Lateral pterygoid muscle	47 (45–54)	52 (46–59)	**.028**	**0.64**
Medial pterygoid muscle	40 (36–42)	40 (39–44)	.116	0.45
Intrinsic tongue muscle	53 (49–66)	55 (47–65)	.345	0.27
Extrinsic tongue muscle	42 (39-46)	40 (39–44)	.116	0.45
Suprahyoid muscles	37 (36–40)	47 (43–50)	**.028**	**0.64**
Infrahyoid muscles	35 (34–44)	39 (36–46)	**.028**	**0.64**
Sternocleidomastoid muscle	37 (32–49)	39 (31–45)	.345	0.27
Superior pharyngeal constrictor muscles	44 (41–47)	44 (39–48)	.917	0.03

Abbreviations: + = exercise performed with swallow exercise aid, CTAR = chin tuck against resistance, ES = effortful swallow, JOAR = jaw opening against resistance, *r* = effect size, SD = standard deviation.

Table 4 Median T2 values (in milliseconds) per muscle (group) before and after conventional exercises. *P* values of Wilcoxon signed rank test are presented. Bold faced *p* values are below .05 and effect sizes are above 0.50.

	T2-value before exercise (ms) Median (min–max)	**T2-value after exercise (ms)** Median (min–max)	***p* value**	**|r|**
cES				
Masseter muscle	45 (40–46)	45 (40–48)	.345	0.27
Lateral pterygoid muscle	44 (41–52)	44 (41–50)	.345	0.27
Medial pterygoid muscle	41 (38–42)	42 (39–43)	.293	0.30
Intrinsic tongue muscle	48 (42–53)	51 (41–57)	.345	0.27
Extrinsic tongue muscle	47 (44–56)	50 (46–55)	.600	0.15
Suprahyoid muscles	38 (36–42)	40 (39–44)	.116	0.45
Infrahyoid muscles	39 (36–43)	40 (38–45)	.116	0.45
Sternocleidomastoid muscle	37 (33–43)	35 (34–42)	.463	0.21
Superior pharyngeal constrictor muscles	48 (42–51)	49 (44–53)	.345	0.27
Masako exercise				
Masseter muscle	44 (42–46)	44 (42–47)	.249	0.33
Lateral pterygoid muscle	45 (43–49)	44 (38–46)	.116	0.45
Medial pterygoid muscle	40 (38–42)	40 (39–44)	.463	0.21
Intrinsic tongue muscle	50 (39–51)	50 (44–56)	.116	0.45
Extrinsic tongue muscle	48 (40–51)	42 (39–45)	.116	0.45
Suprahyoid muscles	39 (36–40)	41 (39–43)	.116	0.45
Infrahyoid muscles	39 (35–45)	38 (34–45)	.463	0.21
Sternocleidomastoid muscle	36 (34–41)	35 (35–37)	.600	0.15
Superior pharyngeal constrictor muscles	47 (43–53)	46 (43–50)	.753	0.09
Shaker exercise				
Masseter muscle	45 (42–50)	43 (42–53)	.916	0.03
Lateral pterygoid muscle	42 (40–52)	42 (40–44)	.345	0.27
Medial pterygoid muscle	40 (39–42)	41 (40–42)	.173	0.39
Intrinsic tongue muscle	50 (44–55)	51 (44–52)	.753	0.09
Extrinsic tongue muscle	42 (40–44)	43 (41–48)	.173	0.39
Suprahyoid muscles	39 (36–41)	44 (41–45)	**.028**	**0.64**
Infrahyoid muscles	40 (35–43)	43 (41–50)	**.046**	**0.58**
Sternocleidomastoid muscle	36 (34–42)	48 (37–50)	**.028**	**0.64**
Superior pharyngeal constrictor muscles	45 (43–56)	46 (41–51)	.917	0.03

Abbreviations: cES = conventional effortful swallow, *r* = effect size, SD = standard deviation.

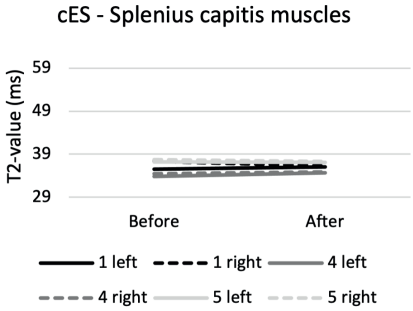

Figure 4 Change in T2 values (in milliseconds) of individual participants after the conventional effortful swallow of the splenius capitis muscles, chosen as non-activated muscle. Ascending or descending line indicates increased or decreased T2 value respectively.
Abbreviations: cES = conventional effortful swallow, ms = milliseconds.

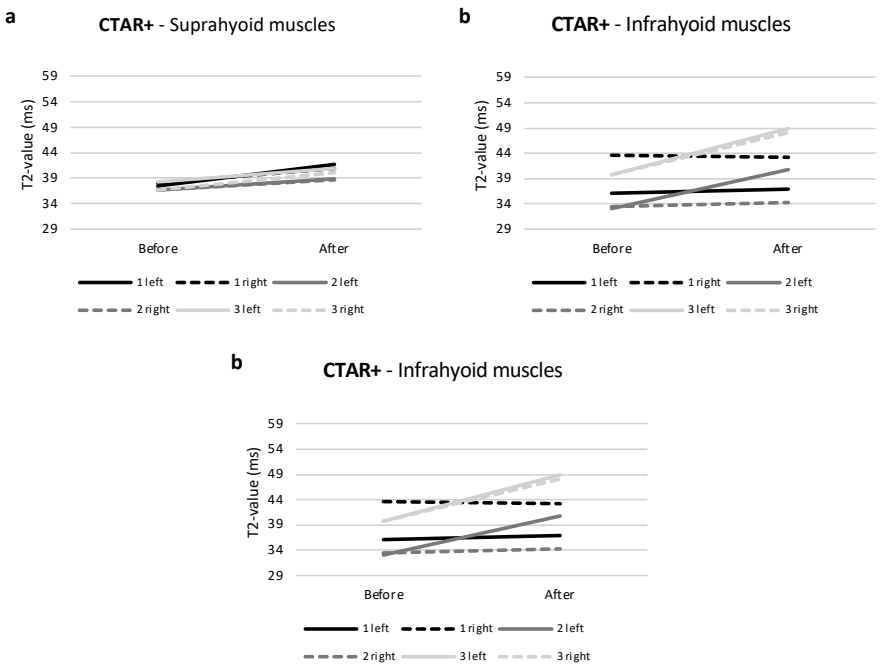

Figure 5 Change in T2 values (in milliseconds) of muscles with significant increased T2 values of individual participants after chin tuck against resistance exercise performed with the swallow exercise aid. Ascending or descending line indicates increased or decreased T2 value respectively.
Abbreviations: CTAR+ = chin tuck against resistance performed with swallow exercise aid, ms = milliseconds, SCM = sternocleidomastoid

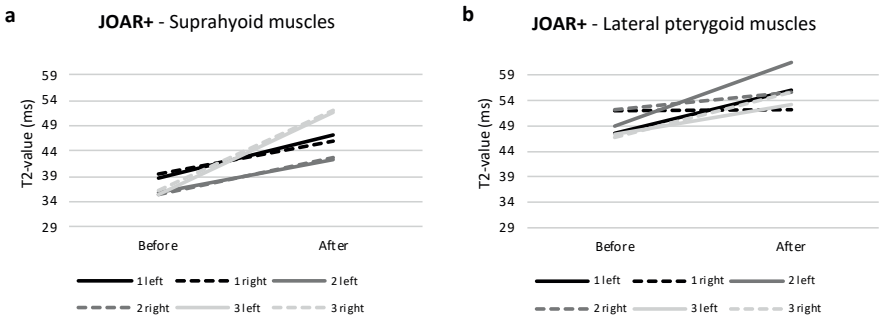

Figure 6 Change in T2 values (in milliseconds) of muscles with significant increased T2 values of individual participants after jaw opening against resistance exercise performed with the swallow exercise aid. Ascending or descending line indicates increased or decreased T2 value respectively.
Abbreviations: JOAR+ = jaw opening against resistance performed with swallow exercise aid, ms = milliseconds.

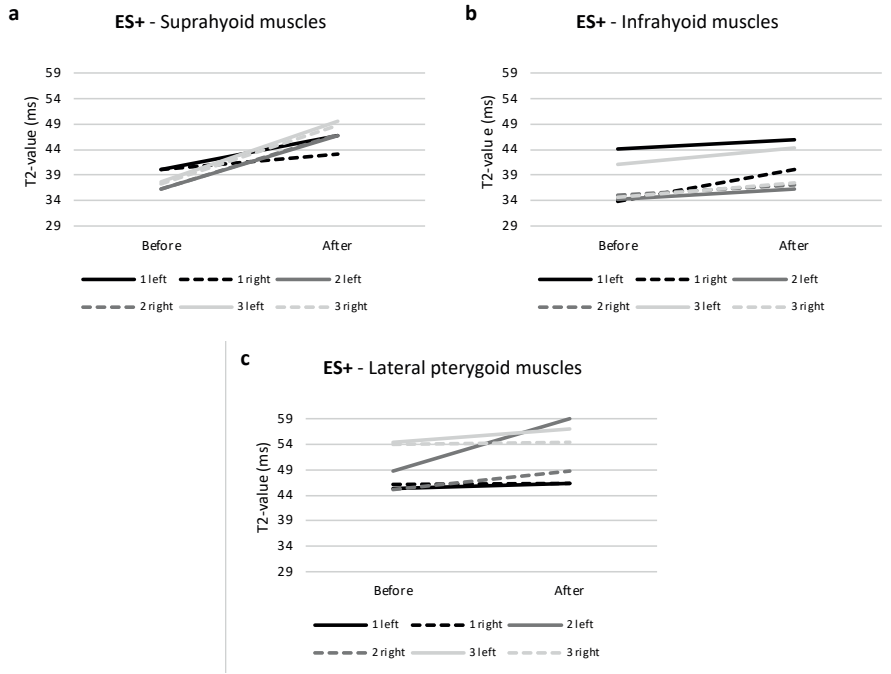

Figure 7 Change in T2 values (in milliseconds) of muscles with significant increased T2 values of individual participants after effortful swallow exercise performed with the swallow exercise aid. Ascending or descending line indicates increased or decreased T2 value respectively.
Abbreviations: ES+ = effortful swallow performed with swallow exercise aid, ms = milliseconds.

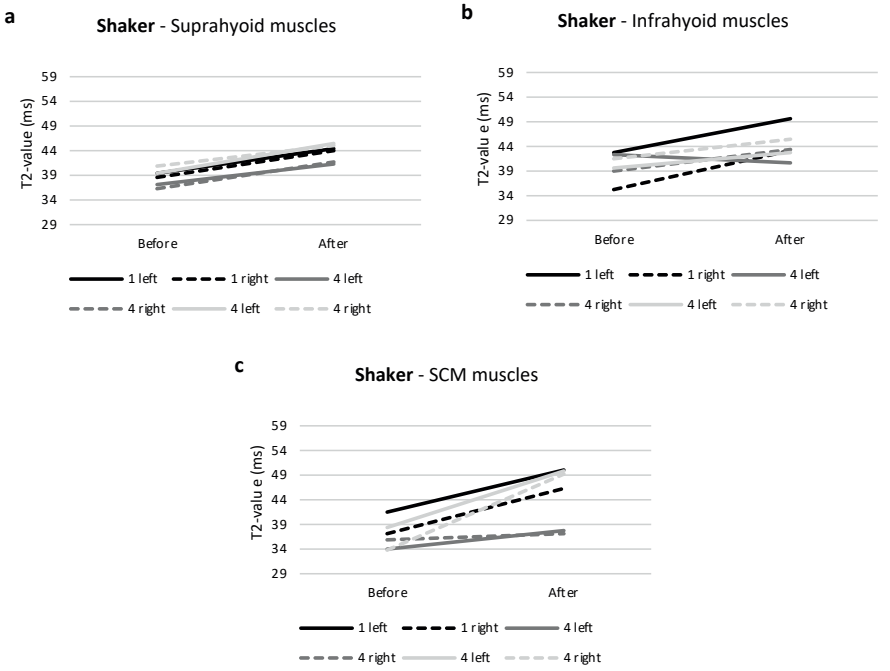

Figure 8 Change in T2 values (in milliseconds) of muscles with significant increased T2 values of individual participants after Shaker exercise. Ascending or descending line indicates increased or decreased T2 value respectively. Abbreviations: ms = milliseconds, SCM = sternocleidomastoid.

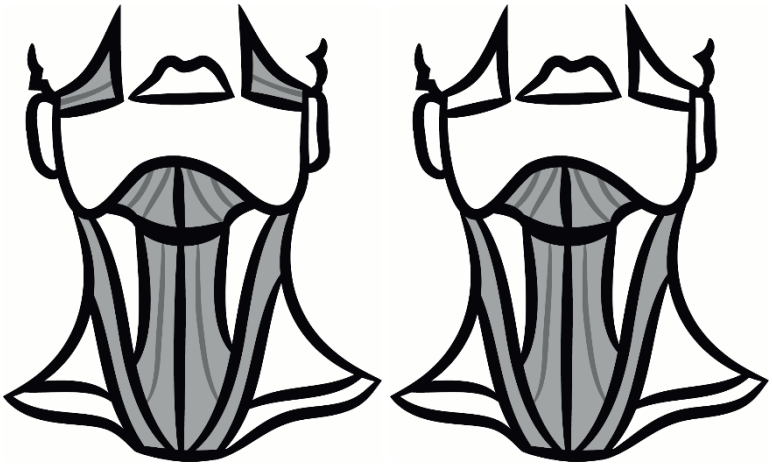

Figure 9 Schematic overview of activated muscles. Gray colored muscle groups are activated after SEA exercises (left) and conventional exercises (right).

DISCUSSION

The aim of this explorative biomechanical study was to identify the muscles activated during swallowing muscle strength exercises with the SEA (CTAR+, JOAR+ and ES+ exercise) and conventional swallowing exercises without an exercise tool providing external load (cES, Masako and Shaker exercise), by means of mfMRI T2-mapping using 12 echo-times, resulting in precise estimation of the true T2-values. The three SEA exercises caused a significant increase of the T2-value, indicating activation of three relevant muscle groups (i.e., lateral pterygoid, suprahyoid and infrahyoid muscles) plus the sternocleidomastoid muscles. After the conventional exercises, two relevant muscle groups (i.e., suprahyoid and infrahyoid muscles) plus the sternocleidomastoid muscles showed a significant increase of the T2-value. Mouth opening muscles (masseter and medial pterygoid muscles), tongue muscles and superior pharyngeal constrictor muscle did not show a significant increase of the T2-value in this experiment.

Swallowing is a complex function which is facilitated by over thirty muscles of the head and neck area (1, 2). After head and neck cancer treatment, jaw opening, tongue strength, pharyngeal constriction as well as laryngeal elevation might be impaired. Muscles involved in these functions are firstly the lateral pterygoid muscle which enables mouth opening by depressing the mandible. Tongue strength comprises of the strength of the intrinsic and extrinsic tongue musculature which contribute to the oral transport phase of the swallow. The superior, middle and pharyngeal constrictors cause pharyngeal constriction and the stylopharyngeus, salpingopharyngeus, and palatopharyngeus muscles elevate the pharynx. Laryngeal elevation is facilitated by the suprahyoid muscles, including the geniohyoid, mylohyoid, stylohyoid and digastric muscles. These muscles also contribute to depression of the mandible and stabilizing the hyoid. The infrahyoid muscles mainly depress the larynx, but also play a role in the elevation, mainly the thyrohyoid muscle.

The SEA exercises were designed to target jaw opening, tongue strength, pharyngeal constriction as well as laryngeal elevation. Specifically, we hypothesized that the SEA exercises would target the suprahyoid muscles (CTAR+, JOAR+, and ES+), pharyngeal musculature (ES+), jaw opening musculature (JOAR+ , ES+), and tongue muscles (ES+). The present study indicates that during the SEA exercises suprahyoid and jaw opening musculature are indeed activated, but tongue musculature and the superior pharyngeal constrictor muscle do not show significant activation.

The absence of a measurable effect in the superior pharyngeal constrictor muscle, both after the cES and after the ES+, might be due to insufficient activation of the pharyngeal constrictors, even not when additional load is provided by the SEA. Another issue might be the small size of the superior pharyngeal constrictor muscle, making the selection of a substantial region of interest harder, resulting in higher uncertainty of the measured T2-value. This is also reflected in the relatively low inter-rater reliability of the measurements of the superior pharyngeal constrictor muscle (ICC = 0.68 (95%-CI 0.49-0.80)).

The absence of evidence for activation of the tongue musculature is somewhat surprising in view of the results of Kraaijenga et al., who found a significant increased tongue strength in healthy volunteers (n = 10) as well as chronic dysphagia patients (n = 18) after an SEA training period of six weeks (18, 35). Also, Clark et al. reported increased tongue pressures in healthy participants (n = 40) after a training period of four weeks including the cES exercise (43). This contradiction might be because the effects of the single ES+ as well as the single conventional exercises on tongue muscle strength are so small that they can only be measured after a long-term training period. However, the contradiction might also be due to the fact that the exercises in this study were performed in supine instead of upright position, with tongue retraction possibly being accomplished easier due to gravity. Testing in supine position in the present study, however, was unavoidable given the direct decrease of T2-values after exercise with a half-life of approximately seven minutes (24). Performing the exercise outside of the MRI and repositioning the subject in the MRI would take over five minutes. Therefore, despite the fact the T2 mapping acquisition only takes four minutes, at least almost half of the effect of exercise on T2-value would be gone.

The SEA exercises were based on the conventional exercises and were hypothesized to target the same muscles but with greater extent due to the use of progressive load. Our results, although explorative, suggest that the SEA exercises activated the same muscle groups as the conventional swallowing exercises plus the lateral pterygoid muscles (Figure 10). The lateral pterygoid muscle, an important jaw opening muscle, is a quite relevant target to prevent trismus, which is highly prevalent in patients after treatment for head and neck cancer (12).

Of the conventional swallowing exercises, especially the Shaker exercise has shown to be effective in improving swallowing function (13, 14). However, the disadvantage of this maneuver is that it has to be performed in supine position. This position is not feasible for a substantial proportion of head and neck cancer patients due to their physical condition including stiffness of the neck musculature. To avoid this supine position, Mishra et al. have developed a variant of the Shaker exercise in 45° reclined position (44). However, evidence of effectiveness of this exercise in head and neck cancer patients is not available yet. The SEA also avoids supine position, to increase feasibility and thus compliance to the exercises (19). Our results suggest that all muscles activated by the Shaker exercise (i.e., suprahyoid muscles, infrahyoid muscles and sternocleidomastoid muscles) were also activated by the SEA exercises indicating that the goal to find a substitute for the Shaker with a more feasible position is accomplished. Thus, application of the SEA both seems to targets more muscle groups, and likely increases compliance due to the more feasible upright position in which the exercises can be performed (19).

MfMRI with T2-maps is a non-invasive method to visualize muscle activation patterns during exercise. T2-mapping values are strongly correlated with results of electromyography, an invasive method to assess muscle activity (21-24). The hypothesis regarding the mechanism of increased T2-values after exercise, is that during exercise water shifts to the intracellular space

of the muscle mediated by osmosis increasing the amount of water molecules and therefore the T2-value (45). Since muscles activated with overload will strengthen, we may assume that exercises with the SEA results in strengthening of essential swallowing muscles (46).

Although increased T2-values can be interpreted as evidence for muscle activation, it is unknown what absolute increase in T2-value represents clinically meaningful muscle exertion expected to yield improvements in strength. Effects of the exercises on muscle strength should therefore further be objectified with other measuring instruments, such as the swallow muscle measuring system developed by Kraaijenga et al. (18). This instrument consists of a dynamometer mounted on the chin rest of an adapted ophthalmic examination frame enabling measurement of the effects of the CTAR+, and JOAR+ exercises. Additionally, the Iowa Oral Performance Instrument (IOPI) could be used to measure tongue strength, although intrinsic nor extrinsic tongue muscles seemed activated during exercises in this study (47).

Higher loading of individual muscles is more effective to quickly gain strength of those muscles, compared to lower loading. For patients with swallowing muscle strength below the minimum required strength to allow effective swallowing, this could translate into more effective rehabilitation on the level of muscle strength. It is, however, uncertain whether this will also lead to more effective swallowing rehabilitation in terms of clinical outcomes, as effective swallowing is not only dependent on the strength of individual muscles, but also, among other things, on intermuscular coordination. To demonstrate the added value of the SEA compared to conventional exercises, a randomized controlled trial is needed.

Limitations

Given the explorative nature of this study, the results presented have to be interpreted as inductive rather than conclusive. The T2-value is expected to increase substantially in activated muscles, and only a limited number of subjects was required for this study to indicate an effect with adequate precision. Nevertheless, the small sample size is still a limitation of this study as there is always a risk of atypical sampling. Also, again given this small sample size and the explorative nature of the study we refrained from correcting for multiple testing. However, our findings are largely consistent with expectations based on physiological understanding, which increases our confidence in the results. Still, we noted that in some muscles, the T2-value was lower after exercise, possibly due to variation between and within individuals or the measurements not being taken at the exact same position. Also, the used segmentation method included tissues other than muscle, such as blood vessels and fat. Therefore, concentration of non-muscular tissue might have influenced the susceptibility of T2-value increase after exercise. Another limitation is the supine position in which the exercises were performed in the scanner. Except for the Shaker, for which this is the prescribed position, the other exercises are supposed to be performed in upright position. The somewhat unnatural supine position may have caused the subjects to underperform, in which case effect sizes may have been underestimated.

CONCLUSION

Results of this explorative biomechanical study suggest that during conventional (Shaker) exercises, the suprahyoid, infrahyoid, and sternocleidomastoid muscles are activated. During exercises with the SEA, suprahyoid, infrahyoid, sternocleidomastoid, and lateral pterygoid muscles, are effectively targeted. These findings further support the potential of the SEA to improve swallowing rehabilitation using progressive resistance exercise.

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Chapter 7

From reactive to proactive tube feeding during chemoradiotherapy for head and neck cancer: a clinical prediction model-based approach

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ABSTRACT

Objectives: Feeding tubes are placed unnecessarily in a proportion of head and neck cancer (HNC) patients treated with chemoradiotherapy (CRT) when prophylactic tube placement protocols are used. This may have a negative impact on the risk of long-term dysphagia. Reactive tube placement protocols, on the other hand, might result in weight loss and treatment interruption. The objective of this study is to identify patients at risk for prolonged tube dependency in order to implement a personalized strategy regarding proactive tube placement.

Materials and Methods: A retrospective study was performed in a consecutive cohort of HNC patients treated with primary CRT for whom a reactive tube placement protocol was used. A prediction model was developed to predict prolonged (> 90 days) feeding tube dependency. Model performance and clinical net benefit of the model were assessed.

Results: Of the 336 included patients, 229 (68%) needed a feeding tube during CRT and 151 (45%) were prolonged feeding tube dependent. The prediction model includes the predictors pretreatment BMI, weight loss, Functional Oral Intake Scale and T-stage. Discriminatory ability is fair (area under the ROC-curve of 0.69) and calibration is adequate (Hosmer and Lemeshow test $p = .254$). The model shows net benefit over current practice for probability thresholds from 35–80%.

Conclusion: The developed model can be used to select patients for proactive feeding tube placement during primary CRT for HNC. The nomogram with easily obtainable parameters is a useful tool for clinicians to support shared decision making regarding proactive tube placement.

INTRODUCTION

Chemoradiotherapy (CRT) is widely used in advanced stage head and neck cancer (HNC). Common side effects of radiotherapy are dysphagia and weight loss (1), and concomitant chemotherapy increases the prevalence of these toxicities (2). Malnourishment and/or dehydration resulting from mucositis, loss of taste, xerostomia, and impaired swallowing function can cause feeding tube dependency in a proportion of patients during treatment (3). However, numerous studies have shown that still a considerable proportion of patients maintain their oral intake during CRT (4, 5).

Reactive feeding tube (RFT) placement, placement of a feeding tube (i.e., nasogastric tube (NGT) or a percutaneous radiological gastrostomy (PRG)) reactive to excessive weight loss (> 5% over three months or > 10% over six months), dehydration or aspiration, has a role in decreasing the incidence of (long-term) functional problems. Maintaining oral intake, along with targeted preventive exercises, prevents non-use atrophy of the swallowing muscles (6-9). This is therefore standard of care in HNC patients treated with CRT in the Netherlands Cancer Institute. Frequent monitoring of patients' oral intake is thereby mandatory to timely identify patients requiring a feeding tube to lower the risk of weight loss, dehydration and treatment interruption associated with RFT (10-13). On the other hand, prophylactic feeding tube placement may prevent this (14-16), but at the same time convicts all patients tube feeding, whereas this would be unnecessary in a substantial proportion.

Both protocols thus have advantages and disadvantages and it would be beneficial if one could predict whether a reactive or prophylactic approach would be most appropriate for a given patient (i.e., personalized medicine) (17). Predictive factors for tube placement and (prolonged) dependency have been identified (16, 18-27). These factors include radiotherapy variables, tumor and nodal stage, and weight loss prior treatment. However, a clinically applicable prediction model to select HNC patients treated with CRT for proactive tube feeding in high risk patients is, to our knowledge, still lacking.

Therefore, we hypothesized that clinical decision-making on proactive tube placement could be aided by a prediction model based on the known predictive factors. The model should enable accurate identification of patients at risk of prolonged (> 90 days) tube dependency during primary CRT. This would allow for a personalized strategy regarding proactive/reactive tube placement, feeding and supportive care (e.g., swallowing exercises).

MATERIALS AND METHODS

Ethical considerations

This study does not fall under de scope of the Medical Research Involving Human Subjects Act, which was confirmed by the medical research ethics committee of the Netherlands Cancer Institute (METC18.0589/N18TFC).

Patient selection

All patients treated with primary, cisplatin-based CRT for head and neck squamous cell carcinoma in the Netherlands Cancer Institute between January 2008 and October 2016, were included. Patients with previous treatment in the head and neck area (except neck dissections and skin malignancies), more than one primary tumor, or distant metastases were excluded.

Data collection

We extracted the following variables retrospectively from the medical file: gender, age, comorbidity including the Adult Comorbidity Evaluation-27 (ACE-27) index, tumor site-, T- and N-stage (AJCC 7th edition), general tumor stage, tumor human papilloma virus (HPV) status, tongue base involvement, and radiotherapy and chemotherapy doses. Clinical parameters, assessed prior to CRT at the first appointment, included Body Mass Index (BMI), weight loss (none, < or > 10% over six months), pain in the throat and/or mouth and dysphagia (patient-reported swallowing problems). Additionally, the Functional Oral Intake Scale (FOIS) was obtained, which is a validated tool reflecting functional oral intake, scored by health professionals on a seven-point ordinal scale with lower scores indicating more problems (1 = no oral intake; 7 = total oral intake without restrictions) (28). When not explicitly mentioned in the medical record, the FOIS was scored in retrospect. The timing of tube placement, tube type (nasogastric tube (NGT) or a percutaneous radiological gastrostomy (PRG)), and length of dependency were assessed, with time between tube placement and removal defined as length of dependency. Finally, neck dissections within the first 90 days after CRT were assessed.

Chemoradiotherapy, feeding tube policy and swallowing exercises

According to protocol, radiotherapy was given with 6 MV photons up to 70 Gray (Gy) in 35 fractions in seven weeks with sequential or simultaneous integrated boost according to the IMRT technique (either step and shoot or VMAT). Patients receiving sequential boost got an elective dosage of 46 Gy (23 fractions of 2 Gy) on the primary tumor and bilateral neck, with a total dosage of 70 Gy (35 fractions of 2 Gy) on the tumor and involved lymph nodes. Patients receiving simultaneous integrated boost were given an elective dosage of 54.25 Gy (35 fractions of 1.55 Gy) with a total dosage of 70 Gy (35 fractions of 2 Gy). Concurrent chemotherapy consisted of cisplatin. This was administered intravenously in low-dose (6mg/m^2 daily during the first five weeks of radiotherapy), intermediate-dose (40mg/m^2 weekly), or high-dose (100mg/m^2 at day 1, 22 and 43 of radiotherapy).

A reactive tube placement protocol was used for all patients, with placement reactive to excessive weight loss (>5% over three months or >10% over six months), dehydration or proven aspiration based on videofluoroscopy. Tubes are removed in case oral intake is adequate and/or aspiration is resolved. All patients are seen by the SLP and dietitian for clinical check-up and counseling before CRT and all were enrolled in the preventive swallowing exercise program according to the Institution's protocol (29). We expect high compliance to the program because of intensive monitoring by an SLP at least until 90 days post CRT.

Endpoint definition

The endpoint of the prediction model was prolonged feeding tube dependency, defined as placement of a tube (NGT or PRG) before the end of CRT, which stayed in situ for more than ninety days, because by that time the acute local treatment-related toxicities have subsided and ongoing functional impairment like xerostomia and dysgeusia have become more stable. Also, in all patients with a feeding tube the need for the tube is reassessed every two weeks by the dietitian.

Statistical analysis

Analyses were performed using IBM® SPSS® Statistics 23.0 and R 3.3.2 (30, 31). *P* values < .05 were considered statistically significant. Univariable logistic regression analysis was used to assess the association of baseline variables with prolonged feeding tube dependency in this sample. Subsequently, a multivariable logistic regression model was developed, for which we considered known predictors based on theoretical considerations and pre-existing evidence. These candidate predictors were T-stage, BMI, dysphagia, weight loss and FOIS. The FOIS was dichotomized (7 = normal diet and < 7 = abnormal diet) due to the low number of patients with scores < 7. Variables were not subject to selection based on statistical significance (32), but variables with a contradicting sign of the regression coefficient (i.e., contradicting current clinical knowledge and/or biological plausibility) were excluded from the model. Odds ratios (OR) with corresponding 95% confidence intervals (95% CI) and *p* values of the final model are presented. Linear predictor scores were calculated for use in calibration and discrimination analysis.

Discrimination and calibration were assessed to evaluate the performance of the model. The area under the receiver-operation characteristic (ROC) curve was estimated to assess discriminative ability (0.5 = no discriminative ability and 1.0 = perfect discrimination). From a value of 0.7, the discriminative ability of the model is fair. For calibration (agreement between predicted and observed probabilities), the goodness-of-fit test (Hosmer-Lemeshow test) was used, with *p* values >.05 indicating good calibration. Bootstrapping analysis with 200 samples was used to internally validate the model and estimate shrinkage factors per predictor for future use. A nomogram (with regression coefficients after shrinkage) is presented to easily estimate the probability of prolonged tube dependency per patient.

Clinical usefulness was examined by means of decision curve analysis (33). In this analysis, net benefit is calculated as the difference between true positive (i.e., tube placement justified) counts and false positive (i.e., tube placement not-justified) counts, weighted by the relative harm of a false-positive and false-negative result, over a range of threshold probabilities (pt). In the context of the current study, these threshold probabilities indicate the level of risk for long term feeding-tube dependency at which a patient or surgeon would opt for proactive placement. Net benefit can be interpreted as the increase in the proportion of patients receiving the appropriate treatment through use of the prediction model, compared to a situation in which all patients would (or would not) receive the treatment (34).

In a post-hoc secondary analysis, associations between prolonged tube dependency and timing of tube placement during CRT, and neck dissection within 90 days after CRT were assessed univariably.

RESULTS

Patient, tumor and treatment characteristics

Between January 2008 and October 2016, 449 patients were treated with cisplatin-based chemoradiotherapy for head and neck cancer in the Netherlands Cancer Institute. Of this consecutive cohort, 113 were excluded (postoperative CRT ($n = 34$), history of head and neck cancer ($n = 30$), more than one primary tumor ($n = 28$), induction chemotherapy ($n = 14$) and distant metastases ($n = 7$)). Of the final cohort ($n = 336$), most had stage IV disease (87%) and a pharyngeal tumor (86%). In 145 patients (43%), weight loss (less or more than 10%) was present before CRT. Problems with swallowing were reported by 150 patients (45%). Baseline FOIS was normal (7) in 231 patients (69%). The remaining 31% had FOIS 6 ($n = 35$), 5 ($n = 39$), 4 ($n = 21$) or 2 ($n = 1$). The FOIS was scored retrospectively in 226 patients (67%) according to structured and complete reporting of the speech language pathologist (SLP) and/or dietitian. Patient, tumor and treatment characteristics are presented in Table 1a and 1b.

Tube feeding

Of the 336 patients, 229 (68%) received tube feeding during CRT with dependencies ranging from 3–2185 days. Of these 229 patients, 161 patients (70%) received an NGT, of which 112 were converted to a PRG, and 68 patients (30%) only received a PRG. Median dependency was 59 days (range 3–216 days) for patients who only received an NGT, 161 days (range 56–2185 days) for who received an NGT with conversion to a PRG, and 171 days (range 6–1142 days) for who directly received a PRG. In 151 patients (45%) prolonged (> 90 days) tube feeding was needed and 81 patients (24%) needed the tube longer than 180 days. At 90 days post CRT 11 patients (7 (64%) with a tube in situ) had died of pneumonia ($n = 2$), oral bleeding ($n = 1$), multi-organ failure ($n = 1$), progressive disease ($n = 2$), diverticulitis/sepsis ($n = 1$), and in four cases cause of death was unknown.

Figure 1 shows the number of tube placements per week of CRT and the percentage prolonged placements. Of the 41 and 18 patients who started tube feeding before and in the first week of CRT respectively, 55 (93%) became prolonged dependent. Of these 55 patients, 28 (51%) initially received an NGT, which was later converted to a PRG. Most patients received their tube in the fourth week of CRT ($n = 47$) of whom 62% became prolonged dependent.

Table 1a Patient and tumor characteristics with univariable analysis presented in odds ratios and *p* values. Boldfaced *p* values are significant.

		Number of patients (%)				Univariable analysis	
		> 90 days feeding tube dependent (*n*=151)	< 90 days feeding tube dependent (*n*=185)	Total (*n*=336)		OR (95% CI)	*p* value
Length of tube feeding (days) Median (range)		196 (91–2185)	0 (0–89)	77 (0–2185)		-	-
PATIENT CHARACTERISTICS							
Gender							.191
	Male	102 (68)	137 (74)	239 (71)	Male	1.00	
	Female	49 (33)	48 (26)	97 (29)	Female	1.37 (0.85–2.20)	
Age (years) Mean (SD)		60 (9)	60 (10)	60 (9)		1.00 (0.97–1.02)	.695
ACE-27							.409
	0	51 (34)	78 (42)	129 (38)	0	1.00	
	1	55 (36)	60 (32)	115 (34)	1	1. 40 (0.84–2.33)	.193
	2	36 (24)	35 (19)	71 (21)	2	1.57 (0.88–2.82)	.128
	3	9 (6)	12 (7)	21 (6)	3	1.15 (0.45–2.92)	.773
TUMOR CHARACTERISTICS							
Tumor site							.432
	Oral cavity	11 (7)	7 (4)	18 (5)	Oral cavity	1.00	
	Oropharynx	79 (52)	107 (58)	186 (55)	Oropharynx	0.47 (0.17–1.27)	.135
	Nasopharynx	17 (11)	22 (12)	39 (12)	Nasopharynx	0.49 (0.16–1.54)	.222
	Hypopharynx	34 (23)	31 (17)	65 (19)	Hypopharynx	0.70 (0.24–2.03)	.508
	Larynx	9 (6)	15 (8)	24 (7)	Larynx	0.38 (0.11–1.34)	.133
	Nose/paranasal sinus	1 (1)	3 (2)	4 (1)	Nose/ paranasal sinus	0.21 (0.02–2.47)	.215
T-stage							**.003**
	T1	11 (7)	28 (15)	39 (12)	T1	1.00	
	T2	24 (16)	46 (25)	70 (21)	T2	1.33 (0.57–3.12)	.515
	T3	45 (30)	56 (30)	101 (30)	T3	2.05 (0.92–4.55)	.080
	T4	71 (47)	55 (30)	126 (38)	T4	3.29 (1.50–7.18)	**.003**
N-stage							.197
	N0	19 (13)	19 (10)	38 (11)	N0	1.00	
	N1	11 (7)	27 (15)	38 (11)	N1	0.41 (0.16–1.05)	.063
	N2	111 (74)	125 (68)	236 (70)	N2	0.89 (0.45–1.76)	.734
	N3	10 (7)	14 (8)	24 (7)	N3	0.71 (0.26–2.00)	.522
Tumor stage							.096
	Stage II	2 (1)	1 (1)	3 (1)	Stage II/III	1.00	
	Stage III	13 (9)	29 (16)	42 (13)	Stage IV	1.76 (0.91–3.40)	
	Stage IV	136 (90)	155 (84)	291 (87)			

Table 1a Continued

		Number of patients (%)				Univariable analysis	
		> 90 days feeding tube dependent (*n*=151)	< 90 days feeding tube dependent (*n*=185)	Total (*n*=336)		OR (95% CI)	*p* value
HPV status							.094
	Negative	66 (44)	78 (42)	144 (43)	Negative	1.00	
	Positive	24 (16)	47 (25)	71 (21)	Positive	0.60 (0.33–1.09)	
	Unknown	61 (40)	60 (32)	121 (36)			
Tongue base involved							.456
	No	95 (63)	109 (59)	204 (61)	No	1.00	
	Yes	56 (37)	76 (41)	132 (39)	Yes	0.85 (0.54–1.32)	

NB: Not all percentages sum up exactly to 100% due to rounding.

Abbreviations: ACE-27 = Adult Comorbidity Evaluation-27, CI = confidence interval, FOIS = Functional Oral Intake Scale, OR = odds ratio, SD = standard deviation.

Table 1b Treatment characteristics and clinical parameters with univariable analysis presented in odds ratios and *p* values. Boldfaced *p* values are significant.

		Number of patients (%)				Univariable analysis	
		> 90 days feeding tube dependent (*n*=151)	< 90 days feeding tube dependent (*n*=185)	Total (*n*=336)		OR (95% CI)	*p* value
TREATMENT CHARACTERISTICS							
High dose irradiation on bilateral neck							.534
	No	88 (58)	114 (62)	202 (60)	No	1.00	
	Yes	63 (42)	71 (38)	134 (40)	Yes	1.15 (0.74–1.78)	
Planned dose chemotherapy							.965
		41 (27)	48 (26)	89 (27)	Low	1.00	
	Intermediate	3 (2)	4 (2)	7 (2)	Intermediate	0.88 (0.19–4.15)	.870
	High	107 (71)	133 (72)	240 (71)	High	0.94 (0. 58–1.54)	.810
CLINICAL PARAMETERS (OBTAINED PRIOR TO CRT)							
BMI Mean (SD)		23.3 (4.5)	25.4 (4.4)	24.5 (4.6)		0.89 (0.85–0.94)	**<.001**
Pretreatment weight loss							**<.001**
	No	65 (43)	126 (68)	191 (57)	No	1.00	
	< 10%	46 (31)	46 (25)	92 (27)	< 10%	1.94 (1.17–3.22)	**.010**
	> 10%	40 (27)	13 (7)	53 (16)	> 10%	5.96 (2.98–11.94)	**<.001**

Table 1b Continued

	Number of patients (%)				Univariable analysis	
	> 90 days feeding tube dependent (*n*=151)	< 90 days feeding tube dependent (*n*=185)	Total (*n*=336)		OR (95% CI)	*p* value
Pretreatment pain						**.013**
No	59 (39)	97 (52)	156 (46)	No	1.00	
Yes	92 (61)	87 (47)	179 (53)	Yes	1.74 (1.12–2.69)	
Unknown	0 (0)	1 (1)	1 (0)			
Pretreatment dysphagia						**.001**
No	68 (45)	118 (64)	186 (55)	No	1.00	
Yes	83 (55)	67 (36)	150 (45)	Yes	2.15 (1.39–3.33)	
Pretreatment FOIS						**<.001**
7 (normal diet)	83 (55)	148 (80)	231 (69)	7	1.00	
6	18 (12)	17 (9)	35 (10)	< 7	3.36 (2.05–5.51)	
5	27 (18)	12 (7)	39 (12)			
4	16 (11)	5 (3)	21 (6)			
2	1 (1)	0 (0)	1 (0)			
Unknown	6 (4)	3 (2)	9 (3)			

NB: Not all percentages sum up exactly to 100% due to rounding.

Abbreviations: CI = confidence interval, FOIS = Functional Oral Intake Scale, OR = odds ratio, SD = standard deviation.

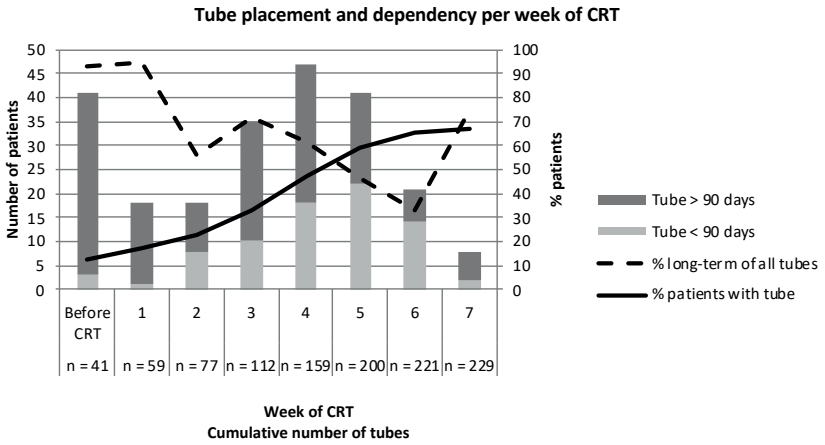

Figure 1 Left y-axis: Number of tube placements (< and > 90 days in situ) per week of CRT Right y-axis: Percentages of patients with a tube and percentage of prolonged (> 90 days) tube placements of all tube placements. Cumulative numbers of patients with tubes below x-axis.

Univariable analysis

Univariable logistic regression analysis indicated that T4-stage tumor (OR 3.29; 95% CI 1.50–7.18, $p = .003$), initially lower BMI (per 1 unit increase OR 0.89; 95% CI 0.85–0.94, $p < .001$), weight loss over the past six months (< 10% OR 1.94; 95% CI 1.17–3.22, $p = .010$ and > 10% OR 5.96; 95% CI 2.98–11.94, $p < .001$), pain (OR 1.74; 95% CI 1.12–2.69, $p = .013$), dysphagia (OR 2.15; 95% CI 1.39–3.33, $p = .001$) and an FOIS below 7 (OR 3.36; 95% CI 2.05–5.51, $p < .001$) were associated with an increased risk of prolonged feeding tube dependency (Table 1a and 1b).

Risk prediction model

The initial multivariable model included the known predictors T-stage, BMI, dysphagia, weight loss and the FOIS. The regression coefficient of dysphagia was -0.09 (SE 0.32) and was therefore excluded from the final model. Statistically significant prediction in the final model were BMI (OR 0.93; 95% CI 0.88–0.99, $p = .019$) and > 10% weight loss over the last six months before treatment (OR 2.66; 95% CI 1.15–6.39, $p = .024$) (see Table 2).

Table 2 Multivariable logistic regression analysis with prolonged (> 90 days) feeding tube dependency as outcome presented in odds ratios and *p* values. Boldfaced *p* values are significant. The regression coefficients and shrinkage factors assessed by bootstrap analysis with 200 repetitions are also presented.

		Multivariable analysis		Regression coefficient (SE)	Shrinkage factor (SE)
		OR (95% CI)	*p* value		
T-stage	T1	1.00			
	T2	1.16 (0.48–2.90)	.750	0.15 (0.46)	-0.012 (0.544)
	T3	1.46 (0.64–3.54)	.381	0.38 (0.44)	-0.025 (0.516)
	T4	2.07 (0.92–4.91)	.087	0.73 (0.43)	-0.005 (0.488)
BMI (1 unit increase)		0.93 (0.88–0.99)	**.019**	-0.07 (0.03)	-0.002 (0.034)
Weight loss	No	1.00			
	< 10%	1.43 (0.82–2.48)	.207	0.36 (0.28)	0.009 (0.296)
	> 10%	2.66 (1.15–6.39)	**.024**	0.98 (0.43)	0.051 (0.492)
FOIS	7	1.00			
	< 7	1.72 (0.94–3.14)	.076	0.54 (0.31)	0.018 (0.308)

Abbreviations: BMI = body mass index, CI = confidence interval, FOIS = Functional Oral Intake Scale, OR = odds ratio, SE = standard error.

Model performance

The area under the ROC-curve was 0.69 indicating fair discrimination (see Figure 2). The Hosmer and Lemeshow test showed agreement between predicted and observed probabilities within risk strata, indicating adequate calibration ($p = .254$).

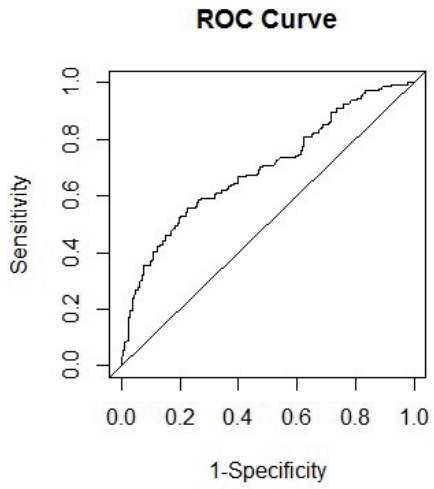

Figure 2 Discriminative ability of the model displayed in an ROC-curve. Area under the ROC-curve is 0.69.

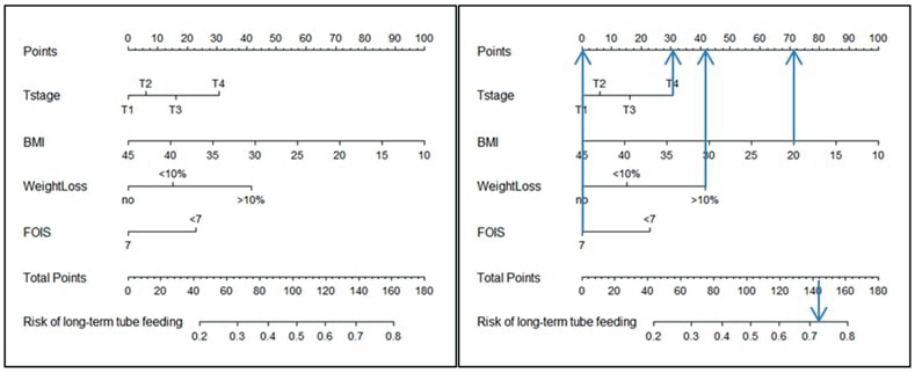

Figure 3 Left: Nomogram of prediction model. With this nomogram the risk of tube feeding can easily be calculated for each patient by drawing a line from the line of each predictor to the points-scale at the top of the nomogram. If these points are added, a line from the total points scale below to the risk of tube feeding scale can be drawn to obtain the risk of prolonged tube feeding. Right: Patient example with T4 tumor, BMI of 20, > 10% weight loss and an FOIS of 7. Risk of prolonged feeding tube dependency is 73%.

Decision curve analysis

Figure 4 represents the net benefit of applying the model for each risk threshold. The decision curve shows that the prediction model has net benefit over current practice which includes reactive feeding tube placement (treat none), for probability thresholds from 35–80%.

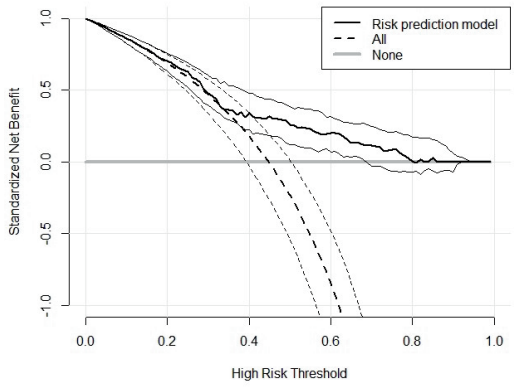

Figure 4 Decision curve analysis. Solid black line: Net benefit of risk prediction model relative to reactive feeding tube placement protocol in all patients with 95% confidence intervals. Dashed black line: Net benefit of providing all patients a prophylactic feeding tube or treat all with 95% confidence intervals ("All"). Solid grey line: Reference, reactive feeding tube placement protocol in all patients or treat none ("None"). The decision curve shows that the prediction model has net benefit for risks from 35–80% over current practice which includes reactive feeding tube placement (treat none).

Influence of factors after (start of) CRT

Timing of placement is associated with prolonged tube dependency. Patients who received a tube before or in the first week of CRT ($n = 59$) have a higher risk of prolonged tube dependency (OR 25.92; 95% CI 9.12–73.69, $p < .001$). Per day later after start of CRT, patients have a lower risk of prolonged tube dependency (OR 0.95; 95% CI 0.93–0.97, $p < .001$).

Patients who received a neck dissection within the first 90 days after CRT ($n = 8$) did not have a significantly higher risk of prolonged feeding tube dependency (OR 2.08; 95% CI 0.49–8.84, $p = .322$), however, group size was small.

DISCUSSION

The aim was to develop a prediction model to estimate the risk of prolonged (> 90 days) feeding tube dependency, which can be helpful in deciding on proactive tube placement for patients receiving primary CRT for HNC. In univariable analysis, T4-stage tumor, BMI, weight loss, pain, dysphagia and FOIS below 7 were significant risk factors. The multivariable prediction model included T-stage, BMI, weight loss, and FOIS which resulted in a model with fair discriminative ability and adequate agreement between predicted and observed probabilities.

The model and corresponding nomogram include easily obtainable parameters and are therefore a practical tool for clinicians to estimate the risk of prolonged feeding tube dependency. This aids in shared decision making regarding proactive placement in high risk patients, preventing treatment interruption with benefits on tumor control (35). Identifying low risk patients can prevent unnecessary tube placements, reducing complications of placement (e.g., infection, bleeding, and perforation), reducing costs and preventing non-use atrophy of swallowing muscles (36). With a shift from authority-based medicine towards shared decision-based practice, the estimated risk can be used to inform patients and make educated decisions (37).

To assess the clinical net benefit of decisions based on the prediction model, decision curve analysis was performed (33). This analysis showed that a decision regarding proactive placement based on the model instead of providing all or no patients a prophylactic tube, has net benefit for probability thresholds between 35 and 80%. Since this falls within a plausible range of probability thresholds likely to be considered by clinicians and patients, we assume use of the model has clinical benefit in most cases. For patients or clinicians who would consider proactive placement at probability thresholds below 35% however, a treat all policy would yield the same net benefit (33).

Patients who receive a feeding tube before the start of CRT have an increased risk on prolonged feeding tube dependency. The vast majority (n = 55/59; 93%) of patients who received a feeding tube before or in the first week of CRT became prolonged feeding tube dependent. We therefore advise to directly place a PRG instead of an NGT in these patients, avoiding the disadvantages of an NGT including discomfort, prolonged feeding times, shorter tube lifetime and cosmetic grievances. This study also supports a reactive approach, since the later the placement, the lower the risk of prolonged dependency, thus optimal patient support to maintain oral intake along with preventive swallowing exercises seems to make earlier return to oral intake more likely.

Several studies have investigated predictive factors for prolonged feeding tube dependency in patients treated with CRT for advanced HNC (16, 18, 20, 22, 23, 25, 26). The predictors found in our study were broadly in accordance with these studies except for the predictors dysphagia, nodal stage and high dose bilateral neck irradiation. Firstly, pre-existing (subjective) dysphagia

was a consistent predictive factor in other studies (16, 24, 25). In our study, univariable analysis showed a significant association but this association was no longer present in multivariable analysis. An explanation for this might be that in some previous studies dysphagia was assessed by means of validated questionnaires whereas in our study the variable was less reliably obtained from notes in the medical file.

The second consistent predictive factor for tube dependency in literature is advanced nodal stage (16, 22, 25, 26, 38). The influence of this factor could not be estimated in our cohort due to the lack of variation among nodal stages (70% of the patients had stage N2). This, however, will most likely not influence generalizability because the other variables in the model are independent predictive factors.

Previous studies suggest a predictive value of radiotherapy dose [16, 26, 39]. We, however, did not use parameters such as bilateral neck irradiation or constrictor dose as predictors, because we aimed to develop a prediction model based on readily available clinical parameters, easy to use in daily practice. Despite the advantage of this model concept, the absence of such radiotherapy data has to be considered one of the limitations of this study.

A few studies have made an attempt at predicting the risk on prolonged tube feeding dependency (19, 21, 27, 39). In contrast to ours, these included heterogeneous populations with regard to tumor stage and treatment modalities with only a proportion of patients being treated with primary CRT (17-60%), which compromises their generalizability to the CRT population. Also, all studies included patients who received a prophylactic feeding tube, which puts them at risk for selection bias.

The strengths of this study include the large dataset with all patients treated with primary CRT for a broad range of tumor localizations compared to previously published work, which enables the construction of an accurate prediction model. Also, a reactive placement protocol was used for all patients. In case a prophylactic placement strategy would have been applied in a proportion of patients, the risk of selection bias would have been high.

Limitations of the study include its retrospective nature. We do not think that the results are affected by this because the number of missing variables was low and most likely random. A prospective study design is preferred in developing a prediction model. However, considerable amount of time is needed to include sufficient patients prospectively. The current data is therefore the best available and the only way to enable risk estimation of prolonged feeding tube dependency. Another limitation of this study is the lack of consistent criteria used in practice to decide the timing of tube feeding, which contributed to disagreement of observed and predicted probabilities. Moreover, some misclassification of high and low risk patients can also be explained by patients who refused tube feeding.

The model was developed for use with patients receiving primary CRT and all included patients were offered preventive swallowing exercises. Given the specific population for which the model is intended (advanced head and neck cancer patients with CRT, all enrolled in a preventive exercise program), we would not recommend using it for clinical decision making tool with patients receiving other HNC-treatment, unless with utmost caution.

The same data was used to develop as well as evaluate the model. Ideally, future research includes external validation of the models discrimination, calibration and net benefit, in comparable as well as more heterogeneous populations. However, since the currently presented model is the best available evidence and its application is not associated with serious risks, in our view the model can be used in clinical practice prior to external validation to provide the clinician with an estimation of the risk.
The risk on prolonged feeding tube dependency may also be influenced by timing of tube placement and by other factors that are not known prior CRT, such as weight loss and mucositis evolving during treatment. Future research should look into the value of including such factors as predictors in a time-updated risk prediction model, which allows for recalculation of the risk at each moment in time, by incorporating the change in clinical status.

CONCLUSION

The developed risk prediction model can be used to select patients for proactive feeding tube placement during primary CRT for HNC. The nomogram with easily obtainable parameters is a useful tool for clinicians to estimate the risk on prolonged feeding tube dependency to support shared decision making regarding tube placement.

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Chapter 8

Sarcopenia, a strong determinant for prolonged feeding tube dependency after chemoradiotherapy for head and neck cancer

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ABSTRACT

Background: Sarcopenia might be a relevant lead for optimization of head and neck cancer (HNC) patients' condition before chemoradiotherapy to prevent long-term functional swallowing impairment, such as feeding tube dependency.

Methods: Regression analyses were performed to assess the association between skeletal muscle mass index (SMI), as a measure of sarcopenia, and prolonged (> 90 days) feeding tube dependency in 128 HNC patients treated with primary chemoradiotherapy.

Results: 61 patients (48%) became prolonged feeding tube dependent. Lower SMI increased the risk of prolonged feeding tube dependency in multivariable analysis (RR 1.08; 95% CI 1.02–1.14, $p = .013$) adjusted for body mass index, abnormal diet and socioeconomic status.

Conclusions: Sarcopenia contributes to the risk of prolonged feeding tube dependency of HNC patients treated with primary CRT. Since sarcopenia might be a modifiable factor prior to treatment, it should be explored as a target for pretreatment patients' condition.

INTRODUCTION

Sarcopenia is a condition characterized by loss of skeletal muscle mass (1). It is mainly prevalent in the elderly, but also occurs in younger patients with diseases that affect mobility and nutrition (2). Most retrospective studies on sarcopenia in cancer patients consider CT assessed skeletal muscle mass only, as muscle function tests are often not available (3). In several cancer types, pretreatment sarcopenia is associated with inferior treatment outcomes (4) including postoperative complications (5, 6) and treatment-related toxicity (7, 8). Recent studies confirm this association in head and neck cancer (HNC) with regard to treatment outcomes (i.e., chemotherapy dose-limiting toxicity) and survival after concomitant chemoradiotherapy (CRT) and postoperative complications including pharyngocutaneous fistula after total laryngectomy (9-15). There is a paucity of information, however, on the influence of sarcopenia on functional outcomes.

One of the most important functional outcomes for patients with head and neck cancer is swallowing function, which is often compromised after CRT, due to an often multifactorial etiology (16). First, the extent of tumor and treatment disrupt normal swallowing physiology, and with more extensive tumor and treatment the risk for developing swallowing problems is increased (17-24). Second, poor nutritional status can also contribute to swallowing dysfunction, due to loss of muscle mass and function (19-24). As a result of swallowing dysfunction, a substantial proportion (50-70%) of patients becomes feeding tube dependent during CRT (23). Due to the decline in swallowing muscle activity, non-use atrophy of these muscles is inevitable, which is associated with further loss of swallowing muscle mass and function (23, 25-28). Sarcopenia could be a factor worsening this vicious spiral by co-causing long-term swallowing dysfunction, as patients suffering from sarcopenia have limited reserves with regard to muscle mass and function. Consequently, in these patients, non-use atrophy of the swallowing muscles may even sooner lead to prolonged functional impairment (29, 30).

Results from studies among patients with other cancer types suggest that pretreatment optimization of functional status, also known as prehabilitation, may improve functional outcomes (31, 32). In HNC patients, prehabilitation interventions prior to CRT could include exercise programs targeting the swallowing muscles in combination with nutritional interventions. Especially focusing on high-risk patients for prehabilitation interventions to increase benefit has been suggested in the literature (33). A better understanding of the relationship between pretreatment sarcopenia and risk of long-term swallowing impairment and feeding tube dependency will help identify which patients might benefit from targeted interventions, as well as provide clues to the type of interventions to be used.

Therefore, the objective of this study was to assess the direct relationship of pretreatment sarcopenia with prolonged feeding tube dependency in patients treated with primary CRT for HNC.

MATERIALS AND METHODS

Ethical considerations

This retrospective cohort study was approved by the Institutional Review Board of the Netherlands Cancer Institute (IRB18.374/IRBd18105). As this was a retrospective study based on chart review, no (written) informed consent was necessary.

Patient selection

A consecutive cohort of 128 patients treated with primary high-dose cisplatin-based CRT for a primary head and neck squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx or larynx in the Netherlands Cancer Institute from February 2008 to December 2015 was used for the analysis. Patient characteristics are presented in Table 1. Of the cohort of 128 patients, 90 (70%) were male, the mean age was 59 years (SD 7, ranging from 42 to 73) and 58 patients (45%) had an Adult Comorbidity Evaluation-27 (ACE-27) of 0. Most patients (i.e., 78, 61%) had an oropharyngeal carcinoma and 106 (83%) had stage IV disease. Ten patients (8%) lost more than 10% of their weight prior CRT and 33 (26%) had an abnormal diet (FOIS < 7) prior CRT.

Chemoradiotherapy treatment

According to protocol, all patients were immobilized during radiotherapy planning and treatment in supine treatment position in a custom-made head-and-neck mask. For planning, contrast-enhanced CT-scan simulation was performed. All patients were treated with intensity-modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT). The radiation dose consists of 70 Gy to the primary tumor and the involved node(s) in N+ disease, given in 2 Gy per fraction, 5 fractions a week. Elective irradiation of the neck was given to a dose of 46 Gy in 23 fractions in case of sequential boost and to 54.25 Gy in 35 fractions in case of concomitant boost. Concomitant cisplatin was added to the radiotherapy in case of locally-advanced disease (T3/4, N2c/N3) or extra-capsular extension as assessed at MRI. Patients were scheduled for a 3-weekly intravenous high-dose concomitant cisplatin (100 mg/m^2 on days 1, 22, and 43 of radiotherapy).

Table 1 Patient characteristics.

		Number of patients (%)		
		< 90 days feeding tube dependent (*n* = 67)	> 90 days feeding tube dependent (*n* = 61)	Total cohort (*n* = 128)
Gender	Male	46 (69)	44 (72)	90 (70)
	Female	21 (31)	17 (28)	38 (30)
Age (years) Mean (SD)		60 (44–71)	61 (42–73)	59 (7)
ACE-27	0	34 (51)	24 (39)	58 (45)
	1	22 (33)	23 (38)	45 (35)
	2	7 (10)	12 (20)	19 (15)
	3	4 (6)	2 (3)	6 (5)
Tumor site	Oral cavity	0 (0)	1 (2)	1 (1)
	Oropharynx	44 (66)	34 (56)	78 (61)
	Hypopharynx	17 (25)	22 (36)	39 (31)
	Larynx	6 (9)	4 (7)	10 (8)
T classification	T1	8 (12)	5 (8)	13 (10)
	T2	23 (34)	15 (25)	38 (30)
	T3	23 (34)	16 (26)	39 (31)
	T4	13 (19)	25 (41)	38 (30)
N classification	N0	10 (15)	6 (10)	16 (13)
	N1	11 (16)	5 (8)	16 (13)
	N2	45 (67)	46 (75)	91 (71)
	N3	1 (2)	4 (7)	5 (4)
TNM stage	Stage II	0 (0)	2 (3)	2 (2)
	Stage III	15 (22)	5 (8)	20 (16)
	Stage IV	52 (78)	54 (89)	106 (83)
BMI Mean (SD)		25 (15–35)	23 (16–33)	24 (4)
Pretreatment weight loss	No	51 (76)	29 (48)	80 (63)
	< 10%	16 (24)	22 (36)	38 (30)
	> 10%	0 (0)	10 (16)	10 (8)
Pretreatment FOIS	7 (normal diet)	59 (88)	36 (59)	95 (74)
	< 7	8 (12)	25 (41)	33 (26)
Prolonged feeding tube dependent	No	NA	NA	67 (52)
	Yes	NA	NA	61 (48)
Neck SMI Median (min–max)		13 (9–22)	12 (8–16)	12 (8–22)
Low neck SMI < 12.7	No	38 (57)	17 (28)	55 (43)
	Yes	29 (43)	44 (72)	73 (57)
Socioeconomic status Mean status score (SD)		0.2 (1.1)	0.1 (1.2)	0.1 (1.1)

NB: Not all percentages sum up exactly to 100% due to rounding.

Abbreviations: ACE-27 = Adult Comorbidity Evaluation-27, FOIS = Functional Oral Intake Scale, NA = not applicable, SD = standard deviation, SMI = skeletal muscle index.

Tube placement policy, nutritional policy and swallowing exercises

None of the patients received prophylactic tube feeding (23). Feeding tube placement was either advised to patients or deemed necessary for treatment completion in case of excessive weight loss (> 5% of baseline body weight in three months or > 10% in six months), insufficient oral intake (< 50% of recommended daily calories and protein), dehydration or proven aspiration based on videofluoroscopy at baseline or during the course of CRT. For patients who received a feeding tube, bi-weekly consultations were planned to evaluate weight, possible side effects of the enteral nutrition and oral intake. According to Institution's protocol, all patients were seen by a speech language pathologist and dietitian for clinical check-up and counseling before CRT. All patients were enrolled in a prophylactic swallowing exercise program before treatment (34), and all were advised to take 1.5 g/kg of protein per day and a caloric intake according to the Harris-Benedict 1984 equation with an addition of 30% for disease, up to a BMI of 30 (35).

Data collection

We collected the following variables retrospectively from the medical file: gender, age at diagnosis, comorbidity including the Adult Comorbidity Evaluation-27 (ACE-27) index, tumor site, T and N classification, general tumor (TNM) stage, pretreatment Body Mass Index (BMI), pretreatment weight loss (none, less or more than 10% over the past six months compared to baseline), and pretreatment Functional Oral Intake Scale (FOIS) (scored retrospectively when not available). The FOIS reflects the functional oral intake on a seven-point ordinal scale with a score of 7 indicating a normal diet without restrictions (36). Also, timing of feeding tube placement and duration of dependency were assessed. Prolonged dependency was defined as a tube in situ for more than ninety days after tube placement (nasogastric tube or percutaneous gastrostomy) at any time before or during CRT. This cut-off was chosen based on the consideration that after ninety days, acute local treatment-related toxicities have subsided and ongoing functional impairments can be considered chronic. Socioeconomic status (SES) was assessed by means of status scores according to postal codes with 0 being the mean status score in The Netherlands in 2017 (37). Negative and positive scores indicate SES below and above the mean, respectively.

Measurement of skeletal muscle mass

Skeletal muscle mass was measured on a routinely performed CT scan of the head and neck area using a previously described protocol (see Figure 1). A single CT slice at the level of C3 was selected for skeletal muscle mass measurement. First, the cross-sectional muscle areas (CSMA) of the paravertebral and sternocleidomastoid muscles at the level of the third cervical vertebra (C3) were segmented on the pretreatment head and neck CT scan (38). The total skeletal muscle area at the level of C3 was defined as the CSMA of the paravertebral muscles and the left and right sternocleidomastoid muscles (total CSMA). The total CSMA was then normalized for height in meters, in a similar method compared to research in other cancer types, to calculate the neck skeletal muscle index (39). Lower values of the neck SMI indicate lower skeletal muscle mass. All CT scans were segmented using Worldmatch, an in-house developed radiotherapy planning and image evaluation software tool.

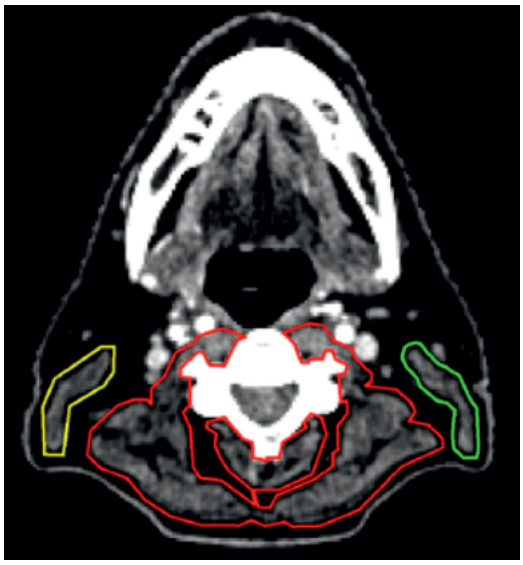

Figure 1 Delineated CT-slide at C3 level

Statistical analysis

Analyses were performed using IBM® SPSS® Statistics 23.0 and R 3.3.2 (40, 41). *P* values < .05 were considered statistically significant. Univariable Poisson regression analysis with a log link was used to assess the crude and adjusted associations of neck SMI and prolonged feeding tube dependency in this sample, which we report as risk ratios (RR), with 95% confidence intervals (CI) and corresponding p values based on robust (sandwich) errors (42).

In the multivariable analysis, the relationship was estimated adjusting for the most relevant confounders. During a consensus meeting a Directed Acyclic Graph (DAG) was constructed to identify potential confounders and mediators (see Figure 2). From the available data, potential confounders and mediators were chosen based on information from previous studies, and expert opinion. The DAG indicated that, to estimate the direct effect of SMI on prolonged feeding tube dependency, the minimal set of adjustment covariables included BMI, FOIS, and SES. To assess the extent to which the effect of neck SMI of prolonged feeding tube dependency was mediated by BMI, the relation was also estimated without adjusting for BMI.

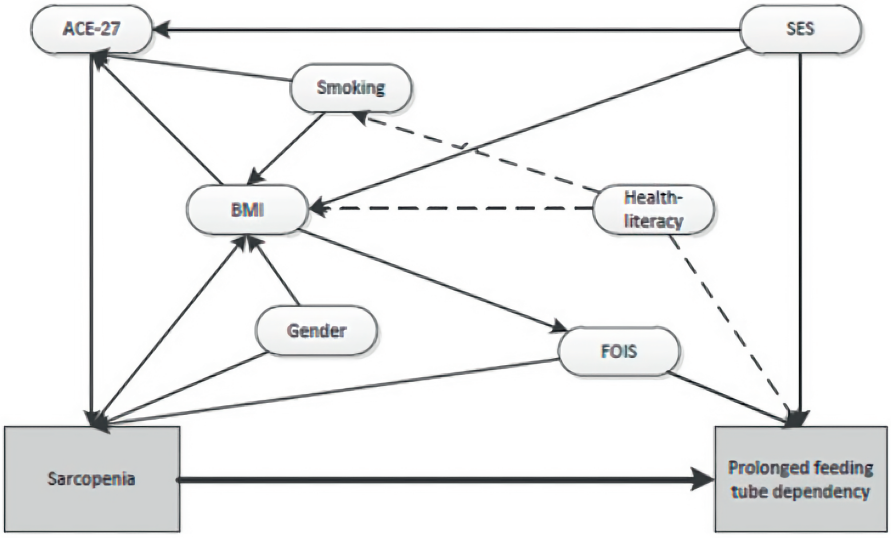

Figure 2 Directed acyclic graph with confounders and mediators in the relation between sarcopenia and prolonged feeding tube dependency. Arrows indicate direction of effect. Dotted arrows indicate direction of effect for unavailable confounder (health literacy). BMI, body mass index; FOIS, functional oral intake scale; SES, socioeconomic status.

Cut-off for sarcopenia

Since no normal values of the neck SMI exist, the optimal cut-off value of the neck SMI for predicting prolonged tube feeding was determined using the Youden point of the receiver operating characteristic (ROC) curve of neck SMI versus prolonged feeding tube dependency. To obtain an indication for clinical usefulness of pretreatment neck SMI measurements, the number of patients below this cut-off value (indicating sarcopenia) was assessed, stratified by their (predicted) probability on prolonged (> 90 days) feeding tube dependency according to our previously published prediction model (23). This model included the clinical predictors FOIS, BMI, weight loss and T classification and had the following formula: $Y = 0.617 + (0.145 \cdot T2 + 0.382 \cdot T3 + 0.727 \cdot T4) + (-0.067 \cdot BMI) + (0.543 \cdot FOIS < 7) + (0.356 \cdot \text{weight loss} < 10\% + 0.980 \cdot \text{weight loss} > 10\%)$.

RESULTS

The median neck SMI was 12 (range 8–22) and 61 patients (48%) became prolonged feeding tube dependent (see Table 1).

Sarcopenia and prolonged feeding tube dependency

Neck SMI was a significant prognostic factor for prolonged feeding tube dependency in univariable analysis, with lower SMI increasing the risk (RR 1.10; 95% CI 1.06–1.15, $p < .001$). The RR after adjustment for BMI, FOIS and SES was largely similar with a RR of 1.08 (95% CI 1.02–1.14, $p = .013$) (see Table 2). This translates to a 26% relative risk increase for prolonged feeding tube dependency per interquartile range decrease in SMI (from 14 to 11). When not adjusting for the mediating effect of BMI, the adjusted RR was 1.09 (95% CI 1.04–1.14, $p = .001$).

Table 2 Results of multivariable Poisson regression analysis with no prolonged (> 90 days) feeding tube dependency as outcome presented in risk ratios and p values.

		Multivariable analysis	
		RR (95% CI)	*p* value
Neck SMI		1.08 (1.02–1.14)	.013
BMI		1.01 (0.97–1.06)	.634
SES		1.08 (0.91–1.27)	.378
FOIS	7	1.00	
	< 7	0.44 (0.24-0.80)	.008

Cut-off value for sarcopenia

The cut-off value of neck SMI in predicting prolonged feeding tube dependency with optimal sensitivity/specificity ratio was 12.7 (area under the ROC-curve 0.64, sensitivity 72%, and specificity 57%). Seventy-three patients (57%) had a neck SMI below this cut-off, indicating sarcopenia with regard to this outcome. The number of patients with a low neck SMI stratified by predicted probability on prolonged (> 90 days) feeding tube dependency according to our previously published prediction model are presented in Figure 3. The higher the predicted probability, the higher the proportion of patients with a low neck SMI. Of the 31 patients with a predicted probability below or equal to 30%, 8 (26%) had a neck SMI below the cut-off value (median SMI 13, range 9–22), compared to a 49 of the 80 patients (61%) with a predicted probability between 30-60% (median SMI 12, range 9–21), and 16 of the 17 (94%) of the patients above 60% (median SMI 11, range 8–13). All of the 16 patients who had a predicted probability above 60% and a neck SMI below the cut-off value became prolonged feeding tube dependent and all had their tubes placed either before ($n = 9$) or in the first four weeks of treatment ($n = 7$).

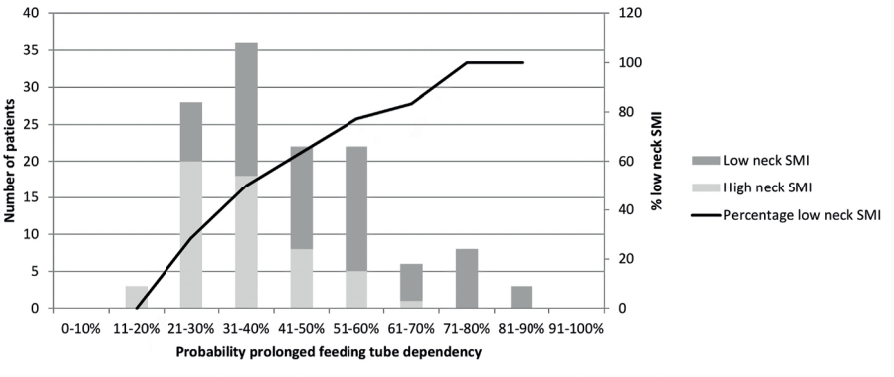

Figure 3 Number of patients with high and low neck SMI per predicted probability of prolonged feeding tube dependency according to the prediction model. SMI, skeletal muscle index

DISCUSSION

To the best of our knowledge, this is the first study reporting on the direct relation between sarcopenia and prolonged feeding tube dependency during primary CRT for HNC. Our results show that SMI measured at C3 level, as measure of sarcopenia, was significantly associated with an increased risk of prolonged feeding tube dependency. Adjusting for BMI, FOIS and SES did not lead to substantial changes of the estimate of the RR, suggesting the relationship was not confounded.

The results support our hypothesis that the relationship between sarcopenia and prolonged tube dependency is a causal one (43). First, the effect of SMI on the risk of tube dependency was substantial: the effect size (RR 1.08) translates into a relative risk increase of 26% for patients per interquartile range decrease in SMI. Second, adjustment for confounders resulted in a minimal change of the estimated RR. Last, the relation between low muscle mass and functional impairment later on (i.e., tube dependency) is biologically plausible, and analogous effects of low skeletal muscle mass have been observed for other clinical and functional outcomes of head and neck cancer treatment (12, 44).

Our findings implicate that muscle mass and function may also modify patients risk of feeding tube dependency. Thus, the presence of sarcopenia may be a relevant indication for optimization of patients' physical condition (through nutritional interventions and exercise programs targeting the (swallowing) muscles) prior to treatment, and routine assessment of neck SMI could be used to identify patients who will benefit most from prehabilitation. Future experimental studies are needed to assess the effect of such a policy.

Recently, we developed and published a clinical prediction model to estimate the risk of prolonged feeding tube dependency (23). This prediction model could be used to select high risk patients for proactive placement of a feeding tube to prevent unnecessary weight loss. In this cohort, 16 of the 17 patients (94%) with a high estimated risk (> 60%) on prolonged feeding tube dependency – for whom clinicians might recommend proactive feeding tube placement – had a neck SMI below 12.7 (median SMI 11 (range 8–13)). Therefore, for these patients, the effort of assessing neck SMI can be saved since it is likely that all patients in this risk category will benefit from pretreatment supportive care focusing on optimizing muscle mass. We would recommend considering routine assessment of neck SMI for patients with an estimated risk below 60%, however, especially the intermediate risk category (30-60%), since 49 of the 80 patients (61%) with an intermediate estimated risk (30-60%) had a neck SMI below 12.7. Assessment of neck SMI in this risk category has added clinical value, as it enables identification of a modifiable factor. This can aid targeted optimization of patients' pretreatment condition to decrease the risk on swallowing impairment and tube feeding dependency; if low neck SMI is present and considered modifiable, proactive tube placement, with its associated risk for non use atrophy of swallowing musculature, may be postponed. Postponing placement

of a tube lowers the risk for prolonged dependency. Thus, even if prehabilitation would not fully mitigate the risk, postponing tube placement still might result in shorter dependency durations.

Prehabilitation includes the improvement of patients' baseline outcomes between diagnosis and start of treatment in order to prevent or minimalize post treatment impairments (45). Several studies on other cancer types have investigated this strategy and found positive results on body mass and overall physical strength and function (31, 32). In HNC patients receiving CRT, studies have been performed on preventive swallowing exercises before or during treatment to improve swallowing function (46-48). These interventions showed positive effects on post treatment swallowing function.

In order to optimize muscle mass and function prior to treatment to prevent functional impairment, a multifactorial approach to resolve the modifiable factor sarcopenia would be most effective (49). Firstly, increase in muscle strength and mass should be provoked by means of exercises. These exercises ideally include targeted swallowing exercises, preferably with progressive load, to increase swallowing muscle function, as well as overall physical exercises to increase overall muscle strength and mass (50). One has to keep in mind, however, that the time period between diagnosis and start of treatment is short and may be too short to effectively build up muscle mass – if possible, exercises should therefore be continues during treatment. Secondly, patients should be encouraged to adhere to a high protein diet to facilitate muscle growth. Patients treated in our institute, independently of their muscle mass, are advised to increase their protein intake to at least 1.5 g/kg a day. Therefore, as part of prehabilitation, patients should be advised to alter their diet (e.g., consuming protein in portions of 25-30 gram per meal) and prescribing high-protein medical nutrition to supplement their regular meals should be considered (51, 52). Considering the high prevalence of dysphagia in HNC patients before treatment, altering the route of administration using a (temporary) feeding tube could be considered and might be the only way to reach the minimal protein intake of 1.5 g/kg a day to optimize nutritional status. Eventually, the combination of high protein intake and (targeted) exercises might break the vicious spiral of muscle function loss and malnutrition and thus long-term functional outcomes might be improved. However, PEG probe placement as a back-up is not recommended since it is associated with substantial risks for patients who will eventually not need the tube. These risks can be avoided by close monitoring of the patient and placement of a tube when necessary.

A remaining uncertainty in this study, due to its retrospective nature, is that some variables which arguably could confound the association of sarcopenia with tube dependency were not available. In particular, health literacy, the degree to which someone is able to understand information to make health decisions, might be a confounding factor unaccounted for (see figure 1). Also, analyses were performed on a subgroup of HNC patients treated with CRT, and the conclusions may be generalizable to this specific population only. Future studies are needed to confirm the association in more heterogeneous HNC populations. Finally, we estimated

sarcopenia using routinely performed CT imaging of the head and neck area, whereas he most common method for sarcopenia assessment in cancer patients is based on abdominal CT imaging, for instance using the psoas muscle or using total muscle area at the level of lumbar vertebra L3. However, abdominal imaging is not routinely available in head and neck cancer patients which limits its applicability in this population. While the optimal measurement level, measurement method or cut-off value for sarcopenia on CT imaging is still debated, a high correlation of C3 SMI with L3 SMI has been reported before (53, 54). Thus, in head and neck cancer patients, measurement on head and neck CT imaging currently appears to be the most applicable method.

CONCLUSION

Sarcopenia, as measured by SMI at C3 level on routine CT imaging of the head and neck area, contributes to the risk of prolonged feeding tube dependency in HNC patients treated with primary CRT. Due to its non-invasive and time-efficient character, routine measurement of neck SMI could be a valuable addition to clinical practice. Firstly, it could aid in the shared decision making regarding proactive tube placement, especially in the intermediate risk category based on our previously published prediction model on prolonged feeding tube dependency risks. Secondly, sarcopenia might be modifiable prior to treatment, and as such it may present a relevant lead for pretreatment optimization of patients' condition. The results of this study therefore warrant further research on the feasibility and effectiveness of such interventions.

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Chapter 9

General discussion and future perspectives

DISCUSSION

> "My life was saved by the specialists, 15 years ago. An experimental approach rigorously removed the tumor in my base of tongue. Sure, there was 'collateral damage': the right side of the tongue has been paralyzed since then because the nerve was removed too. One of the consequences is that the larynx is no longer closed properly when swallowing before food or liquid is pushed into the esophagus. Result: liquid in particular always leaks a little into the trachea, which then leads to moderate or severe choking. Or, even more serious, if it only leaks a little bit and the 'choke invoking sensor' at the back of the throat does not notice it will cause the occasional scenario of an aspiration pneumonia.
>
> The doctors told me that it can't go on like this. I was strongly advised to accept a feeding tube and start taking all my food intake with it. During the doctor's visit where I was advised to go for the feeding tube, an alternative was, which was suggested almost casually and with a calm, relaxed tone: a laryngectomy. This proposal actually did upset me, although I seemed quiet and relaxed at that moment. The whole idea..., as if an ophthalmologist told someone with cataract, in a calm voice, that it's also an option to replace the eyes with artificial eyes. My immediate answer was a robust and cheery "Well, no way!". It's like exchanging one handicap for another. Sure, the other handicap may be less severe than this one, but in this case, I'm still not convinced of that. I know a lot of people who underwent a laryngectomy and although there are variations between them, I don't envy them. And so, I just keep going on, impatiently waiting for the invention of the century, the invention that actually makes my collateral damage manageable."

This is the story of Peter de Valença, who was treated 15 years ago for a tumor at the base of tongue. As discussed at length in the introduction and in various chapters, and as highlighted by this story, head and neck cancer (HNC) treatment, unfortunately, is a recipe for functional limitations afterwards. This is not only true for organ sacrificing treatment modalities, as in case of Peter de Valença, but also for organ-preserving treatment modalities.

Usually, functional issues occur not only in advanced HNC (stages III and IV), but also in patients with early stage HNC (stage I and II). For early-stage oropharyngeal carcinoma, two treatment options are available: surgery and radiotherapy. These treatment modalities, however, do differ with respect to (type and timing of) post-treatment toxicity. Clarifying what these differences are is relevant for clinical decision making. Results of our prospective, non-randomized

study suggested that surgery is associated with less swallowing impairment compared to radiotherapy, although the difference was not statistically significant (**Chapter 2**) (1). In this cohort, more than half of the patients treated with surgery alone underwent postoperative radiotherapy, which nullified the benefit of surgery regarding favorable swallowing outcomes. After performing this study, results of the randomized ORATOR-trial were published comparing surgery (plus neck dissection) and radiotherapy (with or without chemotherapy) for oropharyngeal carcinoma (2). The authors concluded that there were no clinically meaningful differences with regards to the swallowing-related quality of life, but that there was a difference with respect to toxicity profiles (e.g., more mucositis in the radiotherapy group and more trismus in the surgery group). It can be concluded that when selecting oropharyngeal cancer patients for either surgery or radiotherapy, these different toxicity profiles have to be taken into account and should be matched with the patient's preferences. Also, physicians should try to select those patients for surgery as single-modality treatment who most likely will not need adjuvant radiotherapy, to avoid additional functional impairment caused by multimodality treatment.

Numerous methods for evaluation of swallowing function are available (3). In several studies, objective measures of functional outcomes do not reflect subjective experience of those functions. In our study on long-term functional outcomes ten-years plus after CRT and preventive rehabilitation (described in Chapter 4), this was observed as well (4). None of the patients with objectively measured trismus (mouth opening < 36 mm) perceived their mouth opening as impaired. In contrast, decreased perceived swallowing function, as assessed with the SWAL-QOL questionnaire, was not accompanied by decreased objective swallowing, as assessed by videofluoroscopy. These discrepancies between objective and subjective measures probably have several causes. First, habituation to and acceptance of functional loss may lead to self-reported measures within the normal range, despite deviating objective measures, a phenomenon known as response shift (5). Second, some measures might be more sensitive to change than others. For example, the score of a questionnaire on swallowing function might decrease several points when swallowing speed slightly decreases e.g., it will take more time to finish a meal, while videofluoroscopy might be less sensitive to this change in speed. This also suggests the third possible cause. Aspects of the particular function measured by means of an objective assessment method might not be (the most) relevant for patients' daily functioning and therefore change in currently available objective measures might not ultimately lead to change in the subjective measure. This discrepancy might lead to problems with regard to selection of patients for interventions in the context of rehabilitation.

This discrepancy between subjective and objective swallowing measures can confront clinicians with challenging dilemmas. For example, how are objective disorders, silent aspiration for example, best treated when the patient perceives the swallowing function as normal? But also, how is a perceived disorder best treated when it cannot be objectified? In this thesis, we tried to contribute to the solution to the dilemmas, by introducing a new objective measure for swallowing on the ICF-level of capacity (**Chapter 3**). The current objective swallowing methods measure the physical function needed for eating and drinking

while subjective, patient-reported methods measure mostly swallowing perception, that is: perceived swallowing ability and functioning in daily life. What lacks in these two categories of measures is the swallowing capacity or transport capacity of the upper digestive tract (in grams per second), which is defined as the time needed to ingest boluses of different consistencies, as measured under standardized circumstances. Swallowing capacity can therefore be operationalized as the speed at which a person can eat and drink. Swallowing capacity is in that sense comparable with a measure like vital capacity for the lungs (in liters per second), although compared to this measure, it is influenced stronger by the patient's ability to adapt to functional impairments, since swallowing is a complex action. We hypothesized that a method that measures eating and drinking speed under standardized circumstances would more accurately reflect the impact of swallowing function impairments on functioning in daily life. We therefore developed the Swallowing Performance Eating And Drinking (SPEAD)-test which measures the time needed to ingest three boluses of different consistencies. In the development and preliminary validation study reported in Chapter 3, we showed that the outcome of this easily manageable test was correlated with objective as well as with subjective swallowing measures, which supports its construct validity. Also, results of the study supported feasibility and showed good to excellent reliability. This indicates that the SPEAD-test could be valuable in clinical practice as well as for research purposes to evaluate the swallowing capacity.

In the present thesis, functional results were presented of a patient cohort more than ten years after chemoradiotherapy and preventive swallowing rehabilitation (**Chapter 4**) (4). Function appeared to be well maintained up until the ten-year plus follow-up assessment, which was not quite expected given the substantial prevalence of late-onset dysphagia, which can occur or progress years after initial HNC treatment due to neuropathy, continuing fibrosis, and non-use atrophy (6). Thus, the findings described in chapter 4 are suggestive of a positive influence of the preventive rehabilitation strategies applied in these patients, next to the positive contribution of improved radiotherapy techniques, such as IMRT and VMAT (7). Also, when considering the 'use it or lose it'-principle, it is likely that training the muscles of the head and neck area that are relevant for swallowing and speaking, before, during, and after HNC treatment, positively affects functional outcomes (8). Therefore, although evidence is still scarce and many questions regarding optimal frequency, intensity (e.g., intensity during initial rehabilitation and benefit of continued use of exercises), time, and type (e.g., combination of exercises) of rehabilitation are still left unanswered, it is understandable why preventive rehabilitation protocols have emerged into clinical HNC care.

As a consequence of the biological comprehension of the effectiveness of preventive rehabilitation, and the positive results of clinical studies, including the one performed at our institute, implementation into clinical practice seemed warranted. To assess the clinical outcomes after implementation, we studied the results on swallowing, mouth opening, and voice/speech outcomes of patients with oropharyngeal cancer treated with (C)RT, obtained between the first full year of its implementation (2013) and 2018 (**Chapter 5**). Implementation of a new clinical approach takes time. Over the studied period, the percentage of eligible patients enrolled in

the program increased from 19% up to 79%. With respect to the clinical results, we found that none of the patients were feeding tube dependent and only 4% had experienced pneumonia in the past six months. However, still a substantial proportion of the patients experienced dysphagia (25%), trismus (20%), and speech problems (58%) at one-year post-treatment. A comparison with other studies was not feasible given the heterogeneity of patient populations and outcome measures. However, it was clear that, despite the efforts of the implementation of the rehabilitation program, a substantial proportion of patients still experience functional limitations. This suggests there is either still room for further improvement of rehabilitation approach or some sequels cannot be prevented.

Several years ago, the idea emerged that the TheraBite, a tool to treat and prevent trismus, could be modified to train swallowing musculature. Kraaijenga et al. developed the Swallow Exercise Aid (SEA) as a tool to not only perform preventive but also reactive (swallowing) exercises (9, 10). From these first two successful SEA studies, questions remained regarding several aspects of an optimal (preventive) rehabilitation protocol. For example, optimal training duration, exercise frequency, and the need for maintenance therapy are still unsettled. Also, although improvement of function was seen and the effectiveness of the principle was suggested, it was yet unclear whether the muscles hypothesized to be targeted, indeed were trained, and whether the combination of exercises within the protocol was targeting all relevant muscles to improve swallowing function.

Therefore, we performed a biomechanical study on muscle activation during treatment with the SEA versus conventional exercises using a non-invasive Magnetic Resonance Imaging technique (**Chapter 6**) (11). This study revealed that the suprahyoid, infrahyoid, and sternocleidomastoid muscles were activated during both SEA and conventional exercises (i.e., conventional effortful swallow, Shaker and Masako), but that in addition to those muscle groups, during SEA exercises also the lateral pterygoid muscles were activated. Therefore, we were able to conclude that besides laryngeal elevation also mouth opening mechanisms were targeted. Tongue and pharyngeal muscles also play an important role in swallowing and other functions of the head and neck area. However, in our MRI study we could not conclude that these muscles were activated as well, although this was most likely due to the relatively small muscle size, which resulted in less precise measurements. However, given the improved tongue strength in the previous two studies on the effectiveness of the SEA by Kraaijenga et al. (9, 10), and the use of pharyngeal muscles during the effortful swallow, we still assume that these muscles are targeted by the SEA, as well. To be really certain, more invasive techniques are probably needed, such as EMG, to visualize activation of these muscles. The use of EMG needles in often high dose RT areas was deemed undesirable and not justified for the purpose of this study.

Post-treatment functional status can be improved by the previously discussed active preventive rehabilitation strategies, but also by strategies regarding tube feeding before and during treatment. A long-standing discussion exists on the appropriate timing of feeding tube

placement during (C)RT for HNC. One approach is a reactive tube placement strategy in which patients only receive a feeding tube when unacceptable weight loss, dehydration, or aspiration occur during treatment. A benefit of this approach is that oral intake is maintained as long as possible, preventing non-use atrophy of the swallowing musculature. The only pitfall of this approach is that the patient should be carefully monitored on an almost daily basis. The other approach is to use a prophylactic strategy, in which all patients receive a feeding tube, which might better prevent unacceptable weight loss, dehydration, and aspiration, and with that – in some cases – interruption of the (chemotherapy) treatment. Another advantage of the prophylactic placement would be that frequent monitoring the patient is less demanding. The obvious drawback is that non-use atrophy of the swallowing musculature, which is a prelude to long-term swallowing impairment, is more likely to occur. This is especially unfortunate when patients who could have managed without a tube do get one, unnecessarily increasing their risk for function loss and complications associated with tube placement. To facilitate this discussion, we developed a prediction model to estimate the risk for prolonged feeding tube dependency with the aim to enable selection of high-risk patients for 'proactive' feeding tube placement (**Chapter 7**) (12). Risk factors included the simple and clinically readily available parameters T-stage, BMI, and pretreatment weight loss and dysphagia. The estimated risk enables informed and shared decision making on the timing of feeding tube placement in individual patients, trading off the risk of weight loss/dehydration versus the risk of loss of (swallowing) function. Future research should reveal whether clinical decision making with aid of this prediction tool indeed results in less functional loss after treatment, especially when feeding tube placement is combined with (SEA-based) preventive swallowing rehabilitation exercises.

Prediction models are best developed based on consistently observed and strong predictors, in order to precisely estimate the individual risk for tube feeding. Such predictors are not only useful for the previously mentioned purpose of selecting patients for proactive tube feeding, but – when modifiable – could also serve as a clue for strategies to improve function and minimize the risk of poor outcome. Not all risk factors and possible predictors for feeding tube dependency have been identified or studied in depth. One interesting candidate predictor is pretreatment sarcopenia. Therefore, we explored the association of pretreatment sarcopenia, i.e., loss of skeletal muscle mass, with prolonged feeding tube dependency (**Chapter 8**) (13). We hypothesized this association might exist because patients with sarcopenia have limited reserves with regard to muscle mass and function, and therefore would be more prone to develop swallowing problems than patients with an adequate skeletal muscle mass to begin with. Results of our study, in which we measured skeletal muscle mass on the level of C3 on routine CT imaging prior to treatment, revealed a strong association between lower pretreatment muscle mass and a higher risk for prolonged feeding tube dependency. Thus, skeletal muscle mass measurement prior to treatment should be considered as additional predictor for feeding tube dependency, and can improve the clinical prediction model. A suggestion for clinical use of the model with muscle mass measurement is illustrated in figure 1 and further discussed in the future perspective section below. Pre-treatment sarcopenia also seems to be associated with other functional limitations, such as trismus and speech/voice

impairment, and may have value in predicting those, as suggested by the results in chapter 5. Skeletal muscle mass is a relatively easily available parameter from routine pretreatment CT-scans (14). Since this parameter is associated with function loss and considering that it is potentially modifiable, we argue that routine assessment of muscle mass could be of clinical value in this population.

FUTURE PERSPECTIVES

The results of the studies presented in this thesis all warrant implementation into clinical practice to a greater or lesser extent.

The clinical pro- and retrospective results discussed in **Chapters 2** (on patient-reported swallowing function after surgery and radiotherapy for stage I and II oropharyngeal carcinoma), **4** (on long-term results after CRT and preventive rehabilitation) and **5** (on the one-year results after (C)RT for oropharyngeal carcinoma) are quite relevant for current clinical practice. They have broadened our insight in the short- and long-term issues following treatment, and the success rate of the implementation of a dedicated rehabilitation program. These results are valuable for further improving patient counselling and optimization of (preventive) rehabilitation strategies. They also underline that continued follow-up and audit are indispensable for maintaining and improving patient care standards.

The SPEAD-test, discussed in **Chapter 3**, is a likely candidate for clinical implementation. It is an easily manageable test, requiring minimal equipment, time, and money to execute and which provides a reproducible value (in grams per second) for the swallowing capacity. Ideally, after further validation and optimization of the test, integration into regular care is justified with multiple possible applications. It might be useful for pretreatment work-up to enable (early) identification of swallowing impairment, and act accordingly, as well as to determine baseline function to be able to further monitor deteriorations or progress during and after treatment. The test might also be useful in already treated patients. Moreover, the SPEAD-test might also be a useful test to evaluate swallowing capacity in patients with dysphagia caused by diseases other than HNC.

Now that we know that relevant (swallowing) muscles are targeted (**Chapter 6**) with the SEA, and the SEA has shown potential value in improving swallowing function, future studies should target the optimization of this exercise tool (e.g., optimizing protocol length and exercise frequency) and the assessment of its effects in randomized settings. In our institute, we are planning to not only evaluate the effect of the SEA in a randomized clinical trial comparing the SEA-based exercise protocol versus standard care, but also focus on laryngectomized patients with dysphagia. After total laryngectomy, some important muscles involved in swallowing are removed or transected with a high postoperative prevalence of dysphagia as a result (15-17). Within the planned studies, the effectiveness of maintenance exercises will also be evaluated in order to optimize the exercise protocol for a maximal and sustainable effect. Today, efforts are being made to further optimize the versatility and ergonomics of the tool and to make it more widely available.

Another obvious implementation concerns our clinical prediction model (**Chapter 7**), which would aid in estimating the risk for prolonged tube feeding during CRT for HNC into regular pretreatment work-up, to decide on the timing for tube feeding during CRT treatment. In

addition, as sarcopenia has proven to also be relevant in predicting this risk, we propose to add this parameter (measured as neck skeletal muscle index (SMI) on routine CT-scans) to the decision-making process (**Chapter 8**). A proposed flow chart is presented in figure 1. Within this protocol, first, the risk for prolonged feeding tube dependence is estimated on the basis of the identified clinical parameters (T-stage, BMI, and pretreatment weight loss and dysphagia). In case of an estimated risk below 30%, no additional action would be needed, except for encouraging and supporting the patient to optimally maintain oral intake. In case of an estimated risk between 30% and 60% measurement of the neck SMI is advised. Pretreatment optimization of the patient's condition in case of a neck SMI below 12.7 might be beneficial and can therefore be discussed with the patient. In case of an estimated risk above 60%, pretreatment optimization of the patient's condition might be beneficial regardless neck SMI. Additional research still has to be performed to (externally) validate this or a comparable protocol, and especially the suggested cut-off percentages.

Regarding the association between sarcopenia and feeding tube risk, one has to keep in mind that this does not immediately imply that when skeletal muscle mass throughout the body increases, functions of the head and neck area also improve. It could be that the association only works one way: when swallowing function decreases, oral intake is less, and skeletal muscle mass also decreases, and not the other way around: more skeletal muscle mass increases swallowing function.

In conclusion, after treatment for HNC, people, including Peter de Valença – whos story is depicted above – have to live with functional sequelae of the treatment. Although considerable effort has been put into minimalizing functional loss, these limitations still cannot be prevented or cured. Preventive as well as reactive rehabilitation, including swallowing muscle exercises with for example the SEA, most likely will continue to play an important role in preserving and improving the functional endresult by targeting swallowing as well as mouth opening mechanisms. By using adequate tools to assess swallowing status, including the newly developed SPEAD-test, and prediction models (including sarcopenia), the risk for functional impairment later on can be anticipated and timely and proper action can be taken, including proactive placement of a feeding tube or initiation of (SEA) rehabilitation.

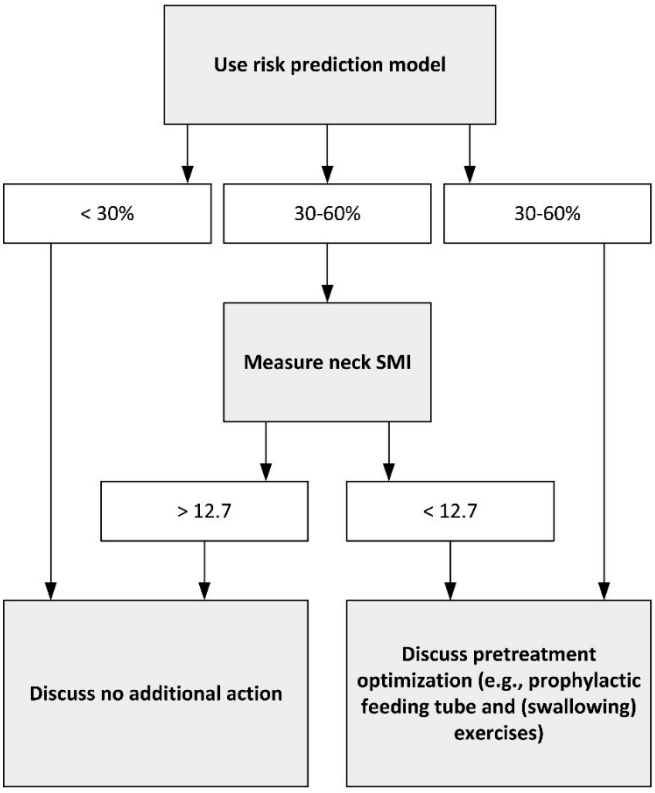

Figure 1 Example of a proposed flow chart to implement prediction model to estimate risk for prolonged tube feeding and sarcopenia (neck skeletal muscle mass (SMI)) on routine CT-scans measurements into clinical practice before the start of treatment.

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Chapter 10

English summary

Nederlandse samenvatting

ENGLISH SUMMARY

The objective of this thesis was to further explore functional impairment in patients treated for head and neck cancer (HNC), find relevant risk factors for functional loss and aid in the improvement of rehabilitation to improve quality of life of HNC survivors.

Chapter 1 provides a general introduction on the epidemiology of HNC, it's treatment, the associated (functional) toxicities, and rehabilitation strategies. Despite the efforts put into minimalizing the toxicity of treatment in combination with the optimization of individualized training programs, the impaired functions of the head and neck area are still important issues in the lives of HNC survivors, suggesting considerable room for optimization.

In **Chapter 2**, surgery and radiotherapy (RT) for early-stage stage (T1-2N0-2bM0) oropharyngeal carcinoma are compared with respect to patient-reported swallowing function, to enable informed decisions on treatment choice and inform patients prior to treatment on the likely outcome of their intended treatment. For this purpose, data from an existing large UK-wide multicentre prospective cohort study (HN5000) was used. Patients offered RT ($n = 150$) had less favorable baseline characteristics than those offered surgery ($n = 150$). At 12-month follow-up, RT participants reported more swallowing problems (35% vs. 23%, risk ratio 1.3; 95% confidence interval 0.8–2.3, $p = .277$) in models adjusted for baseline characteristics. In those allocated to surgery who received adjuvant therapy ($n = 78$, 52%), the proportion with swallowing problems was similar to those allocated to RT alone. We concluded that participants offered surgery alone had similar mortality but less impaired swallowing, although the latter was statistically not significant. However, over half of participants offered surgery alone also received adjuvant radiotherapy, negating the slight advantage of surgery alone. Therefore, more effort should be put into defining the indications for postoperative RT and selecting the patients for surgery who most likely will not need adjuvant therapy.

Several methods are available to evaluate swallowing function, including objective as well as subjective methods. Objective swallowing outcomes measure the physical swallowing function while subjective outcomes measure swallowing perception. A test for swallowing capacity, measuring the ingestion of all consistencies, was not yet available. Therefore, the Swallowing Proficiency for Eating And Drinking (SPEAD) test was developed, which entails the timed ingestion of thin liquid, thick liquid and solid, presented in **Chapter 3**. The feasibility, reliability and validity of the SPEAD-test were evaluated in 38 patients with dysphagia after treatment for head and neck cancer (HNC) and 40 healthy participants. Test-retest, intra-rater and interrater reliability of ingestion duration was good to excellent. All hypotheses with regard to magnitude and direction of correlations with objective (e.g., videofluoroscopy and functional oral intake scale) and subjective (e.g., swallowing related quality of life questionnaire) swallowing outcomes were confirmed, supporting construct validity of the test. Results of this development and initial validation study suggest that the SPEAD-test reliably measures the transport capacity of the upper digestive tract (in grams per second) and that this test can be useful to objectively evaluate and monitor the swallowing capacity in HNC patients, in both research as well as daily clinical practice.

In **Chapter 4**, the swallowing, trismus and speech function ten years after chemoradiotherapy (CRT) combined with preventive swallowing rehabilitation for advanced stage HNC are described. These outcomes were also compared to previously published six-year results of the same cohort. Fourteen of the 22 patients who participated in the six-year follow-up study still were evaluable, after ten years. Although objective swallowing-related outcomes showed no deterioration (e.g., no feeding tube dependency and no pneumonia), swallowing-related quality of life slightly deteriorated over time. None of the patients had or perceived trismus. Voice and speech questionnaires showed little problems in daily life. Overall quality of life was good. We concluded that after CRT with preventive rehabilitation exercises for advanced HNC, swallowing-, trismus- and speech-related outcomes moderately deteriorated from six- to ten-years, with all patients maintaining full oral intake and an on average good overall quality of life.

Chapter 5 describes the functional limitations, including dysphagia, trismus, and speech problems, within the first year after radiation-based treatment for advanced stage oropharyngeal carcinoma. This cohort includes patients from the implementation of a dedicated rehabilitation program (2013) until 2019, and therefore the study also facilitates the evaluation of implementation of such a program in clinical practice. Accrual increased from 19% in 2013 to 85% in 2018, with a slight decrease to 79% in 2019. Objective and patient-perceived function deteriorated until six months and improved until twelve months after treatment, but did not return to baseline levels with 25%, 20% and 58% of the patients with respect to objective dysphagia, trismus and speech problems, respectively. Feeding tube dependency and pneumonia prevalence were low. From these results, we concluded that a substantial proportion of patients still experience functional limitations at one-year post radiation-based treatment for OPC, suggesting room for improvement of the current rehabilitation program. Results also showed that pretreatment sarcopenia seems to be associated with worse functional outcomes and that this issue might therefore be a relevant target for rehabilitation strategies.

Swallowing-muscle strength exercises with or without progressive load, are effective in restoring swallowing function. For performing the most likely effective exercises with progressive load, earlier, a tool called the Swallow Exercise Aid (SEA) was developed in our institute. For these exercises, including those with the SEA, precise knowledge on which muscles are activated is lacking. This knowledge could aid in optimizing the training program to target the relevant swallowing muscles, if necessary. In **Chapter 6**, the MRI assessment of swallowing muscle activation with the SEA exercises (i.e., chin tuck against resistance, jaw opening against resistance and effortful swallow) and with conventional exercises (i.e., conventional effortful swallow, Shaker (head lift in supine position) and Masako (effortful swallow with tongue protrusion)) is described. Three healthy volunteers performed the exercises in supine position inside an MRI scanner. Fast muscle-functional MRI scans (generating quantitative T2-maps) were made immediately before and after the exercises. Median T2-values at rest and after exercise were compared to identify activated muscles. We conclude that the conventional exercises activate the suprahyoid, infrahyoid, and sternocleidomastoid muscles. During the SEA exercises, these muscles are also activated as well as the lateral pterygoid muscles, the

latter being especially relevant for prevention and/or treatment of trismus. The findings of this explorative study further support the potential of the SEA to improve swallowing rehabilitation.

In **Chapter 7**, a prediction model is developed to predict the risk for long-term feeding tube dependency before CRT for head and neck cancer, to select patients for proactive tube placement and to avoid unnecessary prophylactic tube placement. A retrospective study was performed in a consecutive cohort of HNC patients treated with primary CRT, for whom a reactive tube placement protocol was used. A prediction model was developed to prognosticate prolonged (> 90 days) feeding tube dependency. Model performance and clinical net benefit of the model were assessed. Of the 336 included patients, 229 (68%) needed a feeding tube during CRT and 151 (45%) were prolonged feeding tube dependent. The prediction model includes the parameters pretreatment BMI, weight loss, Functional Oral Intake Scale and T-stage. Discriminatory ability is fair (area under the ROC-curve of 0.69) and calibration is adequate (Hosmer and Lemeshow test $p = .254$). The model shows net benefit over current practice for probability thresholds from 35–80%. Therefore, the developed model can be used to select patients for proactive feeding tube placement during primary CRT for HNC. The presented nomogram with easily obtainable parameters is a useful tool for clinicians to support shared decision making regarding proactive tube placement.

Sarcopenia, loss of skeletal muscle mass, was hypothesized to be a relevant lead for optimization of head and neck cancer (HNC) patients' condition before chemoradiotherapy to prevent long-term functional swallowing impairment, such as feeding tube dependency. To test this hypothesis, regression analyses were performed in **Chapter 8** to assess the association between skeletal muscle mass index (SMI), as a measure of sarcopenia, and prolonged (> 90 days) feeding tube dependency in 128 HNC patients treated with primary CRT. Sixty-one patients (48%) became prolonged feeding tube dependent. Lower SMI increased the risk of prolonged feeding tube dependency in multivariable analysis (risk ratio 1.08; 95% confidence interval 1.02–1.14, $p = .013$) adjusted for body mass index, abnormal diet and socioeconomic status. Sarcopenia contributes to the risk of prolonged feeding tube dependency of HNC patients treated with primary CRT. Since sarcopenia might be a modifiable issue prior to treatment, it should be explored as a target for pretreatment optimization of patients' condition.

In **Chapter 9** the results of these studies and related future perspectives are discussed. Although considerable effort has been put into minimalizing functional loss, functional limitations after treatment for HNC still cannot be prevented or cured. Preventive as well as reactive rehabilitation, including swallowing muscle exercises with for example the SEA, most likely will continue to play an important role in preserving and improving the functional endresult by targeting swallowing as well as mouth opening mechanisms. By using adequate tools to assess swallowing status, including the newly developed SPEAD-test, and prediction models (including sarcopenia), the risk for functional impairment later on can be anticipated and timely and proper action can be taken, including proactive placement of a feeding tube or initiation of (SEA) rehabilitation.

NEDERLANDSE SAMENVATTING

Dit proefschrift heeft als doel het verder beschrijven van functionele stoornissen bij hoofd-halskankerpatiënten, het identificeren van relevante risicofactoren voor functieverlies en het verbeteren van de revalidatie. Dit met als uiteindelijk doel om kwaliteit van leven van hoofd-halskankerpatiënten verder te verbeteren.

Hoofdstuk 1 geeft een algemene inleiding over de epidemiologie van hoofd-halskanker, de behandeling ervan, de bijbehorende (functionele) toxiciteiten en reeds bestaande revalidatiestrategieën. Ondanks de inspanningen om de toxiciteit van de behandeling te minimaliseren door deze te combineren met geoptimaliseerde en geïndividualiseerde trainingsprogramma's, is functieverlies in het hoofd-halsgebied na behandeling nog steeds een belangrijk probleem in het leven van hoofd-halskankerpatiënten. Dit suggereert dat er ruimte is voor optimalisatie.

In **Hoofdstuk 2** wordt het verschil in patiënt-gerapporteerde slikfunctie tussen chirurgie en radiotherapie (RT) voor vroeg-stadium orofarynxcarcinoom (T1-2N0-2bM0) vergeleken. Het doel van deze studie was om beter geïnformeerde beslissingen te kunnen nemen over de keuze van de behandeling en om patiënten voorafgaand aan de behandeling beter te kunnen informeren over de te verwachten gevolgen van de beoogde behandeling wat betreft de slikfunctie. Voor deze studie werden gegevens gebruikt van een bestaande grote Britse prospectieve multicenter cohortstudie (HN5000). Patiënten die behandeld werden met RT (n = 150) hadden minder gunstige uitgangskenmerken dan degenen die een operatie kregen (n = 150). Na twaalf maanden rapporteerden RT-patiënten meer slikproblemen (35% vs. 23%, relatief risico 1,3; 95%-betrouwbaarheidsinterval 0,8-2,3, p = ,277), gecorrigeerd voor uitgangskenmerken. Bij chirurgie patiënten die adjuvante radiotherapie kregen (n = 78, 52%) was het aandeel met slikproblemen vergelijkbaar met patiënten die alleen met RT werden behandeld. We konden concluderen dat patiënten die met chirurgie worden behandeld een vergelijkbare mortaliteit hebben, maar minder slikproblemen rapporteren na de behandeling dan de RT-patiënten, hoewel dit voordeel statistisch niet significant was. Echter, meer dan de helft van de chirurgie patiënten kreeg ook adjuvante radiotherapie, waardoor het kleine voordeel wat betreft slikproblemen teniet werd gedaan. Het is daarom belangrijk om goede indicaties voor postoperatieve RT te definiëren en alleen patiënten voor chirurgie te selecteren die hoogst waarschijnlijk geen aanvullende radiotherapie nodig hebben.

Er zijn verschillende methoden beschikbaar om de slikfunctie te evalueren, zowel objectieve als subjectieve methoden. Objectieve methoden meten de fysieke slikfunctie, terwijl subjectieve uitkomsten de slikperceptie meten. Een test voor de slikcapaciteit waarin de verwerkingssnelheid van alle voedselconsistenties worden gemeten was nog niet beschikbaar. Daarom hebben we de Swallowing Proficiency for Eating And Drinking (SPEAD)-test ontwikkeld, waarbij de tijd die een proefpersoon nodig heeft voor het wegslikken van een dun-vloeibare, een dik-vloeibare en een vaste bolus wordt gemeten. In **Hoofdstuk 3** staat beschreven hoe de haalbaarheid,

betrouwbaarheid en validiteit van de SPEAD-test werd geëvalueerd bij 38 patiënten met dysfagie na behandeling voor hoofd-halskanker (HNC) en 40 gezonde deelnemers. De test-hertest, en de intra- en interbeoordelaar betrouwbaarheid van de innameduur bleken goed tot uitstekend. Alle hypothesen met betrekking tot de omvang en richting van correlaties met objectieve slikmaten (bijv. een slikvideo en een functionele schaal voor orale voedselinname) en subjectieve slikmaten (bijv. vragenlijst over slik-gerelateerde kwaliteit van leven) werden bevestigd, wat de constructvaliditeit van de test ondersteunt. Resultaten van deze ontwikkelings- en initiële validatiestudie suggereren dat de SPEAD-test op betrouwbare wijze de transportcapaciteit van het bovenste spijsverteringskanaal meet (in gram per seconde) en dat deze test nuttig kan zijn om de slikcapaciteit bij hoofd-halskankerpatiënten objectief te evalueren en te volgen in de periode na de behandeling, in zowel onderzoek als de klinische praktijk.

In **Hoofdstuk 4** worden de slikfunctie, mondopening en spraakfunctie tien jaar na chemo-radiotherapie (CRT) en preventieve slikrevalidatie voor hoofd-halskanker beschreven. Deze uitkomsten werden ook vergeleken met eerder gepubliceerde resultaten na zes jaar follow-up van hetzelfde cohort. Veertien van de 22 patiënten die deelnamen aan de zes jaar follow-up studie konden nog worden geëvalueerd na tien jaar. Hoewel objectieve slikmaten geen verslechtering lieten zien (bijv. geen sondevoeding afhankelijkheid en geen longontsteking in de laatste zes maanden), was er sprake van een lichte achteruitgang van de slik-gerelateerde kwaliteit van leven. Geen enkele patiënt had of ervoer trismus. Stem- en spraakvragenlijsten lieten weinig problemen zien in het dagelijks leven. De algehele kwaliteit van leven was goed. We concludeerden dat na CRT met preventieve revalidatieoefeningen voor hoofd-halskanker, slik-, trismus- en spraak-gerelateerde uitkomsten iets verslechterden in de periode tussen zes en tien jaar na CRT, met een gemiddeld goede algehele kwaliteit van leven.

In **Hoofdstuk 5** worden de functionele beperkingen, waaronder dysfagie, trismus en spraakproblemen, beschreven tijdens het eerste jaar na een orgaansparende behandeling voor stadium III-IV orofarynxcarcinoom. Dit cohort bestaat uit patiënten die vanaf de implementatie in 2013 tot 2019 hebben deelgenomen aan een geïntegreerd revalidatieprogramma. Het onderzoek faciliteert daarmee ook de evaluatie van de implementatie van dit programma in de klinische praktijk. De inclusie steeg van 19% in 2013 tot 85% in 2018, met een lichte daling tot 79% in 2019. De gemeten functionele uitkomsten toonden verslechtering van functie tot zes maanden en verbetering daarna tot twaalf maanden na de behandeling zonder dat het uitgangsniveau weer werd bereikt. Na twaalf maanden had respectievelijk 25 %, 20% en 58% van de patiënten objectieve dysfagie, trismus en spraakproblemen. De prevalentie van sondevoeding afhankelijkheid en het ontwikkelen van een longontsteking waren laag. Uit deze resultaten concludeerden we dat de implementatie over de observatieperiode acceptabel was maar ook dat een aanzienlijk deel van de patiënten na een jaar nog functionele beperkingen ervaart na orgaansparende behandeling voor stadium III-IV orofarynxcarcinoom. Er is dus ruimte voor verbetering van het huidige revalidatieprogramma. De resultaten toonden ook aan dat sarcopenie ten tijde van de start van de behandeling geassocieerd lijkt te zijn met

slechtere functionele resultaten en daarom een relevant uitgangspunt zou kunnen zijn voor (p) revalidatiestrategieën.

De slikfunctie kan effectief verbeterd worden met spierversterkende (slik)oefeningen. Om deze oefeningen ook met progressieve spierbelasting uit te kunnen voeren werd eerder in ons instituut een speciaal hulpmiddel ontwikkeld, de Swallow Exercise Aid (SEA). Welke spieren er precies worden geactiveerd bij de spierversterkende (slik)oefeningen, al dan niet met de SEA, was nog niet onderzocht. Kennis hiervan is nuttig voor het optimaliseren van het trainingsprogramma gericht op de relevante slikspieren. In **Hoofdstuk 6** wordt middels MRI naar de slikspieractivatie tijdens de drie SEA oefeningen ('chin tuck against resistance' of 'kin op de borst tegen weerstand', 'jaw opening against resistance' of 'mond openen tegen weerstand' en de 'effortful swallow' of 'krachtig slikken') en drie conventionele oefeningen (conventionele 'effortful swallow' of 'krachtig slikken', Shaker (hoofd lift methode in rugligging) en Masako (krachtig slikken met uitgestoken tong)) gekeken. De spieractivatie werd gemeten door middel van de T2-waarden in 'Fast muscle-functional MRI' scans. Drie gezonde vrijwilligers voerden de oefeningen in rugligging uit in de MRI-scanner. De MRI scans werden vóór en direct na de oefeningen vervaardigd waarbij de T2-waarde in de spier bepaald kon worden. Mediane T2-waarden in rust en na inspanning werden vergeleken om geactiveerde spieren te identificeren. We concludeerden dat de conventionele oefeningen de suprahyoidale, infrahyoidale en sternocleidomastoideus spieren activeren. De SEA-oefeningen activeren diezelfde spieren, maar daarnaast ook de laterale pterygoïdeus spieren, welke met name belangrijk zijn bij het voorkomen en behandelen van trismus. De meerwaarde van de SEA bij het verbeteren van de slikfunctie wordt daarmee verder onderbouwd.

In **Hoofdstuk 7** wordt de ontwikkeling van een predictiemodel beschreven om het risico op langdurige sondeafhankelijkheid tijdens primaire CRT voor hoofd-halskanker te voorspellen. Dit met als doel om patiënten te selecteren voor proactieve sondeplaatsing en daarmee onnodige profylactische sondeplaatsing te voorkomen. Er werd een retrospectieve cohortstudie uitgevoerd om predictieparameters voor langdurige (> 90 dagen) sondevoeding afhankelijkheid te bepalen. Van de 336 geïncludeerde patiënten hadden 229 (68%) een voedingssonde nodig tijdens CRT en 151 (45%) waren langdurig sondevoeding afhankelijk. De volgende parameters bleken van waarde voor het predictiemodel: body mass index (BMI), gewichtsverlies en de Functional Oral Intake Scale voor start van de behandeling en het T-stadium. Het discriminerende vermogen van het model is redelijk (area under the ROC-curve van 0,69) en de kalibratie is voldoende (Hosmer en Lemeshow-test $p = ,254$). Het model toont een netto voordeel ten opzichte van de huidige praktijk voor risico's op langdurig sondevoeding afhankelijkheid van 35 tot 80%. Het ontwikkelde model kan dus worden gebruikt om patiënten te selecteren voor proactieve plaatsing van een voedingssonde tijdens primaire CRT voor hoofd-halskanker. Het bijbehorende nomogram dat met behulp van dit model is opgesteld, is na invoering van de voornoemde, eenvoudig verkrijgbare predictie parameters een goed hulpmiddel ter ondersteuning van de clinici om samen met de patiënt te besluiten of proactieve sondeplaatsing wenselijk is.

Sarcopenie, het verlies van skeletspiermassa, zou een relevant aangrijpingspunt kunnen zijn om de functionele toestand van hoofd-halskankerpatiënten voorafgaand aan chemoradiotherapie te optimaliseren. Deze hypothese werd getest in **Hoofdstuk 8**, door regressieanalyses uit te voeren om zo de associatie te bepalen tussen skeletspiermassa-index (SMI), als maat voor sarcopenie, en langdurige (> 90 dagen) sondeafhankelijkheid bij 128 HNC-patiënten die werden behandeld met primaire CRT. Eenenzestig patiënten (48%) bleken meer dan 90 dagen afhankelijk te zijn van sondevoeding. In de multivariabele analyse was een lagere SMI geassocieerd met een verhoogd risico op langdurige sondevoeding afhankelijkheid (relatief risico 1,08; 95%-betrouwbaarheidsinterval 1,02-1,14, $p = ,013$) gecorrigeerd voor BMI, afwijkend dieet en sociaaleconomische status. Sarcopenie draagt dus bij aan een verhoogd risico van langdurige sondevoeding afhankelijkheid van hoofd-halskankerpatiënten die met primaire CRT worden behandeld. Aangezien sarcopenie voorafgaand aan de behandeling een beïnvloedbare factor zou kunnen zijn, moet worden onderzocht of dit een relevant aangrijpingspunt is voor (p)revalidatiestrategieën.

In **Hoofdstuk 9** worden de resultaten van deze studies en gerelateerde toekomstperspectieven bediscussieerd. Ondanks dat er aanzienlijke inspanningen zijn geleverd om functieverlies na de behandeling van hoofd-halskanker te minimaliseren, is dit verlies nog steeds niet te voorkomen of te genezen. Zowel preventieve als reactieve revalidatie, waaronder slikspieroefeningen met bijvoorbeeld de SEA, zullen hoogstwaarschijnlijk een belangrijke rol blijven spelen bij het minimaliseren van dit verlies, door zich te richten op de slikfunctie en het openen van de mond. Door de klinische implementatie van de SPEAD-test, en voorspellingsmodellen (inclusief sarcopenie), kan het risico op functionele beperkingen beter worden ingeschat en kan er tijdig(er) actie worden ondernomen, waaronder het proactief plaatsen van een voedingssonde of het starten van (SEA) revalidatie.

Appendices

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Chapter 2 (Patient-reported swallowing function after treatment for early-stage oropharyngeal carcinoma: a population-based study)

Study concepts and design	ARN, KI, RK, SL, ST
Data acquisition	ARN, KI, RK, SL, ST
Data analysis and interpretation	ARN, RK, SL, ST
Statistical analysis	ARN, RK, SL
Manuscript preparation	AN, ARN, LS, MB, RK, ST
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Chapter 3 (The timed Swallowing Proficiency for Eating And Drinking (SPEAD) test to objectify (impaired) swallowing capacity in head and neck cancer patients and healthy controls)

Study concepts and design	FH, RK
Data acquisition	KS, LM, RK
Data analysis and interpretation	FH, MM, RK
Statistical analysis	MM, RK
Manuscript preparation	FH, MM, RK
Manuscript editing and review	FH, KS, LM, LS, MM, RK

Chapter 4 (Long-term swallowing, trismus and speech outcomes aftercombined chemoradiotherapy and preventive rehabilitation for head and neck cancer; a ten-year plus update)

Study concepts and design	FH, MM, LS, LM, RK
Data acquisition	LM, RK
Data analysis and interpretation	FH, LM, LS, MM, RK, RS
Statistical analysis	MM, RK
Manuscript preparation	FH, MM, RK
Manuscript editing and review	FH, LM, LS, MB, MM, OH, RK, RS

Chapter 5 (Dysphagia, trismus and speech impairment following (chemo) radiation for oropharyngeal carcinoma: a one-year course)

Study concepts and design	LM, FH, LS, MB, MM, NC, RK
Data acquisition	LM, RK
Data analysis and interpretation	FH, LM, LS, MM, NC, RK, RS
Statistical analysis	MM, RK
Manuscript preparation	FH, MM, NC, RK
Manuscript editing and review	AA, FH, LM, LS, MB, MM, NC, RB, RK, RS

Chapter 6 (MRI assessment of swallow muscle activation with the Swallow Exercise Aid and with conventional exercises in healthy volunteers: an explorative biomechanical study)

Study concepts and design	BJ, FH, LB, LM, LS, MA, MM, RK
Data acquisition	LB, MA, RK
Data analysis and interpretation	BJ, LB, RK
Statistical analysis	MM, RK
Manuscript preparation	FH, LB, MM, RK
Manuscript editing and review	BJ, FH, JP, LB, LE, LM, MA, MM, RK

Chapter 7 (From reactive to proactive tube feeding during chemoradiotherapy for head and neck cancer: a clinical prediction model-based approach)

Study concepts and design	FH, LM, LS, MM, RK
Data acquisition	LM, RK
Data analysis and interpretation	FH, LM, LS, MM, RK
Statistical analysis	MM, RK
Manuscript preparation	FH, LM, MM, RK
Manuscript editing and review	AN, FH, JB, LM, LS, MM, MK, RK

Chapter 8 (Sarcopenia, a strong determinant for prolonged feeding tube dependency after chemoradiotherapy for head and neck cancer)

Study concepts and design	AA, FH, LM, LS, MB, MM, RK
Data acquisition	RK, SB
Data analysis and interpretation	FH, LS, LM, MM, RK, SB
Statistical analysis	MM, RK
Manuscript preparation	AA, FH, MM, RK
Manuscript editing and review	AA, FH, JB, LM, LS, MB, MM, RK, SB, STJ

PHD PORTFOLIO

PhD period	December 2016 – December 2020
PhD supervisors	Prof. dr. L.E. Smele
	Prof. dr. M.W.M. van den Brekel

Courses

2017	e-Practical Biostatistics, AMC Graduate School, Amsterdam
2017	How to write high impact papers and what to do when your manuscript is rejected, Onderzoekschool Oncologie Amsterdam (OOA), Amsterdam
2017	Scientific writing, Onderzoekschool Oncologie Amsterdam (OOA), Amsterdam
2017	Medical Business Masterclass, Amsterdam
2017	Good Clinical Practice, Antoni van Leeuwenhoek ziekenhuis, Amsterdam
2018	Scientific integrity, ACTA, Amsterdam
2018	Oral presenting, AMC Graduate School, Amsterdam
2018	Clinical Epidemiology: Randomized Clinical Trials, AMC Graduate School, Amsterdam
2018	Clinical Epidemiology: Evaluation of Medical Tests, AMC Graduate School, Amsterdam
2018	Dentistry for non-dentists, ACTA, Amsterdam
2018	eBROK, Examenbureau Medisch-Wetenschappelijk Onderzoek, Amersfoort
2018	Contemporary Methods for Functional Success After Head and Neck Cancer: The MD Anderson Cancer Center Approach, MD Anderson Cancer Center, Houston, Texas
2018	Clinical Epidemiology: Searching for a Systematic Review, AMC Graduate School, Amsterdam
2018	MRI: basic understanding for (bio)medical research, AMC Graduate School, Amsterdam
2018	Project management, AMC Graduate School, Amsterdam
2018	Didactical skills, AMC Graduate School, Amsterdam
2019 – 2021	Master Evidence Based Practice (Epidemiologie), Universiteit van Amsterdam, Amsterdam

Conferences

2016-2020	KNO Ledenvergadering
2016-2020	Jonge Onderzoekersdag (JOD)
2016-2020	NWHHT Vergadering
2016-2020	Onderzoekschool Oncologie Amsterdam (OOA) Retreat
2017	European Society for Swallowing Disorders (ESSD) Conference, Barcelona
2017	13th International Netherlands Cancer Institute Head and Neck Cancer Symposium, Amsterdam
2018	Society for Medical Decision Making (SMDM) Conference, Leiden
2018	International PhD Student Cancer Conference, London

2018	5th World Congress of the International Federation of Head and Neck Oncologic Societies (IFHNOS), Buenos Aires
2019	14th International Netherlands Cancer Institute Head and Neck Cancer Symposium, Amsterdam
2019	Symposium Experimenteel Onderzoek Heelkundige Specialismen (SEOHS), Amsterdam
2019	7th World Congress of the International Academy of Oral Oncology (IAOO), Rome
2019	Najaarsvergadering NVMKA, Hoorn

Supervising

2017	Judith Quik (medical student), scientific internship
2017	Nine de Graaf (medical student), scientific internship
2018	Jasmine de Jong (medical student), scientific internship
2019	Michelle Hagemeijer (student speech language pathology), scientific internship
2019	Pamela Raaff (medical student), scientific internship
2020	Bernard van den Dorpel (dentistry student), scientific internship
2020	Annamaria Al-Azawi and Lilian Zandi (dentistry students), scientific internship
2020	Irem Toprak (medical student), scientific internship

Presentations

2017	Direct postoperatieve complicaties na een totale laryngectomie: is IC opname nodig? Poster –Jonge Onderzoekersdag, Den Haag
2017	Chronische slikproblemen bij hoofd-halskanker patiënten: nieuwe (oefentherapie) mogelijkheden? Presentation – AVL Symposium, Amsterdam
2017	Feasibility and potential value of lipofilling in patients with post-treatment oropharyngeal dysfunction. Poster - European Society for Swallowing Disorders (ESSD) Conference, Barcelona
2017	Effectiveness of lipofilling in patients with oropharyngeal dysfunction after treatment for head and neck cancer – preliminary results and a study design. Presentation – Onderzoekschool Oncologie Amsterdam (OOA) Retreat, Renesse
2017	Totale laryngectomie: postoperatieve opname op de intensive care noodzakelijk? Presentation – KNO Najaarsvergadering, Nieuwegein
2018	The development of a prediction model of long-term tube feeding during chemoradiotherapy for head and neck cancer. Poster – International PhD Student Cancer Conference, London

2018 The development of a prediction model of long-term tube feeding during chemoradiotherapy for head and neck cancer. Presentation – 5th World Congress of the International Federation of Head and Neck Oncologic Societies (IFHNOS), Buenos Aires

2018 Reactive or prophylactic tube feeding during chemoradiotherapy for head and neck cancer: a clinical prediction model-based approach. Presentation – Onderzoekschool Oncologie Amsterdam (OOA) Retreat, Renesse

2018 Reactieve of profylactische sondevoeding tijdens chemoradiotherapie voor hoofd-halskanker: een klinisch predictiemodel. Presentation – KNO Najaarsvergadering, Nieuwegein

2019 Surgery or radiotherapy for early T-stage oropharyngeal carcinoma: difference in swallowing function. Poster – 14th International Netherlands Cancer Institute Head and Neck Cancer Symposium, Amsterdam

2019 Patiënt-gerapporteerde slikfunctie na chirurgie of radiotherapie voor vroeg-stadium orofarynxcarcinoom. Presentation – KNO Voorjaarsvergadering, Nieuwegein

2019 Patiënt-gerapporteerde slikfunctie na chirurgie of radiotherapie voor vroeg-stadium orofarynxcarcinoom. Presentation – Jonge Onderzoekersdag, Amsterdam

2019 Sarcopenia, a strong determinant for prolonged feeding tube dependency after chemoradiotherapy for head and neck cancer. Presentation – 7th World Congress of the International Academy of Oral Oncology (IAOO), Rome

2019 Patient-reported swallowing function after surgery or radiotherapy for early T-stage oropharyngeal carcinoma: a population-based study. Presentation – 7th World Congress of the International Academy of Oral Oncology (IAOO), Rome

2019 Keuzehulp voor patiënten met een vroeg-stadium orofarynxtumor. Presentation – NWHHT vergadering, Maastricht

2019 Lipofilling ter behandeling van dysfagie na hoofdhalskanker. Presentation – NWHHT vergadering, Maastricht

2019 Sarcopenie en sondevoeding afhankelijkheid na chemoradiotherapy voor hoofd-halskanker. Presentation – NWHHT vergadering, Maastricht

2019 Patient-reported swallowing function after surgery or radiotherapy for early T-stage oropharyngeal carcinoma: a population-based study. Presentation – Onderzoekschool Oncologie Amsterdam (OOA) Retreat, Renesse

2019 MRI evaluatie van slikspieractivatie met de Swallow Exercise Aid vs. conventionele slikoefeningen. Presentation – KNO Najaarsvergadering, Nieuwegein

2019 Lipofilling ter behandeling van slikproblemen na hoofd-halskanker. Presentation – Symposium Experimenteel Onderzoek Heelkundige Specialismen (SEOHS), Amsterdam

Grants

2017 Maurits en Anna de Kock Stichting for purchase of a manometer (€40.000)

2018 Michel Keijzerfonds for the development of a decision aid tool for patients with oropharyngeal cancer (€27.260)

List of publications

2017 Direct Complications and Routine ICU Admission after Total Laryngectomy
R. T. Karsten, A.J. Timmermans, J. ten Cate, M.M. Stuiver, M.W.M. van den Brekel
Acta Oto-Laryngologica

2019 From reactive to proactive tube feeding during chemoradiotherapy for head and neck cancer: A clinical prediction model based approach
R.T. Karsten, M.M. Stuiver, L. van der Molen, A. Navran, J.P. de Boer, F.J.M. Hilgers, W.M.C. Klop, L.E. Smeele
Oral Oncology

2019 Sarcopenia, a strong determinant for prolonged feeding tube dependency after chemoradiotherapy for head and neck cancer
R.T. Karsten, A. Al-Mamgani, S.I. Bril, S. Tjon-A-Joe, L. van der Molen, J.P. de Boer, F.J.M. Hilgers, L.E. Smeele, M.W.M. van den Brekel, M.M. Stuiver
Head & Neck

2020 Long-term swallowing, trismus, and speech outcomes after combined chemoradiotherapy and preventive rehabilitation for head and neck cancer; 10-year plus update
R.T. Karsten, L. van der Molen, O. Hamming-Vrieze, R.J.J.H. van Sons, F.J.M. Hilgers, M.W.M. van den Brekel, M.M. Stuiver, L.E. Smeele
Head & Neck

2020 Patient-reported swallowing function after treatment for early-stage oropharyngeal carcinoma: Population-based study
R.T. Karsten, M.W.M. van den Brekel, L.E. Smeele, A. Navran, S. Leary, K.I. Ingarfield, M. Pawlita, T. Waterboer, S.J. Thomas, A.R. Ness
Head & Neck

2021 MRI Assessment of Swallow Muscle Activation with the Swallow Exercise Aid and with Conventional Exercises in Healthy Volunteers: An Explorative Biomechanical Study
R.T. Karsten, L.C. ter Beek, B. Jasperse, M.J.A. van Alphen, J.M. Peeters, L. van der Molen, F.J.M. Hilgers, M.M. Stuiver, L.E. Smeele
Dysphagia

2021 The Timed Swallowing Proficiency for Eating and Drinking (SPEAD) Test: Development and Initial Validation of an Instrument to Objectify (Impaired) Swallowing Capacity in Head and Neck Cancer Patients
R.T. Karsten, F.J.M. Hilgers, L. van der Molen, K. van Sluis, L.E. Smeele, M.M. Stuiver
Dysphagia

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Mijn promotor, Michiel van den Brekel, beste **Michiel**. Jij was de allereerste persoon die ik in het AVL sprak, nadat ik je mailde of je een onderzoeksproject voor me had. Door me een leuke onderzoeksvraag voor te leggen heb je mijn enthousiasme over de wetenschap laten groeien. Ik heb me altijd verbaasd over hoeveel ballen je tegelijkertijd hooghoudt en hoe goed je altijd op de hoogte bent van alle onderzoeksresultaten, ook als die pas enkele uren daarvoor online verschenen zijn. Als afdelingshoofd heb je ook buiten kantooruren activiteiten als afdelingsuitjes, congressen, wintersportvakanties, vrijdagmiddagborrels en het jaarlijkse kerstontbijt (waarbij je met gezonde tegenzin altijd in kerstmannenpak stond) altijd erg gestimuleerd. Dit doet de sfeer binnen de afdeling heel erg goed en daar heb ik de afgelopen jaren van mee mogen genieten.

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Samen naar de Marktkantine, Lowlands, weekendjes partyen en ga zo maar door. Het is nooit te laat voor 0900-BELWILLEM. Naast al het grappen en grollen waardeer ik het ook heel erg dat je altijd eerlijk bent en kritiek durft te geven en we het ook vaak over serieuze dingen hebben zoals toekomstplannen en (liefdes)struggles.

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bij Sjefietshe, outfit spotten op de KNO-vergadering, het geluksgevoel als Tiffs broodje bal met satésaus op de vrijdag serveerde (lifesaver), jij die altijd verliefd wordt op Wintersport, Noord Gestoord, raketsessie in Maastricht, en ga zo maar door. Ik ben je heel erg dankbaar voor de leuke tijd die ik met je heb gehad en de mensen die ik door jou heb leren kennen. Helaas zit je nu voor (hopelijk maar) twee jaar in New York, maar we houden contact! ;-)

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