LONG-TERM OROPHARYNGEAL AND LARYNGEAL FUNCTION IN PATIENTS WITH ADVANCED HEAD AND NECK CANCER

SOPHIE ANNE CHARLOTTE KRAAIJENGA

LONG-TERM OROPHARYNGEAL AND LARYNGEAL FUNCTION IN PATIENTS WITH ADVANCED HEAD AND NECK CANCER

SOPHIE ANNE CHARLOTTE KRAAIJENGA

COLOFON

Cover by:	Anne Olde Kalter | www.lafarme.nl
Layout by:	Nicole Nijhuis | Gildeprint
Printed by:	Gildeprint | Enschede
ISBN:	978-94-6233-316-1
Online:	http://dare.uva.nl

Printing of this thesis was kindly supported by:
ACTA | NKI-AVL | Patiëntenvereniging Hoofd-Hals | Nederlandse Vereniging voor KNO-Heelkunde | Straumann | Olympus Nederland BV | ALK-Albello BV | ATOS Medical BV | Chipsoft | MediTop Medical Products | PENTAX Nederland BV | Dos Medical BV- kno-winkel.nl | Daleco Pharma BV | Meda Pharma BV |

The research described in this thesis was performed at the Netherlands Cancer Institute – Antoni van Leeuwenhoek, Amsterdam, the Netherlands. The research was partly funded by W.M. de Hoop and the Verwelius Foundation.

LONG-TERM OROPHARYNGEAL AND LARYNGEAL FUNCTION IN PATIENTS WITH ADVANCED HEAD AND NECK CANCER

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus
prof. dr. D.C. van den Boom

ten overstaan van een door het College voor Promoties ingestelde commissie,
in het openbaar te verdedigen in de Aula der Universiteit

op vrijdag 8 juli 2016, te 11:00 uur

door

Sophie Anne Charlotte Kraaijenga
geboren te Utrecht

PROMOTIECOMMISSIE

Promotores:	Prof. dr. M.W.M. van den Brekel, University of Amsterdam Prof. dr. F.J.M. Hilgers, University of Amsterdam
Co-promotor:	Dr. L. van der Molen, The Netherlands Cancer Institute, Amsterdam
Overige leden:	Prof. dr. A.J.M. Balm, University of Amsterdam Prof. dr. J.J. de Lange, University of Amsterdam Prof. dr. C.R.N. Rasch, University of Amsterdam Prof. dr. H.A.M. Marres, Radboud University Nijmegen Dr. L.W.J. Baijens, University of Maastricht

Faculteit der Tandheelkunde

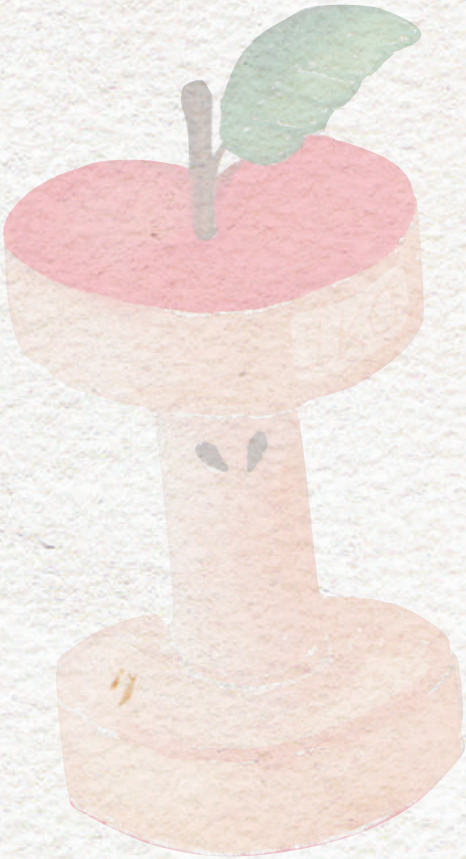
CONTENTS

CHAPTER 1.	General introduction and outline of thesis	9
CHAPTER 2.	Current assessment and treatment strategies of dysphagia in head and neck cancer patients: a systematic review of the 2012/13 literature. Curr Opin Support Palliat Care. 2014; 8: 152-163.	29
PART 1.	**LONG-TERM EVALUATION**	
CHAPTER 3.	Evaluation of long-term (10 years+) dysphagia and trismus in patients treated with concurrent chemoradiotherapy for advanced head and neck cancer. Oral Oncol. 2015; 51: 787-94.	51
CHAPTER 4.	Assessment of voice, speech, and related quality of life in advanced head and neck cancer patients 10 years+ after chemoradiotherapy. Oral Oncol. 2016; 55: 24-30.	71
CHAPTER 5.	Prospective clinical study on long-term swallowing function and voice quality in advanced head and neck cancer patients treated with concurrent chemoradiotherapy and preventive swallowing exercises. Eur Arch Otorhinolaryngol. 2015; 272: 3521-31.	91
CHAPTER 6.	Hyoid bone displacement as parameter for swallowing impairment in patients treated for advanced head and neck cancer. Eur Arch Otorhinolaryngol. Online 2016 Apr 16.	113
PART 2.	**PROSPECTIVE STUDIES**	
CHAPTER 7.	Effects of strengthening exercises on swallowing musculature and function in senior healthy subjects: a prospective effectiveness and feasibility study. Dysphagia. 2015; 30: 392-403.	135

CHAPTER 8.	Efficacy of a novel swallowing exercise program for chronic dysphagia in long-term head and neck cancer survivors. Submitted.	161
CHAPTER 9.	Feasibility and potential value of lipofilling in post-treatment oropharyngeal dysfunction. The Laryngoscope. Online 2016 Apr 14.	187
CHAPTER 10.	General discussion and future perspectives	203
CHAPTER 11.	Summary	221
	Summary in Dutch | Samenvatting	227
	List of Abbreviations	233
	Authors and affiliations	235
	PhD portfolio	237
	About the author	243
	Acknowledgement | Dankwoord	245

CHAPTER 1

General introduction and outline of thesis



GENERAL INTRODUCTION

Head and neck cancer

The head and neck region is frequently affected by cancer. With approximately 550.000 new cases of head and neck cancer (HNC) annually[1], it accounts for the sixth most common malignancy globally. In the Netherlands, in 2014 there were almost 3000 patients diagnosed with a new primary HNC[2]. Males are significantly more affected than females, with a ratio ranging from 2:1 to 4:1[3].

Tumors of the head and neck are mostly squamous cell carcinomas, arising from the mucosal lining of the upper aerodigestive tract[4]. The sites of origin of squamous cell tumors include the oral cavity, nasal cavities, nasopharynx, oropharynx, hypopharynx, and larynx (Figure 1). Since the upper aerodigestive tract is easily exposed to inhaled or ingested carcinogens, it is not surprising that the primary risk factors associated with HNC are tobacco use, alcohol consumption, human papillomavirus infection (for oropharyngeal cancers), and Epstein-Barr virus infection (for nasopharyngeal cancers)[5].

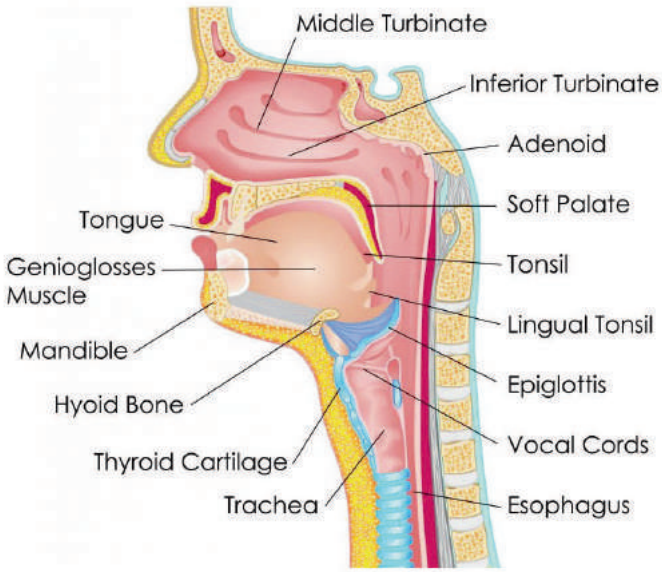


Figure 1. Illustration of various tumor sites in the head and neck region[6].

- Oral cavity: lip, floor of mouth, oral tongue, alveolar ridge, retromolar trigone, hard palate, and buccal mucosa;
- Nasopharynx and nasal cavities;
- Oropharynx: soft palate, tonsils, posterior and lateral pharyngeal walls, base of the tongue, and vallecula;
- Hypopharynx: pyriform sinus, lateral and posterior hypopharyngeal walls, and post-cricoid region;
- Larynx: supraglottic, glottic, and subglottic larynx

Treatment

Management of HNC requires consideration of tumor site and stage (including regional lymph nodes and distant metastases), treatment-related oncological and functional outcomes and morbidity, physician preferences and skills, and patient-specific factors such as comorbidity and preference[4, 7]. The main treatment modalities consist of surgery, radiotherapy (RT), and chemotherapy, as single modality or as combined treatment. Currently, patients with localized (stage I, II) disease generally receive either single modality surgery or RT. Patients with (locally) advanced (stage III, IV) tumors on the other hand increasingly are receiving multimodality treatment, like surgery combined with (chemo)radiation or organ-preservation treatment, mostly consisting of concurrent chemoradiotherapy (CRT)[5, 7].

Meta-analytic data from randomized controlled clinical trials have demonstrated improved loco-regional control and significant survival advantages for these combined CRT protocols compared to single modality RT[8-10]. Unfortunately, preservation of the organ does not necessarily mean that also its (oropharyngeal and/or laryngeal) function is preserved, as it has become clear that these intensified regimens are accompanied by more acute and late toxicities[7, 11-14]. This means that increasingly the challenge is to choose the optimal treatment for the individual patient, not only from a survival but also from a functional perspective, to assure the patient receives the best chance for cure at the expense of the most acceptable/least debilitating side effects[4].

Oropharyngeal function

Swallowing in general, and the various phases of this process (oral, pharyngeal, and esophageal), requires a complex interaction between the muscles in the tongue, floor of mouth, pharynx, and larynx (Figure 2). During the oral preparatory and transport phase of the swallowing process, the extrinsic tongue muscles are involved by pushing the food bolus backwards into the oropharynx. Subsequently, the pharyngeal phase starts when the food bolus reaches receptors in the pharynx, which trigger the swallowing reflex[15]. This phase is the most complex one because it involves many events, which occur in a rapid, entirely reflexive sequence. The palatal muscles are activated to tighten and pull the soft palate upwards to prevent food material from entering the nasopharynx. The larynx and pharynx are also pulled upward and the hyoid bone is pulled into an anterior-superior direction, by contraction of the longitudinal pharyngeal and the suprahyoid muscles, which assists in cricopharyngeal sphincter relaxation too. Laryngeal closure by the epiglottis is achieved by contraction of the base of tongue, in order to prevent aspiration. Further, the true and false vocal cords adduct to protect the airway. Simultaneously, the fibers of the superior, middle, and inferior constrictor pharyngeal muscles contract consecutively to squeeze the food bolus downwards through the pharynx. Finally, during the esophageal phase, the food bolus is transported into the esophagus. After this third and final phase the swallowing act is finished[15-17]. This

complex physiologic course of muscle events and interactions is at risk in patients treated for HNC, and unfortunately, swallowing impairment/ dysphagia is not uncommon in this patient population[12, 13].

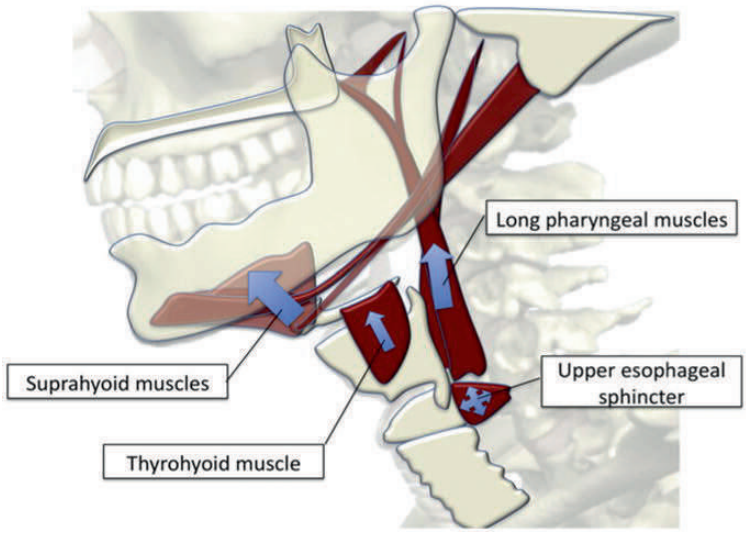


Figure 2. Swallowing requires a complex interaction between the muscles in the tongue, floor of mouth, pharynx, and larynx[17].

Laryngeal function

Normal voice and speech require precise coordination of several rapid, complex neuromuscular actions in the larynx, thorax, and associated structures. The phonatory process, or *voicing*, starts when air is ejected from the lungs through the glottis, creating a pressure drop across the larynx, and eventually initiating oscillation (through the Bernoulli-effect, see Figure 3)[18, 19]. The rapid vibrations of the vocal folds then regulate the pressure and flow of air through the larynx, and generate sound[20]. The frequency of these mucosal waves defines the fundamental frequency (pitch) of the voice, whereas the pressure of the pulmonary air blown through the vocal folds determines voice volume[18]. The quality of voice is dependent on the myo-elastic characteristics of the vocal folds[21]. Also saliva, vocal fold lubrication, and hydration are important factors for phonation[22]. The quality of voice is only slightly affected by the resonances and characteristics of other parts of the vocal tract[18, 21]. In Figure 3 a schematic overview of the vocal tract is shown.

Speech requires movement of sound waves through the air. When the initial sound generated in the larynx travels through the vocal tract (consisting of the oro- and nasopharynx, the oral and nasal cavities, and the lips), it alters based on the position of the pharynx, tongue, mouth, and lips. In this way, individual speech sounds are produced[20], and this process is

known as articulation. Because speech is based on the volitional coordinated movements of the articulators, it can be affected severely by changes in muscle or tissue properties of e.g. the tongue, or the soft palate[21].

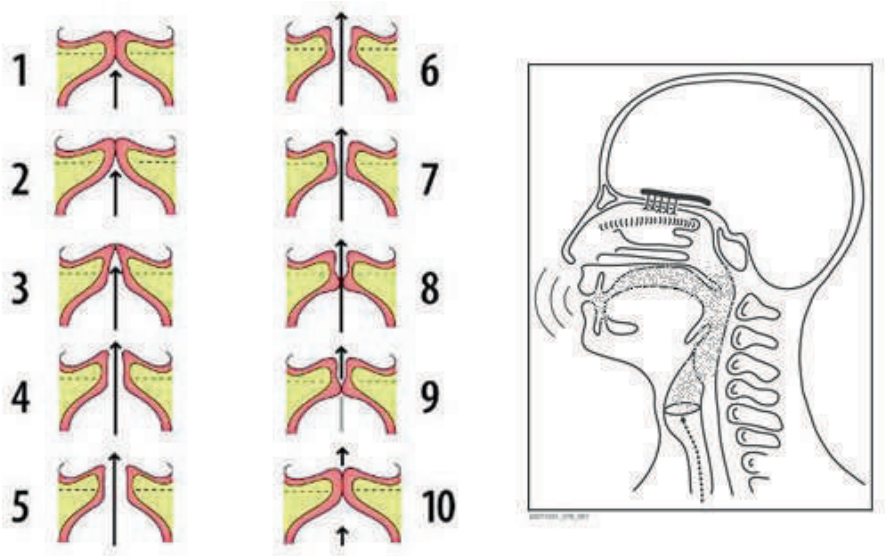


Figure 3. Air passes through the vocal tract (shaded area right[23]), as it is expelled from the lungs through the actively closed glottis, and the pressure drop across the larynx initiates oscillation through the Bernoulli-effect (left[24]) and thus voice.

Treatment-induced toxicities

Since the head and neck region encompasses several complex anatomical structures essential for vital (oropharyngeal and laryngeal) functions such as swallowing, voice, and speech, considerable functional deficits may occur following treatment. Obviously, functional disorders can occur after surgical treatment, depending on the extent of the resection and the reconstruction techniques used[25]. However, also organ-preservation treatment with (C) RT, the focal point of this thesis, may result in acute or delayed complications. The most common acute toxicities of CRT for HNC are mucositis, pain, dermatitis, xerostomia, loss of taste, hoarseness, weight loss, myelosuppression, ototoxicity, nephrotoxicity, nausea, and dysphagia. The most frequent late side effects of CRT are ototoxicity, xerostomia, loss of taste, dysarthria, progressive fibrosis, trismus, and again dysphagia[7].

Swallowing impairment

Dysphagia, acute and chronic, is currently the most critical and potentially life threatening clinical problem in patients with advanced HNC. With a potential risk for aspiration, it may even result in death due to aspiration pneumonia[7, 26-28]. The etiology is multifactorial. Before

treatment, the tumor in the upper digestive and respiratory tract already by itself can cause swallowing problems or aspiration. After organ-preservation treatment, exposure of the swallowing structures to radiation – even more so if combined with chemotherapy[29] – might lead to decreased sensitivity and pharyngeal residue, with high risk of concomitant (silent) aspiration[30]. Additionally, post-treatment radiation-induced sequelae such as xerostomia, fibrosis, and/or muscle atrophy can profoundly affect the ability to clear the bolus, or to protect the airway during swallowing[31-33]. A combination of decreased tongue strength, reduced hyolaryngeal elevation, lack of pharyngeal constrictor activity, lack of velopharyngeal or laryngeal valving forces, and/or insufficient opening of the esophageal inlet may all contribute to dysphagia[34-36]. Eventually, the inability to swallow may lead to problems of proper nutritional intake. Tube feeding is often unavoidable in the acute phase of treatment, and 10 to 30% of patients stay confined to this substitute intake route at long-term as well[37-39]. Consequently, the quality of life in these patients is often significantly reduced[13, 40].

Voice and speech problems

Voice quality and speech production can be affected by tumors involving the tongue, soft palate, tonsils, or larynx. In patients with cancers of the oral cavity and oropharynx, destructive effects of the tumor will mainly affect patients' articulation and/or speech, whereas in laryngeal cancer patients, the tumor often has negative effects on voice quality[21, 41]. Moreover, organ-preservation treatment may have adverse effects on both voice and speech, related to radiation doses to the oral cavity, pharynx, salivary glands, and/or larynx[22, 42]. The addition of concurrent chemotherapy to high-dose RT at least doubles the risk of laryngeal edema and thus dysfunction[21, 22, 43-47]. As mentioned above, sufficient airflow, saliva, and especially pharyngeal and vocal fold lubrication play an important role during voicing. Hence, radiation-induced vocal problems may occur due to observable dryness of the laryngeal mucosa, muscle atrophy, fibrosis, edema, and erythema[22]. Consequently, irregular vocal fold vibration and/or insufficient glottic closure will result in deteriorated voice quality[18, 20]. Patients mainly complain about hoarseness, increased vocal effort, and breathiness. Recent studies that evaluated decreased voice quality post-treatment showed significant impact on quality of life and emotional distress[43-46, 48].

During speech/articulation, the initial sound is modulated by variations of the vocal tract, to produce different vowels. Speech can be affected as result of radiation to the tongue, soft palate, or surrounding musculature or soft tissue of the vocal tract[21]. Reduced speech intelligibility and impaired articulation can occur when the tumor affects the tongue, velopharyngeal function (challenging the capacity to build and release intraoral pressure), and/or the ability to build breathing pressures[49]. Consequently, the disorders can hamper speech intelligibility and verbal communication, and may affect patients' daily life activities and interactions, which are associated with severe functional and psychosocial problems, and reduced quality of life[47, 49, 50].

Preventive rehabilitation

Over the last decades, survival rates for many HNC sites are increasing, and the focus in HNC treatment has evolved from overall survival and loco-regional control, towards long-term quality of life and late side effects. Hence, speech and swallowing rehabilitation has become an inherent part of the multidisciplinary treatment of HNC patients. Several intervention strategies exist, including the application of compensatory techniques (postural changes, diet/bolus modifications) and swallow or non-swallow maneuvers and/or exercises. Successful rehabilitation depends largely on the cause of (oropharyngeal) dysphagia. However, although preventive rehabilitation therapy is often effective in solving some of the (less severe) swallowing problems, in more critical scenarios a permanent gastrostomy is often necessary[39, 51].

Various methods have been considered to prevent or reduce long-term toxicities. Initially, advanced RT treatment planning techniques such as Intensity-Modulated Radiation Therapy (IMRT) were developed, as relationships were found between radiation dosage to pharyngeal structures and swallowing function or trismus[52-55]. Compared with 3-dimensional (3D) conformal RT, IMRT has the ability to precisely deliver a very high dose to the tumor, while at the same time minimizing the amount of radiation to the tumor's surrounding normal tissues[56]. This reduces the radiation dose to the pharyngeal musculature and structures (i.e. the pharyngeal constrictor muscles and salivary glands) and limits the extent of the irradiation fields, resulting in less post-treatment dysphagia and trismus[30, 56-58].

Additionally, multiple studies have demonstrated benefits of maintained use of the swallowing musculature during treatment (the 'use it or lose it' concept, see below). This can be achieved by avoiding periods of nothing per oral (e.g. feeding tube dependency) during and after treatment as long as possible, and by adherence to targeted (preventive) swallowing exercises that keep all structures involved in swallowing 'in motion' to prevent non-use atrophy. Maintained oral intake (instead of standard/prophylactic gastrostomy tube placement without any intake) has been shown to lead to better swallowing function after CRT, probably due to continued use of the swallowing musculature[33, 59, 60]. However, some studies reported better (swallowing) outcomes with prophylactically placed percutaneous endoscopic gastrostomy (PEG) tubes to maintain weight and nutrition during treatment, as compared to those placed reactively[61, 62]. To date, there is no actual consensus on whether to place a PEG tube prophylactically or reactively. For preventive rehabilitation programs, benefits already have been demonstrated. These programs have been associated with a long list of positive effects: improved quality of life[63], better base of tongue retraction and better maintained epiglottic inversion[64], superior muscle maintenance and functional swallowing ability[65], better oral intake and clinician-rated swallowing function[66], improved mouth opening[67, 68], better oral intake and shorter duration of feeding tube dependency[60, 69, 70], and less aspiration, less PEG dependency, and less hospitalization[39] post-treatment. Moreover,

van der Molen et al. in the first RCT on this topic demonstrated that compliance with these preventive exercises was quite good, with a majority of patients (69%) being able to perform the exercises both during the course of their treatment, and after its completion for up to 10 weeks post-treatment[67, 68]. In order to further limit restrictions in daily life activity and functioning after treatment, multidisciplinary HNC rehabilitation programs subsequently also have shown significant and clinically relevant improvements in health-related quality of life[71]. However, since dysphagia can develop and/or progress years after CRT[37, 72], long-term, preferably prospective, functional data should be collected to assess deglutition and other functions (i.e. voice, speech) in HNC survivors[73].

Exercise therapy

As mentioned before, prevention of non-use atrophy has become increasingly important in patients with advanced HNC undergoing (C)RT. Many exercises have been developed in the field of dysphagia[74]. These include range of motion or resistance exercises (with or without medical devices such as the TheraBite® device), behavioural swallow exercises such as the (super-)supraglottic swallow[15, 75, 76], the effortful swallow[15, 77, 78], the Mendelsohn maneuver [75, 79], and the Masako (tongue-holding) maneuver[78], and non-swallow exercises such as the Shaker (head-raising) exercise[80] (Table 1).

Especially the Shaker exercise, a combination of an isometric and isokinetic head-lift exercise, has proven to be effective in strengthening the suprahyoid musculature and reducing post-swallow aspiration in patients with dysphagia, by improving elevation and anterior excursion of the hyolaryngeal complex, and upper oesophageal sphincter (UES) opening[74, 81, 82]. The effectiveness of the Shaker exercise as preventive rehabilitation exercise for HNC patients undergoing CRT was recently also demonstrated[36]. As an alternative therapeutic intervention for patients who find the Shaker exercise in the supine position physically challenging[83], Yoon et al. investigated another exercise to activate the suprahyoid musculature: the chin tuck against resistance (CTAR)[84]. This exercise involves tucking the chin as hard as possible on a rubber ball. Though the CTAR exercise is performed in a seating position, the trajectory of the head and neck flexion during the CTAR exercise mirrors that of the Shaker exercise. The CTAR exercise can be carried out for both isometric and isokinetic tasks too, and strengthens the suprahyoid muscles in the same way as the Shaker exercise does[84]. Moreover, it was demonstrated that the CTAR exercise generates even greater muscle activity in the suprahyoid musculature compared to the head-lift exercise. Similarly, the jaw opening against resistance (JOAR) exercise, which is thought to improve hyolaryngeal elevation, UES opening, and time for pharynx passage as well[85, 86], can be applied in an isometric and an isokinetic manner. These reports suggest that the goal of strengthening the suprahyoid musculature with an associated increase in UES opening might be accomplished with a variety of techniques[74]. However, although these training maneuvers have some proven efficacy, it is not entirely

clear whether these maneuvers actually result in better swallowing function in patients with dysphagia.

Table 1. Summary of behavioural swallow and non-swallow maneuvers or exercises commonly used in dysphagia therapy (adapted from *Dysphagia Management in Adults and Children, by Groher and Crary, 2016*[74]).

Technique	Performance	Intent	Physiology	Outcomes
Side-lying	Lie down with stronger side lower	Slows bolus; Provides time to adjust and protect airway	Emphasizes pharyngeal contraction	Less aspiration
Chin-up	Elevate chin	Propel bolus to back of mouth	Widens oropharynx; Increases PES pressure	Better oral transport
Chin-down	Lower chin	Improves airway protection	Narrows oropharynx	Less aspiration
Head-turn	Turn head to right or left	Reduces post-swallow residue and aspiration	Redirects bolus to stronger side of pharynx; Lowers PES pressure	Increased amount swallowed; Less residue and lower risk of aspiration
Supraglottic swallow	Hold breath Swallow Gentle cough	Reduces aspiration by increasing glottal closure	Horizontal glottal closure; Increased movement of swallow structures	Reduced aspiration; Increased laryngeal excursion
Super-supraglottic swallow	Hold breath Bear down Swallow Gentle cough	Reduces aspiration by increasing glottcal closure	Horizontal and anteroposterior glottal closure; Increased movement of swallow structures	Reduced aspiration; Increased laryngeal excursion
Mendelsohn maneuver	Squeeze swallow at apex	Improves swallowing coordination	Increased and prolonged hyolaryngeal excursion	Improved swallowing coordination; Less post-swallow residue; Less aspiration
Effortful swallow	Swallow harder	Increases lingual force on bolus	Increased tongue-palate pressures; Increased duration of swallow; Increased tongue base movement	Less residue
Head-lift (Shaker) exercise	Isokinetic and isometric head-lift from supine position	Reduces post-swallow aspiration	Improved elevation and anterior excursion of the hyolaryngeal complex; Improved UES opening	Less aspiration

Abbreviations: PES = pharyngo-esophageal sphincter; UES = upper esophageal sphincter.

Swallowing rehabilitation principles

Currently, the possibilities of achieving permanent changes in swallowing physiology by exercise-based dysphagia interventions are increasingly investigated[87-89]. The primary objective is to effect changes (i.e. improved strength, duration and timing) in the physiologic components of swallowing, which will have direct influences on bolus flow kinematics through the pharynx[90]. Additionally, in order to achieve long-term effects, the exercise should be 'rehabilitative', meaning that the exercise should result in permanent changes in a swallow (i.e. making the swallow stronger or faster)[89-91].

Based on the same methods used in physical (or sports-) rehabilitation, the rehabilitative exercises should address all principles of strength training (i.e. specificity, individuality, and transference) derived from repeated strength or endurance training[92, 93]. Since dysphagia in HNC patients can be associated with central and peripheral sensorimotor deficits[90], neural plasticity is here the core principle[89]. Neural plasticity means 'the ability of the brain and nervous system to structurally and functionally change'[89]. Several specific principles in this field of exercise rehabilitation should be incorporated into therapy[92]. First, the *use it or lose it* principle, indicating that disuse of the swallowing mechanism, i.e. by a nothing per oral status, will result in muscle atrophy and diminished cortical representation and innervation[89-91]. Second, the *use it and improve it* principle, implicating that patients should purposefully swallow more often to improve swallowing (in other words: it is essential to build competence of swallowing, not just allowing a patient to complete the (simple) act of swallowing)[89-91]. Third, by implementing task *specificity* into a training regimen, the training task will resemble the end-goal as much as possible, and performance of a specific task will be improved. This should be incorporated in a regimen of adequate load, repetition, volume, and duration of exercises, to force central and peripheral motor unit adaptations[89-93]. The principle *transference* means that complex neural, biochemical, and hemodynamic systems activated during exercise can have widespread effects throughout related or parallel systems of the body[89-91, 93]. In this way, other motor units can learn to participate in the task or even take over the task[89]. Finally, *intensity* defines 'the amount of effort necessary in a training program'[90, 91, 93]. Sufficient intensity is achieved with mechanical or resistive loading, the amount or repetition of practice, and with adequate duration of training over time[93]. As recently as August 2015, Langmore et al. reported that increasing or decreasing the 'resistive load' of swallowing is an elusive challenge[89], a challenge worthwhile to be taken on.

As swallowing is considered a submaximal muscular activity, the muscular strength generated to successfully complete the swallowing act is less than the so-called 1-repetition maximum (1RM), i.e. the maximal force that can be generated by the swallowing muscles in a single repetition[93]. Consequently, strength training regimens should start with an initial resistance of 60% to 75% of 1RM[94, 95]. Moreover, to maximize improvements over time, the application of the so-called 'progressive muscle overload' principle during the exercise period has to be an essential part of the training regimen[89, 92, 93].

Correlation with voice and speech

During swallowing, voice and speech production, more or less the same muscle groups are used. As we have seen, oropharyngeal dysfunction is associated with central and peripheral sensorimotor deficits[90], and also laryngeal functions may be affected, resulting in voice deficits or dysarthria[41, 90]. Consequently, as plasticity is experience specific, intensive strength training of the swallowing musculature and structures might have positive effects on voice quality and speech intelligibility as well. It remains to be seen if improvement of swallowing function in patients with chronic dysphagia will result in improved voice and speech outcomes as well.

Surgical procedures

When rehabilitative (conservative) measures are insufficient to help ensure safe oral intake, surgical treatment may be considered. The primary goals of treatment are to improve food transfer, that is, to prevent malnutrition and dehydration, and to reduce the risk of aspiration. The approach chosen depends in part upon the cause of the (oropharyngeal) dysphagia.

Defective relaxation of the upper esophageal sphincter (UES), for instance, resulting in less powerful propulsion, can sometimes be remedied by reducing the tonus of the pharyngeal musculature. This can be obtained by a cricopharyngeal myotomy, either via an open procedure, or endoscopically using a CO2 laser[96-98]. As a result, the food bolus can easier overcome the reduced resistance of the UES, and enter the esophagus. Also temporarily effects of weakening the cricopharyngeal muscle by esophageal dilatation or botulinum toxin injection successfully are described in patients with UES dysfunction based on underlying muscle spasm or hypertonicity[96, 99]. However, both procedures have their risks and possible complications such as pharyngocutaneous fistula formation, (retropharyngeal) infection, or postoperative aspiration pneumonia[98, 100]. Moreover, the improvement rate is much higher for idiopathic dysfunction and neurologic dysphagia, as compared to swallowing dysfunction as result of HNC treatment[98].

Another invasive surgical technique to treat dysphagia and aspiration is hyolaryngeal suspension. As already mentioned, the larynx elevates and moves anteriorly under the tongue base during swallowing, to move it from the path of the food bolus, and to assist in UES opening. If there is serious limitation in laryngeal elevation, a permanent high position of the larynx can be obtained, by suspension of the hyoid bone and adherent thyroid-cricoid complex to the anterior mandible[101]. Since the vocal cords are not manipulated, the voice should remain unimpaired[101]. Currently, the procedure is often combined with a myotomy of the UES, to permanently open the entrance of the esophagus. Kos et al. evaluated the long-term results of laryngeal suspension and UES myotomy in 17 patients with life-threatening aspiration, and 1 year after treatment it was found that full oral intake without aspiration was achieved in most of the patients[36].

Finally, as 'last refuge', a functional total laryngectomy (TL) can be considered in HNC patients with a dysfunctional larynx after organ preservation treatment, if there is no reasonable likelihood of functional recovery. In a series of 25 patients of the Netherlands Cancer Institute, it was shown that swallowing problems, which occurred in all but 1 patient (96%), decreased considerably after functional TL, with only 4 of 14 patients (29%) having persistent dysphagia after 2 years. In concordance, tube feeding also decreased from 80% prior to surgery to 29% at 2 years post-treatment[102].

The above described methods, except TL, play a subordinate role in HNC-related dysphagia after (C)RT, not only because the results are relatively low[98], but also because the complication risks are very high after such surgical procedures. The prior treatment often causes delayed healing. For instance, after TL for a dysfunctional larynx the pharyngocutaneous fistula rate was over 50%[102].

This short description of surgical techniques is given for completeness sake. Since the current thesis focuses on non-surgical or minimal invasive surgical techniques for treatment of chronic dysphagia, no further attention will be paid to these surgical procedures.

OUTLINE OF THIS THESIS

This thesis starts with general aspects of oropharyngeal function following treatment for advanced head and neck cancer. *Chapter 2* consists of a systematic review on the current assessment and treatment strategies of patients with head and neck cancer and dysphagia.

Part 1 consists of cross-sectional cohort studies on long-term oropharyngeal and laryngeal function following organ-preservation treatment for advanced head and neck cancer. In *Chapter 3* and *Chapter 4* a patient population previously treated with concurrent chemoradiotherapy is studied on long-term functional swallowing, mouth opening, and voice and speech outcomes at more than 10 years post-treatment. In *Chapter 5* a cohort of patients previously also treated with preventive swallowing rehabilitation is evaluated more than 5 years post-treatment. In *Chapter 6* the parameter hyoid bone displacement for swallowing impairment is investigated in the rehabilitated patient population.

Part 2 describes prospective studies on non-surgical or minimal invasive treatment strategies for oropharyngeal and laryngeal dysfunction, based on the insights obtained with the cross-sectional studies in Part 2. *Chapter 7* describes a newly developed swallowing exercise aid and the feasibility and effects of strengthening exercises on swallowing musculature and function achievable with this tool in senior healthy subjects. In *Chapter 8* this dedicated treatment regimen is studied in a phase-1/2 clinical trial among patients with chronic, therapy-resistant dysphagia. In *Chapter 9* the feasibility and potential value of an experimental treatment (lipofilling) is studied in patients with post-treatment oropharyngeal dysfunction.

Finally, in *Chapter 10*, the results obtained in the current thesis are discussed. Future perspectives are dwelled upon. This thesis ends with a general summary in *Chapter 11*.

REFERENCES

1. Gatta G, Botta L, Sanchez MJ, Anderson LA, Pierannunzio D, Licitra L. Prognoses and improvement for head and neck cancers diagnosed in Europe in early 2000s: The EUROCARE-5 population-based study. Eur J Cancer. 2015.
2. http://www.cijfersoverkanker.nl
3. Bray F, Ren JS, Masuyer E, Ferlay J. Global estimates of cancer prevalence for 27 sites in the adult population in 2008. Int J Cancer. 2013;132:1133-45.
4. Ward EC, van As-Brooks CJ. Head and neck cancer: treatment, rehabilitation and outcomes: Plural Publishing Inc. 2nd ed; 2014.
5. Argiris A, Karamouzis MV, Raben D, Ferris RL. Head and neck cancer. Lancet. 2008;371:1695-709.
6. http://wisegeekhealth.com/what-are-the-different-types-of-head-and-neck-cancer.htm
7. Platteaux N, Dirix P, Dejaeger E, Nuyts S. Dysphagia in head and neck cancer patients treated with chemoradiotherapy. Dysphagia. 2010;25:139-52.
8. Forastiere AA, Goepfert H, Maor M, Pajak TF, Weber R, Morrison W, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. N Engl J Med. 2003;349:2091-8.
9. Lefebvre JL. Laryngeal preservation in head and neck cancer: multidisciplinary approach. Lancet Oncol. 2006;7:747-55.
10. Pignon JP, le Maitre A, Maillard E, Bourhis J. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol. 2009;92:4-14.
11. Agarwal J, Palwe V, Dutta D, Gupta T, Laskar SG, Budrukkar A, et al. Objective assessment of swallowing function after definitive concurrent (chemo)radiotherapy in patients with head and neck cancer. Dysphagia. 2011;26:399-406.
12. Hutcheson KA, Lewin JS. Functional outcomes after chemoradiotherapy of laryngeal and pharyngeal cancers. Curr Oncol Rep. 2012;14:158-65.
13. Metreau A, Louvel G, Godey B, Le Clech G, Jegoux F. Long-term functional and quality of life evaluation after treatment for advanced pharyngolaryngeal carcinoma. Head Neck. 2014;36:1604-10.
14. Kraaijenga SA, Oskam IM, van der Molen L, Hamming-Vrieze O, Hilgers FJ, van den Brekel MW. Evaluation of long term (10-years+) dysphagia and trismus in patients treated with concurrent chemo-radiotherapy for advanced head and neck cancer. Oral Oncol. 2015;51:787-94.
15. Logemann JA. Evaluation and treatment of swallowing disorders. Texas, Austin: Pro-ed; 1998.
16. Perlman AL, Schulze-Delrieu KS. Deglutition and its disorders. San Diego: Singular Publishing; 1997.
17. Pearson WG, Jr., Hindson DF, Langmore SE, Zumwalt AC. Evaluating swallowing muscles essential for hyolaryngeal elevation by using muscle functional magnetic resonance imaging. Int J Radiat Oncol Biol Phys. 2013;85:735-40.
18. Titze IR. Current topics in voice production mechanisms. Acta Otolaryngol. 1993;113:421-7.
19. Boersma PW, David. Praat: doing phonetics by computer [Computer program]. Version 6.0.05, .Version 6.0.05.
20. Titze IR. The physics of small-amplitude oscillation of the vocal folds. J Acoust Soc Am. 1988;83:1536-52.
21. Jacobi I, van der Molen L, Huiskens H, van Rossum MA, Hilgers FJ. Voice and speech outcomes of chemoradiation for advanced head and neck cancer: a systematic review. Eur Arch Otorhinolaryngol. 2010;267:1495-505.
22. Lazarus CL. Effects of chemoradiotherapy on voice and swallowing. Curr Opin Otolaryngol Head Neck Surg. 2009;17:172-8.
23. © Netherlands Cancer Institute
24. http://voicefoundation.org/health-science/voice-disorders/anatomy-physiology-of-voice-production/

25. Ellabban MA, Shoaib T, Devine J, McMahon J, Morley S, Adly OA, et al. The functional intraoral Glasgow scale in floor of mouth carcinoma: longitudinal assessment of 62 consecutive patients. Eur Arch Otorhinolaryngol. 2013;270:1055-66.

26. Eisbruch A, Lyden T, Bradford CR, Dawson LA, Haxer MJ, Miller AE, et al. Objective assessment of swallowing dysfunction and aspiration after radiation concurrent with chemotherapy for head-and-neck cancer. Int J Radiat Oncol Biol Phys. 2002;53:23-8.

27. Nguyen NP, Frank C, Moltz CC, Vos P, Smith HJ, Karlsson U, et al. Impact of dysphagia on quality of life after treatment of head-and-neck cancer. Int J Radiat Oncol Biol Phys. 2005;61:772-8.

28. Nguyen NP, Frank C, Moltz CC, Vos P, Smith HJ, Bhamidipati PV, et al. Aspiration rate following chemoradiation for head and neck cancer: an underreported occurrence. Radiother Oncol. 2006;80:302-6.

29. Logemann JA, Pauloski BR, Rademaker AW, Lazarus CL, Gaziano J, Stachowiak L, et al. Swallowing disorders in the first year after radiation and chemoradiation. Head Neck. 2008;30:148-58.

30. Eisbruch A, Kim HM, Feng FY, Lyden TH, Haxer MJ, Feng M, et al. Chemo-IMRT of oropharyngeal cancer aiming to reduce dysphagia: swallowing organs late complication probabilities and dosimetric correlates. Int J Radiat Oncol Biol Phys. 2011;81:e93-9.

31. Eisele DW, Koch DG, Tarazi AE, Jones B. Case report: aspiration from delayed radiation fibrosis of the neck. Dysphagia. 1991;6:120-2.

32. Kotz T, Abraham S, Beitler JJ, Wadler S, Smith RV. Pharyngeal transport dysfunction consequent to an organ-sparing protocol. Arch Otolaryngol Head Neck Surg. 1999;125:410-3.

33. Chen AM, Li BQ, Lau DH, Farwell DG, Luu Q, Stuart K, et al. Evaluating the role of prophylactic gastrostomy tube placement prior to definitive chemoradiotherapy for head and neck cancer. Int J Radiat Oncol Biol Phys. 2010;78:1026-32.

34. Lazarus CL, Logemann JA, Pauloski BR, Rademaker AW, Larson CR, Mittal BB, et al. Swallowing and tongue function following treatment for oral and oropharyngeal cancer. J Speech Lang Hear Res. 2000;43:1011-23.

35. Lazarus C, Logemann JA, Pauloski BR, Rademaker AW, Helenowski IB, Vonesh EF, et al. Effects of radiotherapy with or without chemotherapy on tongue strength and swallowing in patients with oral cancer. Head Neck. 2007;29:632-7.

36. Kos MP, David EF, Aalders IJ, Smit CF, Mahieu HF. Long-term results of laryngeal suspension and upper esophageal sphincter myotomy as treatment for life-threatening aspiration. Ann Otol Rhinol Laryngol. 2008;117:574-80.

37. Hutcheson KA, Lewin JS, Barringer DA, Lisec A, Gunn GB, Moore MW, et al. Late dysphagia after radiotherapy-based treatment of head and neck cancer. Cancer. 2012;118:5793-9.

38. Payakachat N, Ounpraseuth S, Suen JY. Late complications and long-term quality of life for survivors (>5 years) with history of head and neck cancer. Head Neck. 2013;35:819-25.

39. Ohba S, Yokoyama J, Kojima M, Fujimaki M, Anzai T, Komatsu H, et al. Significant preservation of swallowing function in chemoradiotherapy for advanced head and neck cancer by prophylactic swallowing exercise. Head Neck. 2014.

40. Ackerstaff AH, Rasch CR, Balm AJ, de Boer JP, Wiggenraad R, Rietveld DH, et al. Five-year quality of life results of the randomized clinical phase III (RADPLAT) trial, comparing concomitant intra-arterial versus intravenous chemoradiotherapy in locally advanced head and neck cancer. Head Neck. 2012;34:974-80.

41. van der Molen L, van Rossum MA, Jacobi I, van Son RJ, Smeele LE, Rasch CR, et al. Pre- and posttreatment voice and speech outcomes in patients with advanced head and neck cancer treated with chemoradiotherapy: expert listeners' and patient's perception. J Voice. 2012;26:664.e25-33.

42. Gamez M, Hu K, Harrison LB. Laryngeal Function After Radiation Therapy. Otolaryngol Clin North Am. 2015;48:585-99.

43. Fung K, Yoo J, Leeper HA, Bogue B, Hawkins S, Hammond JA, et al. Effects of head and neck radiation therapy on vocal function. J Otolaryngol. 2001;30:133-9.

44. Bibby JR, Cotton SM, Perry A, Corry JF. Voice outcomes after radiotherapy treatment for early glottic cancer: assessment using multidimensional tools. Head Neck. 2008;30:600-10.

45. Starmer HM, Tippett DC, Webster KT. Effects of laryngeal cancer on voice and swallowing. Otolaryngol Clin North Am. 2008;41:793-818, vii.

46. Agarwal JP, Baccher GK, Waghmare CM, Mallick I, Ghosh-Laskar S, Budrukkar A, et al. Factors affecting the quality of voice in the early glottic cancer treated with radiotherapy. Radiother Oncol. 2009;90:177-82.

47. Lazarus CL, Husaini H, Hu K, Culliney B, Li Z, Urken M, et al. Functional outcomes and quality of life after chemoradiotherapy: baseline and 3 and 6 months post-treatment. Dysphagia. 2014;29:365-75.

48. Rinkel RN, Verdonck-de Leeuw IM, van den Brakel N, de Bree R, Eerenstein SE, Aaronson N, et al. Patient-reported symptom questionnaires in laryngeal cancer: voice, speech and swallowing. Oral Oncol. 2014;50:759-64.

49. Jacobi I, van Rossum MA, van der Molen L, Hilgers FJ, van den Brekel MW. Acoustic analysis of changes in articulation proficiency in patients with advanced head and neck cancer treated with chemoradiotherapy. Ann Otol Rhinol Laryngol. 2013;122:754-62.

50. Schuster M, Stelzle F. Outcome measurements after oral cancer treatment: speech and speech-related aspects--an overview. Oral Maxillofac Surg. 2012;16:291-8.

51. Nguyen NP, Moltz CC, Frank C, Vos P, Smith HJ, Karlsson U, et al. Long-term aspiration following treatment for head and neck cancer. Oncology. 2008;74:25-30.

52. Levendag PC, Teguh DN, Voet P, van der Est H, Noever I, de Kruijf WJ, et al. Dysphagia disorders in patients with cancer of the oropharynx are significantly affected by the radiation therapy dose to the superior and middle constrictor muscle: a dose-effect relationship. Radiother Oncol. 2007;85:64-73.

53. Teguh DN, Levendag PC, Voet P, van der Est H, Noever I, de Kruijf W, et al. Trismus in patients with oropharyngeal cancer: relationship with dose in structures of mastication apparatus. Head Neck. 2008;30:622-30.

54. van der Molen L, Heemsbergen WD, de Jong R, van Rossum MA, Smeele LE, Rasch CR, et al. Dysphagia and trismus after concomitant chemo-Intensity-Modulated Radiation Therapy (chemo-IMRT) in advanced head and neck cancer; dose-effect relationships for swallowing and mastication structures. Radiother Oncol. 2013;106:364-9.

55. Rao SD, Saleh ZH, Setton J, Tam M, McBride SM, Riaz N, et al. Dose-volume factors correlating with trismus following chemoradiation for head and neck cancer. Acta Oncol. 2016;55:99-104.

56. Gutiontov SI, Shin EJ, Lok B, Lee NY, Cabanillas R. Intensity-modulated radiotherapy for head and neck surgeons. Head Neck. 2015.

57. Roe JW, Carding PN, Dwivedi RC, Kazi RA, Rhys-Evans PH, Harrington KJ, et al. Swallowing outcomes following Intensity Modulated Radiation Therapy (IMRT) for head & neck cancer - a systematic review. Oral Oncol. 2010;46:727-33.

58. Feng FY, Kim HM, Lyden TH, Haxer MJ, Worden FP, Feng M, et al. Intensity-modulated chemoradiotherapy aiming to reduce dysphagia in patients with oropharyngeal cancer: clinical and functional results. J Clin Oncol. 2010;28:2732-8.

59. Langmore S, Krisciunas GP, Miloro KV, Evans SR, Cheng DM. Does PEG use cause dysphagia in head and neck cancer patients? Dysphagia. 2012;27:251-9.

60. Hutcheson KA, Bhayani MK, Beadle BM, Gold KA, Shinn EH, Lai SY, et al. Eat and exercise during radiotherapy or chemoradiotherapy for pharyngeal cancers: use it or lose it. JAMA Otolaryngol Head Neck Surg. 2013;139:1127-34.

61. Silander E, Nyman J, Bove M, Johansson L, Larsson S, Hammerlid E. Impact of prophylactic percutaneous endoscopic gastrostomy on malnutrition and quality of life in patients with head and neck cancer: a randomized study. Head Neck. 2012;34:1-9.

62. Quon H, Myers C, Lambert P, Butler J, Abdoh A, Stimpson R, et al. Impact of feeding tubes on prospective functional outcomes in patients

with locally advanced head and neck cancer undergoing radiation therapy. Pract Radiat Oncol. 2015;5:e567-73.

63. Kulbersh BD, Rosenthal EL, McGrew BM, Duncan RD, McColloch NL, Carroll WR, et al. Pretreatment, preoperative swallowing exercises may improve dysphagia quality of life. Laryngoscope. 2006;116:883-6.

64. Carroll WR, Locher JL, Canon CL, Bohannon IA, McColloch NL, Magnuson JS. Pretreatment swallowing exercises improve swallow function after chemoradiation. Laryngoscope. 2008;118:39-43.

65. Carnaby-Mann G, Crary MA, Schmalfuss I, Amdur R. "Pharyngocise": randomized controlled trial of preventative exercises to maintain muscle structure and swallowing function during head-and-neck chemoradiotherapy. Int J Radiat Oncol Biol Phys. 2012;83:210-9.

66. Kotz T, Federman AD, Kao J, Milman L, Packer S, Lopez-Prieto C, et al. Prophylactic swallowing exercises in patients with head and neck cancer undergoing chemoradiation: a randomized trial. Arch Otolaryngol Head Neck Surg. 2012;138:376-82.

67. van der Molen L, van Rossum MA, Burkhead LM, Smeele LE, Rasch CR, Hilgers FJ. A randomized preventive rehabilitation trial in advanced head and neck cancer patients treated with chemoradiotherapy: feasibility, compliance, and short-term effects. Dysphagia. 2011;26:155-70.

68. van der Molen L, van Rossum MA, Rasch CR, Smeele LE, Hilgers FJ. Two-year results of a prospective preventive swallowing rehabilitation trial in patients treated with chemoradiation for advanced head and neck cancer. Eur Arch Otorhinolaryngol. 2014;271:1257-70.

69. Bhayani MK, Hutcheson KA, Barringer DA, Lisec A, Alvarez CP, Roberts DB, et al. Gastrostomy tube placement in patients with oropharyngeal carcinoma treated with radiotherapy or chemoradiotherapy: factors affecting placement and dependence. Head Neck. 2013;35:1634-40.

70. Bhayani MK, Hutcheson KA, Barringer DA, Roberts DB, Lewin JS, Lai SY. Gastrostomy tube placement in patients with hypopharyngeal cancer treated with radiotherapy or chemoradiotherapy: factors affecting placement and dependence. Head Neck. 2013;35:1641-6.

71. Passchier E, Stuiver MM, van der Molen L, Kerkhof SI, van den Brekel MW, Hilgers FJ. Feasibility and impact of a dedicated multidisciplinary rehabilitation program on health-related quality of life in advanced head and neck cancer patients. Eur Arch Otorhinolaryngol. 2015.

72. Rutten H, Pop LA, Janssens GO, Takes RP, Knuijt S, Rooijakkers AF, et al. Long-term outcome and morbidity after treatment with accelerated radiotherapy and weekly cisplatin for locally advanced head-and-neck cancer: results of a multidisciplinary late morbidity clinic. Int J Radiat Oncol Biol Phys. 2011;81:923-9.

73. Hutcheson KA, Lewin JS, Holsinger FC, Steinhaus G, Lisec A, Barringer DA, et al. Long-term functional and survival outcomes after induction chemotherapy and risk-based definitive therapy for locally advanced squamous cell carcinoma of the head and neck. Head Neck. 2014;36:474-80.

74. Groher ME, Crary MA. Dysphagia: clinical management in adults and children. St. Louis, Missouri: Elsevier; 2016.

75. Lazarus C, Logemann JA, Gibbons P. Effects of maneuvers on swallowing function in a dysphagic oral cancer patient. Head Neck. 1993;15:419-24.

76. Logemann JA, Pauloski BR, Rademaker AW, Colangelo LA. Super-supraglottic swallow in irradiated head and neck cancer patients. Head Neck. 1997;19:535-40.

77. Hind JA, Nicosia MA, Roecker EB, Carnes ML, Robbins J. Comparison of effortful and noneffortful swallows in healthy middle-aged and older adults. Arch Phys Med Rehabil. 2001;82:1661-5.

78. Lazarus C, Logemann JA, Song CW, Rademaker AW, Kahrilas PJ. Effects of voluntary maneuvers on tongue base function for swallowing. Folia Phoniatr Logop. 2002;54:171-6.

79. Kahrilas PJ, Logemann JA, Krugler C, Flanagan E. Volitional augmentation of upper esophageal sphincter opening during swallowing. Am J Physiol. 1991;260:G450-6.

80. Shaker R, Kern M, Bardan E, Taylor A, Stewart ET, Hoffmann RG, et al. Augmentation of deglutitive upper esophageal sphincter opening in the elderly by exercise. Am J Physiol. 1997;272:G1518-22.

81. Shaker R, Easterling C, Kern M, Nitschke T, Massey B, Daniels S, et al. Rehabilitation of swallowing by exercise in tube-fed patients with pharyngeal dysphagia secondary to abnormal UES opening. Gastroenterology. 2002;122:1314-21.

82. Logemann JA, Rademaker A, Pauloski BR, Kelly A, Stangl-McBreen C, Antinoja J, et al. A randomized study comparing the Shaker exercise with traditional therapy: a preliminary study. Dysphagia. 2009;24:403-11.

83. Easterling C, Grande B, Kern M, Sears K, Shaker R. Attaining and maintaining isometric and isokinetic goals of the Shaker exercise. Dysphagia. 2005;20:133-8.

84. Yoon WL, Khoo JK, Rickard Liow SJ. Chin tuck against resistance (CTAR): new method for enhancing suprahyoid muscle activity using a Shaker-type exercise. Dysphagia. 2014;29:243-8.

85. Wada S, Tohara H, Iida T, Inoue M, Sato M, Ueda K. Jaw-opening exercise for insufficient opening of upper esophageal sphincter. Arch Phys Med Rehabil. 2012;93:1995-9.

86. Hara K, Tohara H, Wada S, Iida T, Ueda K, Ansai T. Jaw-opening force test to screen for Dysphagia: preliminary results. Arch Phys Med Rehabil. 2014;95:867-74.

87. Logemann JA. The role of exercise programs for dysphagia patients. Dysphagia. 2005;20:139-40.

88. Steele CM. Exercise-based approaches to dysphagia rehabilitation. Nestle Nutr Inst Workshop Ser. 2012;72:109-17.

89. Langmore SE, Pisegna JM. Efficacy of exercises to rehabilitate dysphagia: A critique of the literature. Int J Speech Lang Pathol. 2015;17:222-9.

90. Robbins J, Butler SG, Daniels SK, Diez Gross R, Langmore S, Lazarus CL, et al. Swallowing and dysphagia rehabilitation: translating principles of neural plasticity into clinically oriented evidence. J Speech Lang Hear Res. 2008;51:S276-300.

91. Kleim JA, Jones TA. Principles of experience-dependent neural plasticity: implications for rehabilitation after brain damage. J Speech Lang Hear Res. 2008;51:S225-39.

92. Powers SK, Howley ET. Exercise Physiology. New York: McGraw-Hill; 2001.

93. Burkhead LM, Sapienza CM, Rosenbek JC. Strength-training exercise in dysphagia rehabilitation: principles, procedures, and directions for future research. Dysphagia. 2007;22:251-65.

94. Robbins J, Gangnon RE, Theis SM, Kays SA, Hewitt AL, Hind JA. The effects of lingual exercise on swallowing in older adults. J Am Geriatr Soc. 2005;53:1483-9.

95. Sapienza CM, Wheeler K. Respiratory muscle strength training: functional outcomes versus plasticity. Semin Speech Lang. 2006;27:236-44.

96. Zaninotto G, Marchese Ragona R, Briani C, Costantini M, Rizzetto C, Portale G, et al. The role of botulinum toxin injection and upper esophageal sphincter myotomy in treating oropharyngeal dysphagia. J Gastrointest Surg. 2004;8:997-1006.

97. Qu SH, Li M, Liang JP, Su ZZ, Chen SQ, He XG. Laryngotracheal closure and cricopharyngeal myotomy for intractable aspiration and dysphagia secondary to cerebrovascular accident. ORL J Otorhinolaryngol Relat Spec. 2009;71:299-304.

98. Hoesseini A, Honings J, Taus-Mohamedradja R, van den Hoogen FJ, Marres HA, van den Broek GB, et al. Outcomes of endoscopic cricopharyngeal myotomy with CO2 laser surgery: A retrospective study of 47 patients. Head Neck. 2016.

99. Ahsan SF, Meleca RJ, Dworkin JP. Botulinum toxin injection of the cricopharyngeus muscle for the treatment of dysphagia. Otolaryngol Head Neck Surg. 2000;122:691-5.

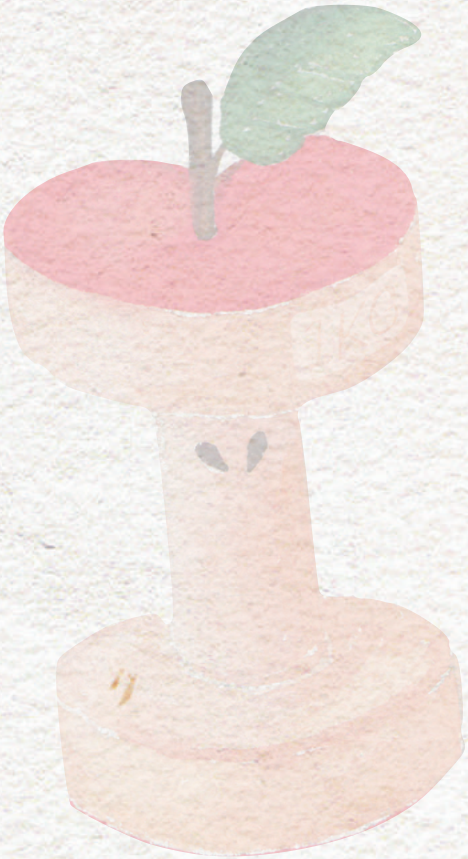
100. Brigand C, Ferraro P, Martin J, Duranceau A. Risk factors in patients undergoing cricopharyngeal myotomy. Br J Surg. 2007;94:978-83.

101. Hillel AD, Goode RL. Lateral laryngeal suspension: a new procedure to minimize swallowing disorders following tongue base resection. Laryngoscope. 1983;93:26-31.

102. Theunissen EA, Timmermans AJ, Zuur CL, Hamming-Vrieze O, Paul de Boer J, Hilgers FJ, et al. Total laryngectomy for a dysfunctional larynx after (chemo)radiotherapy. Arch Otolaryngol Head Neck Surg. 2012;138:548-55.

CHAPTER 2

Current assessment and treatment strategies of dysphagia in head and neck cancer patients: a systematic review of the 2012/13 literature



S.A.C. Kraaijenga
L. van der Molen
M.W.M. van den Brekel
F.J.M. Hilgers

Curr Opin Support Palliat Care. 2014; 8: 152-163.

ABSTRACT

Purpose of review: Dysphagia, or swallowing impairment, is a serious sequel of head and neck cancer (HNC) and its treatment. This review focuses on the rapidly growing literature published during the past two years about the current assessment and treatment strategies of dysphagia in HNC patients.

Recent findings: Functional swallowing assessment has become standard of care in many HNC centres, to prevent or identify (silent) aspiration, to optimize functional outcomes, and to determine the appropriate rehabilitation strategy. Also preventive swallowing exercises are considered more and more in the pre-treatment setting with promising results on (pharyngeal) swallowing function. However, there is a lack of consensus regarding type, frequency, or intensity of the exercises. Furthermore, long-term follow-up of swallowing function might be necessary, given the potential for long-term sequels following HNC treatment.

Summary: Regarding dysphagia evaluation there is still a lack of a uniform 'gold-standard' for both assessment and treatment strategies. More high quality data, adequately controlled, adequately powered and randomized, on prophylactic and therapeutic swallowing exercises are needed, with longer follow-up and better adherence to treatment, for better understanding the effects of chemo- and radiotherapy dosage, and of frequency, timing and duration of treatment, to improve swallowing function and optimize quality of life.

KEY WORDS

Head and Neck Cancer – Functional Outcomes – Dysphagia – Assessment – Treatment – Quality of Life

INTRODUCTION

As swallowing is one of the main functions in which oral, pharyngeal and laryngeal functions cooperate, tumors in this area and treatment sequels can seriously impair swallowing function. Combined chemo-radiotherapy (CRT) regimens are increasingly used as primary treatment of advanced-stage head and neck cancer (HNC). Although these modalities are generally seen as organ-preserving, unfortunately function preservation is not always possible. CRT has significant survival benefit for several tumours compared to radiotherapy alone, but the incidence of acute and long-term toxicities (secondary to xerostomia, radiation fibrosis and changes in innervation) is higher as well[1]. Also surgical treatments affect swallowing function, in terms of delayed pharyngeal transit times and high aspiration incidence (12-50%)[2]. Swallowing disorders depend mainly on extent of resection – especially of tongue(base) and pharyngeal/ laryngeal structures – and reconstruction techniques used[3, 4]. However, even in case of laryngectomy, in which aspiration is precluded, patients can have dysphagia as protrusion in the oro-/neopharynx can become problematic.

There is general consensus that adverse effects of treatment on swallowing function are more pronounced than on other aerodigestive tract functions, such as speech and breathing[1, 5]. Besides, locally destructive effects of the tumour prior to treatment (depending on site and stage), and quality of rehabilitation are influential factors as well. Severe dysphagia limits oral intake and can profoundly affect both compliance to treatment and post-treatment recovery, as it may contribute to malnutrition, dehydration and aspiration pneumonia. Furthermore, long-term dysphagia negatively impacts patient's social contacts and quality of life (QOL) and can be detrimental to patients' nutritional balance (tube feeding dependency).

To date, studies about reducing dysphagia primarily focused on reducing CRT-induced toxicities. Various methods have been considered, such as Intensity Modulated Radiation Therapy (IMRT) to reduce pharyngeal musculature dose[1, 6, 7]. Further on, preventive swallowing exercises seem to benefit HNC patients[8]. However, while IMRT and early swallowing therapy are promising, still up to 2/3 of HNC patients present with dysphagia when diagnosed[4], which may even rise up to 75% post-treatment[9].

Given the lack of an uniform assessment method[10], evaluating dysphagia is still a challenge. Optimal treatment strategies remain uncertain too, since most studies about (preventive and rehabilitation) strategies still are rather limited in size and scope. The purpose of this review was to summarize current assessment and treatment strategies for dysphagia following HNC, and to give directions for the future.

METHODOLOGY

On October 31, 2013, a systematic literature search was performed in MEDLINE/Pubmed, EMBASE, and Cochrane, to identify all recently published articles on assessment and treatment of dysphagia following HNC.

Search strategy

All possible synonyms were included, combined with relevant Mesh- and EMTREE-terms for the search in MEDLINE and EMBASE respectively (Table 1). Limits as publication language in English, publication date since 2012, research in human adults, and relevant study designs were used. Titles/abstracts of all hits were subsequently screened on relevance (matching domain, determinant, and outcome). Possibly relevant articles were obtained full-text and evaluated independently by two reviewers. Successively, related articles and references of the selected articles and reviews were screened by the reviewers.

Table 1. Search terms

MEDLINE, EMBASE* & COCHRANE	#1: ("Head and Neck Neoplasms"[Mesh] OR head and neck cancer [ti/ab] OR HNC[ti/ab])
	#2: (head and neck[ti/ab] OR oral cavity[ti/ab] OR nasopharyn*[ti/ab] OR oropharyn*[ti/ab] OR hypopharyn*[ti/ab] OR laryn*[ti/ab] NOT esophag*[ti/ab])
	#3: ("Neoplasms"[Mesh] OR cancer*[ti/ab] OR tumor[ti/ab] OR tumors[ti/ab] OR tumour*[ti/ab] OR neoplasm*[ti/ab] OR malignanc*[ti/ab] OR carcinoma*[ti/ab])
	#4: #1 OR (#2 AND # 3)
	#5: ("deglutition"[Mesh] OR "deglutition disorders"[Mesh] OR deglutition[ti/ab] OR swallow[ti/ab] OR swallowing[ti/ab] OR dysphagia[ti/ab] OR odynophagia[ti/ab] OR "nutritional status"[Mesh] OR nutritional status[ti/ab] OR nutrition[ti/ab] OR oral intake[ti/ab] OR tube feeding[ti/ab] OR "Respiratory Aspiration"[Mesh] OR aspiration[ti/ab] OR penetration[ti/ab])
	#6: ("diagnosis"[Mesh] OR assessment[ti/ab] OR diagnose[ti/ab] OR diagnostic[ti/ab] OR diagnostics[ti/ab])
	#7: ("therapeutics"[Mesh] OR "rehabilitation"[Mesh] OR therapy[ti/ab] OR treatment[ti/ab] OR therapeutic*[ti/ab] OR rehabilitation[ti/ab] OR intervention[ti/ab] OR exercise[ti/ab] OR therapeutic exercise[ti/ab])
	#8: #6 OR #7
	#9: #4 AND #5 AND #8
	* In Embase EMTREE terms were used instead of Mesh terms

Critical appraisal

Susceptibility to bias was assessed for the selected relevant articles, according to previously defined criteria from the Cochrane Handbook for Systematic Reviews of Interventions[11]. Risk on bias was scored low (A), moderate (B), or high (C) (Table 2). When discordant judgment occurred between reviewers, consensus was gained by discussion. Subsequently, relevant articles with low/moderate risk on bias were summarized and discussed.

Table 2. Criteria and definition of risk on bias, described by the Cochrane Handbook for Systematic Reviews

Criteria			Risk on bias	Interpretation	Relationship to criteria
clear description of	study group	gender, age, tumor stage and location	A. Low	all criteria met	plausible bias very unlikely to seriously alter the results
	followed treatment	exact surgical intervention, type of (C)RT	B. Moderate	one or more criteria partly met	plausible bias that raises some doubt about the results
	patient inclusion criteria	no selection bias			
	follow-up	length; > 3 months	C. High	one or more criteria not met	plausible bias that seriously weakens confidence in the results
	% drop outs	reasons for drop outs			
reliability of outcome measures	referenced, validated or self-made tests, swallowing observation by 1 or more observers, inter- and intra-rater reliability percentage				

RESULTS

The above-described search (January 1, 2012 to October 31, 2013) resulted in 1141 articles (MEDLINE/Pubmed: 459, EMBASE: 681, Cochrane: 1). After screening on title/abstract, 69 articles remained for full-text evaluation of which 26 qualified for risk on bias analysis[1, 3, 4, 8-10, 12-31]. Seven (systematic) review articles[1, 4, 10, 16, 21, 27, 29] were excluded for this assessment and summarized separately (see Table 3). The remaining 19 articles were cohort- or case-control studies, of which 11 were singled out for additional attention based on low/moderate risk on bias (Table 4). Furthermore, related articles and references were screened, which yielded one additional article with low risk on bias[32] (Figure 1 shows consort flow-chart). The results will be discussed in two separate sections. Firstly, dysphagia assessment will be addressed with an emphasis on timing and on the various tools used. Secondly, optimal dysphagia treatment will be discussed with special focus on treatment goals and options.

Assessing Dysphagia

In total 11 studies or reviews discussed dysphagia assessment[3, 4, 8, 9, 14, 18, 19, 21, 23, 29, 30] (Tables 3 and 4).

Timing

Raber-Durlacher e.a. emphasized in their review that dysphagia evaluation should start pre-treatment, since many patients may present with swallowing difficulties already pre-treatment[29]. Also Tippett and Webster stress that patients should be queried about their pre-treatment swallowing status[8]. Moreover, pre-treatment assessment provides information for predicting post-treatment function and for comparison, since all treatment modalities may result in swallowing dysfunction[29]. According to Russi, surgical interventions might cause specific anatomic/neurologic damage conditioning site-specific patterns of dysphagia and aspiration[4], as "in general, surgical procedures with larger defects produce greater deficits". However, swallowing function is more adversely affected after chemotherapy (CT) and/or radiotherapy (RT), predominantly due to generalized weakness and un-coordination in deglutition[4]. Though, as patients generally are treated with both modalities, individual roles of RT/CT in swallowing disorders are difficult to distinguish[4]. Both acute and long-term swallowing dysfunction may occur. Cartmill e.a. reported that swallowing function was significantly worse 2-years post-treatment compared to baseline[14].

Assessment tools

The described swallowing assessment tools include clinical, instrumental, subjective, and global functional evaluations[3, 4, 8, 9, 14, 18, 19, 21, 23, 29, 30].

Evaluation should start with clinical assessments (medical history and physical examination) to screen for dysphagia, identify possible aetiology, determine risk of aspiration, ascertain need for non-oral nutrition, and recommend additional procedures[4, 21].

Secondly, as stressed by several authors, instrumental assessments provide objective information about swallowing function and safety[4, 21, 29], especially Videofluoroscopy of Swallowing (VFS) or Fiberoptic Endoscopic Examination of Swallowing (FEES)[4, 18, 21, 29]. VFS objectively assesses the swallowing process, and findings can be scored using various criteria, e.g. the Penetration-Aspiration-Scale. FEES is another appropriate method to assess dysphagia, which directly visualizes the pharyngeal swallowing phase by using transnasal endoscopy. While observed rates of swallowing-related abnormalities are acceptable and appropriate dietary recommendations and rehabilitation programs can be formulated based on FEES observations, Deutschmann reported that FEES is less suitable for predicting aspiration[18]. Cine-MRI, described by Kreeft e.a. is another (additional) instrument to evaluate swallowing function in patients with oral/oropharyngeal cancer. It directly visualizes the dynamics of swallowing, and abnormal findings are thought to correlate with subjective complaints[23]. Overall, instrumental testing is crucial to document swallowing function in HNC patients. VFS is commonly used, since it is more suitable for diagnosing aspiration during the swallow and more informative for detecting problems below the upper esophageal sphincter. At bedside, however, FEES is often used because of its accessibility. All in all, the

choice of examination seems to depend upon clinical presentation, available instruments and clinician's preferences[4, 21, 29, 30].

Thirdly, some psychometrically validated (patient-reported) QOL forms (EORTC-HN/-C30, FACT-HN, MDADI etc.) are available to assess functional outcomes in HNC patients. Chen e.a. discuss that the MD Anderson Dysphagia Inventory (MDADI), which is specifically validated for HNC patients, is very useful for evaluating the impact of dysphagia on QOL in HNC patients[31, 33]. Other subjective questionnaires applying to specific aspects of swallowing and their impact on QOL include the Sydney Swallow Questionnaire (SSQ), the Swallowing Quality of Life (SWAL-QOL) questionnaire, and the Patient Concerns Inventory (PCI). The SSQ, originally designed for evaluation difficulties in neuromyogenic dysphagia patients, according to Dwivedi is also useful for swallowing evaluation in oral/oropharyngeal cancer patients treated with primary surgery[9]. The SWAL-QOL is validated to identify patients with swallowing problems, especially after treatment for oral, oropharyngeal, and laryngeal cancer, as pointed out by several groups[15, 34]. According to Ghazali e.a. the PCI might be valuable for routine screening of self-reported swallowing dysfunction, since it enables patients' concerns to be addressed during out-patient-clinic consultations[19]. In addition, there are some clinician-rated performance scales. The Performance Status Scale for HNC patients (PSS-HN)[35], an expert-rated instrument with three subscales (eating in public, understandability of speech, and normalcy of diet), is most recommended within HNC treatment. The Dysphagia Outcome and Severity Scale (DOSS) is another simple, easy-to-use scale, developed to systematically rate functional dysphagia severity based on objective assessment, and to make recommendations for diet level, independence level and nutrition[36]. Another simple, comprehensive way to assess patients' functional impairment is the Functional Intraoral Glasgow Scale (FIGS), used by Ellaban e.a. to determine patients' ability to speak, chew and swallow. However, this scale is only useful following surgery of oral cavity tumours[3].

From this systematic literature search it became clear that, although patient-reported measures are commonly applied and provide complementary perspectives[1], in most studies correlation with objective outcomes is poor[10, 29, 37]. Van der Molen e.a. assessed pre-treatment organ function in advanced HNC through various outcome measures and patients' views. VFS identified laryngeal aspiration/penetration in 18% of patients, whereas only 7 patients (13%) perceived this as problematic, and only 2 of 7 patients with objective trismus actually perceived trismus[37]. Therefore, combining several subjective and objective evaluations remains mandatory[21, 29].

Finally, as pointed out by Hutcheson and Lewin, it seems appropriate to record some global indicators of functional status (e.g. changes in body weight/body mass index, dietary changes, tube- and tracheotomy-dependency) as surrogate measures of function, because these are often available in patient records and usually easy to interpret[1].

Table 3. Results included reviews

Study	Focus	Results	Conclusion
Batth, 2013, Review	The current literature about the feasibility and dosimetric parameters of IMRT to maintain swallowing function in HNC patients	RT doses to the swallowing organs at risk should be limited to <40 Gy for the glottic/ supraglottic larynx and to <55 Gy for the pharyngeal constrictors	IMRT is promising for reducing the incidence of dysphagia, but controversies exist regarding the delineation of swallowing structures and the most important dosimetric parameters
Cousins, 2013, Review	Interventions for eating and drinking problems following treatment for HNC	There is some evidence to support interventions aimed at improving swallowing and jaw mobility following HNC treatment, but studies are limited by their size and scope	Larger, high quality studies which include PRO measures are required for patient-centred rehabilitation programmes
Hutcheson, 2012, Review	Dysphagia and other functional outcomes after chemoradiotherapy for laryngeal and pharyngeal cancers	Growing evidence supports the benefit of preventive swallowing therapy to reduce the burden of dysphagia	Analysis of functional outcomes should be included in phase III organ preservation trials to allow reliable comparisons between treatment regimens
Hutcheson, 2013, Review	Clinically functional outcomes, methods of pretreatment functional assessments, strategies to reduce or prevent functional complications, and posttreatment rehabilitation considerations in patients with oral cavity and oropharyngeal cancers	Functional rehabilitation after treatment requires individulized planning and should be guided by a multidisciplinary team	Speech and swallowing outcomes are principal determinants of QOL during HNC survivorship
Paleri, 2013, Review	Strategies to improve long-term swallowing morbidity and quality of life following CRT for HNC	1. Benefits seem to exist for preventative exercise programs to address oral and pharyngeal structures 2. Better swallowing outcomes are likely when nasogastric (in preference to gastrostomy) tubes are used to supplement enteral nutrition during CRT 3. Radiation dose restriction to swallowing structures with IMRT leads to better swallowing outcomes	There is a trend for better swallowing outcomes to be experienced; more prospective studies, taking into account the drawback of the studies published so far, need to be performed to generate more confidence in the previously reported results
Raber-Durlacher, 2012, Review	Dysphagia literature between 1990-2010	Various assessment tools for dysphagia, related to multiple factors, exist	More prospective studies on the course of dysphagia and impact on QOL after various treatment modalities are needed

Russi, 2012, Review	The main causes of dysphagia in HNC patients and recommendations for patients submitted to RT	The causes of dysphagia after CRT might be due to generalized weakness and un-coordination in deglutition. The individual role of CT and RT in dysphagia is difficult to distinguish	In HNC patients, disease control has to be considered together with functional impact on sallowing function. SLPs should be included in a multidisciplinary approach to HNC

RCT = randomized controlled trial, PC = prospective cohort study, RC = retrospective cohort study, HNC = head and neck cancer, QOL = quality of life, CRT = chemoradiation, RT = radiotherapy, CT = chemotherapy, IMRT = intensity modulated radiotherapy, MRI = magnetic resonance imaging, PRO = patient reported outcome, SLP = speech language pathologist, NA = non applicable

Table 4. Results included articles

Study	Focus		Swallowing Outcomes		Results	Conclusion
Author, year, type	Patients	Assessment / Treatment	Primary	Secondary		
Low risk on bias (total score A)						
Carnaby-Mann, 2012, RCT	58 HNC patients treated with CRT	Treatment: Usual care, sham swallowing-, or active swallowing exercises during CRT treatment	Muscle size and composition (T2-weighted MRI)	Functional swallow ability, dietary intake, chemosensory function, nutrition, salivation, and complications	Less deterioration in swallowing musculature, and better functional swallowing, mouth opening, chemosensory acuity, and salivation rate in the active treatment arm	Patients completing the swallowing exercises during CRT treatment demonstrated superior muscle maintenance and functional swallowing ability
Cartmill, 2012, PC	12 oro-pharyngeal cancer patients treated with CRT	Assessment: Toxicity (dysphagia and salivary) ratings, dietary tolerance, weight, and patient-rated swallowing and general function	Swallowing and xerostomia (CTCAE subscales for dysphagia and salivary)	Oral intake, weight, functional swallowing (RBHOMS measures), weight, and patient-rated swallowing (MDADI) and general (FACT-HN) function	Swallowing and salivary toxicity at 2 years post-treatment was significantly deteriorated, with the majority requiring ongoing dietary restriction and reporting a significant negative impact on the physical aspects of swallowing	The longterm swallowing and nutritional problems highlight the need for ongoing speech pathology, dietetic, social work, and psychology involvement in assisting patients to return to their pretreatment oral intake / body weight, and adapt and adjust to potentially lifelong negative HNC treatment related sequels
Ellaban, 2013, PC	62 surgically treated oral cancer patients	Assessment: Functional intraoral Glasgow scale (FIGS)	Oral function (FIGS score) following surgical resection in the floor of mouth (FOM)	Tumor characteristics, surgical- and CRT parameters	Tumor site and size, surgical access, resection and reconstruction showed significant influence on oral function (FIGS score) following surgical resection in the FOM	The FIGS is a simple and comprehensive way of assessing a patient's functional impairment following surgery in the FOM

Hutcheson, 2013, RC	497 pharyngeal cancer patients treated with definitive RT or CRT	Treatment: Proactive swallowing therapy and maintaining oral intake during treatment	Final diet (oral intake status) after treatment, duration of gastrostomy dependence, and adherence to a swallowing exercise regimen	Patient, tumor, and treatment characteristics	Maintenance of oral intake during treatment and swallowing exercise adherence were independently associated with better long-term diet after RT or CRT and shorter duration of gastrostomy dependence (adjusted for tumor and treatment burden)	Maintenance of oral intake throughout RT or CRT and adherence to swallowing exercises are independently associated with better longterm swallowing outcomes; patients who either eat or exercise fare better and patients who do both have the highest rate of return to a regular diet and shortest duration of gastrostomy dependence
Kotz, 2012, RCT	26 HNC patients treated with CRT	Treatment: Targeted swallowing exercises or no exercises throughout CRT treatment	Functional Oral Intake Scale (FOIS) and Performance Status Scale for HNC patients (PSS-H&N)	Patient, tumor, and treatment characteristics	The intervention group had significantly better scores after 3 and 6 months of treatment versus the control group, without significant differences directly and after 9 and 12 months of treatment	Prophylactic swallowing exercises during CRT treatment improved swallowing function at 3 and 6 months post-treatment
Molen van der, 2013, RCT	29 advanced HNC patients treated with CRT	Treatment: Routine swallowing exercises and swallowing exercises based on the TheraBite Jaw Motion Rehabilitation System	Videofluoroscopy: swallowing function, penetration and/or aspiration scale (PAS), and presence of residue	Maximum interincisor mouth opening (MIO), weight changes, Functional Oral Intake Scale (FOIS), and some study-specific questions	All tumor- and treatment-related problems (except xerostomia) diminished at 1 year post-treatment; only weight gain additionally improved at 2 years post-treatment, with a slight but significant benefit for the experimental group	Both rehabilitation programs are feasible and showed good compliance despite the burdensome CRT, with limited overall functional problems at 1 and 2 years post-treatment
Zhen, 2012, PC	46 surgically treated tongue cancer patients	Treatment: Swallowing exercises during 2 weeks following treatment	Swallowing function (MDADI)	Swallowing-related QOL (MDADI)	The overall MDADI score was better in the experimental group compared with the control group	Swallowing exercises improved dysphagia and QOL in surgically treated tongue cancer patients

Moderate risk on bias (total score B)						
Deutschmann, 2013, RC	116 HNC patients after primary treatment	Assessment: Fiber-optic endoscopic evaluation of swallowing (FEES)	Swallowing-related adverse events (aspiration pneumonia, obstruction, presence of a feeding tube for progressive malnutrition)	Other FEES characteristics: sensation of epiglottis and tongue base, vocal fold adduction, pharyngeal residue, PAS, and diet advices	The overall rate of adverse events was 10.1% The PAS score was the only statistically significant predictor of adverse events	The observed rate of swallowing-related adverse events is acceptable; FEES guides appropriate and safe diet recommendations in the HNC population
Dwivedi, 2012, PC	54 oral / oropharyn-geal cancer patients treated with primary surgery	Assessment: Sydney Swallow Questionnaire (SSQ)	Evaluation of swallowing function by PRO difficulties	Clinico-demographic variables	Tumor site and (T) stage, patient's age, and type of reconstruction directly affect post-treatment swallow outcome	The SSQ is a useful tool for evaluation of swallowing in HNC patients
Ghazali, 2012, PC	204 post-treatment oral / oro-pharyngeal patients	Assessment: Patient Concerns Inventory (PCI) and UW-QOL questionnaire	Items on swallowing function (PCI and UW-QOL)		Swallowing problems were reported by respectively 17% of PCI and 21% of UW-QOL respondents	Both surveys concurrently enabled all patients to discuss their swallowing issues and to acces appropriate multi-disciplinaire treatment
Kreeft, 2012, PC	23 patients with advanced oral / oro-pharyngeal cancer	Assessment: cine MRI	Oral mobility on cine MR	Oral mobility on videofluoroscopy (VHS) and QOL questionnaires	Impaired mobility on cine MRI was significantly correlated to more swallowing problems, on videofluoroscopy not	Cine MRI is a promising new technique as an adjunct to standard examinations for evaluation of swallowing in patients with oral and oropharyngeal cancer
Tippet, 2012, RC	53 HNC patients treated with CRT.	Assessment: Videofluoro-scopic studies (VFSS)	Videofluoroscopic swallowing parameters	Xerostomia, Trismus, PEG tube dependency, HPV-status	Pharyngeal impairments were common on posttreatment VFSS, but these did not preclude oral intake during treatment	Futher research directions include determining clinical correlates of dysphagia severity, investigating compliance with treatment, and examining relationship of oral intake and dysphagia

RCT = randomized controlled trial, PC = prospective cohort study, RC = retrospective cohort study, HNC = head and neck cancer, QOL = quality of life, CRT = chemoradiation, RT = radiotherapy, CT = chemotherapy, IMRT = intensity modulated radiotherapy, MRI = magnetic resonance imaging, PRO = patient reported outcome, SLP = speech language pathologist, NA = non applicable

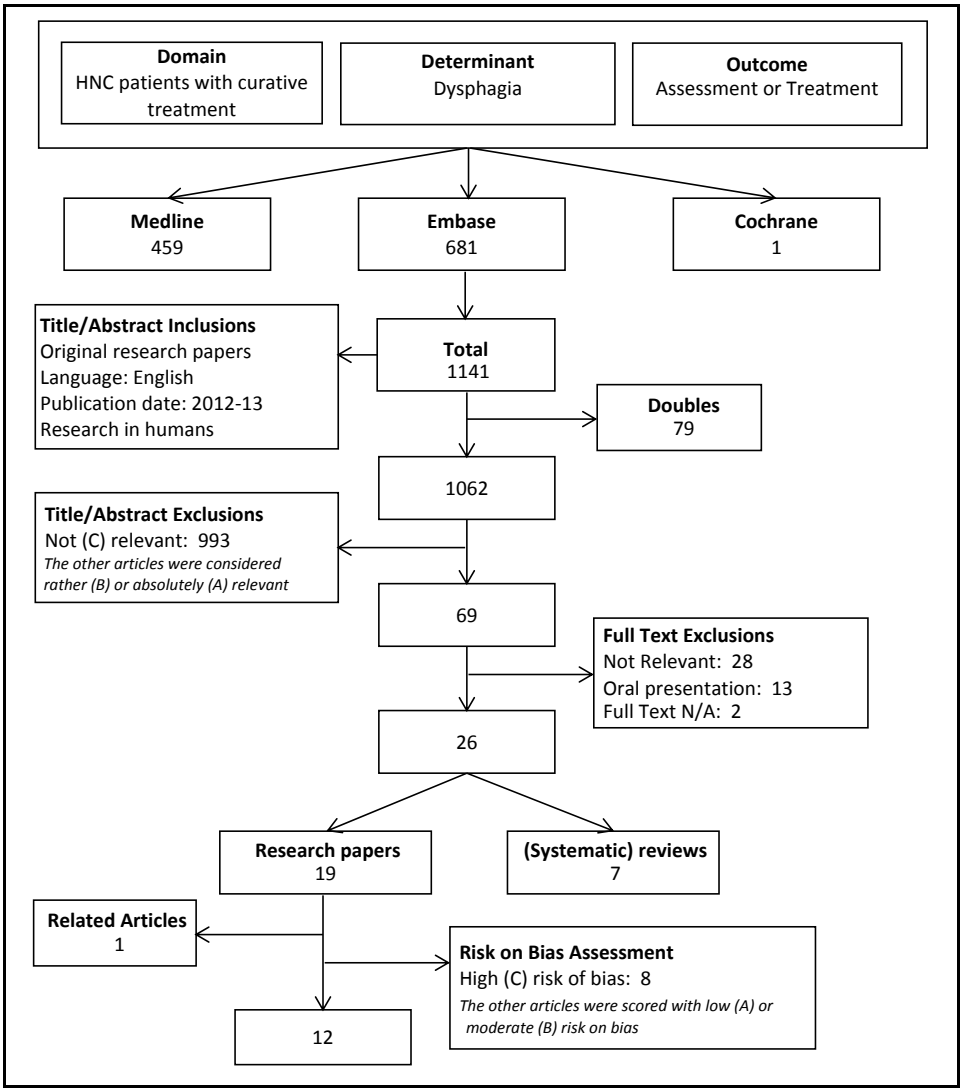


Figure 1.

Treating Dysphagia

Ten studies or reviews reported on dysphagia treatment[1, 8, 10, 12, 13, 16, 21, 22, 27, 31] (Tables 3 and 4).

Treatment goals

All authors stated that efficient management of dysphagia symptoms must be achieved. Goals of treatment are to improve food transfer (preventing malnutrition/dehydration), to reduce aspiration, and to enhance QOL. According to Tippett and Webster[8], absence of pre-

treatment dysphagia is not predictive for post-treatment dysphagia, which is quite obvious, since all treatment modalities have the potential to adversely impact swallowing function. This underscores the need for early (preventive) intervention in all patients (at risk) to address anticipated swallowing-related difficulties[8].

Treatment options

Several strategies are discussed, including compensatory techniques (postural changes, diet modifications), non-swallow (Shaker) exercises, swallowing (Mendelsohn, Masako, effortful swallow, (super-)supraglottic swallow) exercises, and range of motion or resistance exercises. The approach chosen depends upon the aetiology, and an appropriate therapy program may include either one or combinations of the above strategies, all to facilitate bolus transit during swallowing. Additionally, swallow-related issues such as trismus and xerostomia should be taken into account, since these are known to impact QOL as well[8]. There is also evidence now supporting that functional interventions can improve jaw mobility and range of motion following HNC treatment (e.g. by applying the TheraBite® device)[12, 38].

When conservative measures are insufficient to help ensure safe oral intake, surgical interventions or other therapies may be considered. Weakness of pharyngeal musculature (less powerful bolus propulsion) sometimes can be surgically remedied by reducing tonus of the esophageal sphincter. Alternative treatments are neuromuscular electrical stimulation (NMES) or dilatation. Combining these latter rehabilitation regimens might improve swallowing function in patients with radiation-induced dysphagia, as was recently demonstrated by Long and Wu for nasopharyngeal cancer patients[25].

Use it or lose it

Multiple studies have demonstrated benefits of maintained use of swallowing musculature ('use it or lose it') during CRT treatment, by avoiding periods of nothing per oral (NPO) and adherence to targeted swallowing exercises[1, 12, 13, 17, 22, 27, 32]. Van der Molen e.a. in the first randomized controlled trial (RCT) about HNC patients undergoing CRT with rehabilitation, concluded that preventive exercises were helpful in reducing extent and/or severity of various functional short-term effects[12, 38], with limited problems at one- and two-years post-treatment[12]. According to Carnaby-Mann e.a. and Crary, prophylactic exercises may result in maintenance of oral and oropharyngeal musculature, improved (strength of) swallowing function, and less dysphagia-related aspiration pneumoniae[13, 17]. If exercises are introduced pre-treatment, swallowing function is still (more or less) intact and RT- and/or atrophy-related muscle damage has not occurred yet, as was stressed in the review of Cousins and the RCT of van der Molen e.a.[12, 16]. Therefore, rehabilitation should be addressed during pre-treatment counselling and patients should adhere to the exercises during/after the oncologic intervention.

Surgically treated patients benefit from swallowing exercises as well, to improve swallowing function (oral control and pharyngeal transit) and QOL, as Zhen e.a. showed for patients with dysphagia post tongue resection[31]. Hence, referral to a speech language pathologist (SLP), prior to any treatment is considered mandatory in multidisciplinary HNC management[1].

Furthermore, prophylactic tube feeding (with NPO periods) is often applied during treatment for providing adequate nutritional supplementation[27]. However, this reduces patient's need for maintaining oral intake and thus swallowing, which might cause more swallowing problems post-treatment[27, 32]. Hutcheson e.a. evaluated the effects of maintaining oral intake throughout (C)RT treatment and swallowing exercise adherence on post-treatment swallowing outcomes (final diet post-treatment and duration of feeding-tube dependence). They found significant better long-term outcomes (better oral intake status and shorter duration of gastrostomy dependence) for both parameters independently[32].

DISCUSSION

In HNC treatment, (C)RT techniques have evolved rapidly, especially the introduction of IMRT to reduce dysphagia, since relationships were found between dosage to pharyngeal structures and swallowing function[39]. However, although IMRT is the best organ-sparing RT technique that is already widely used and certainly reduces toxicity to pharyngeal structures, it may still significantly impair swallowing function, even 2-years after treatment[14]. Therefore, in recent years, more attention has been drawn to dysphagia and its devastating impact on QOL in HNC patients. Likewise, surgical treatments potentially yield severe functional deficits in HNC patients, most notably with regard to swallowing function, but only limited numbers of studies have been published concerning functional consequences after surgery[2].

The purpose of this review was to evaluate current assessment and treatment strategies of dysphagia in all HNC patients. In general, swallowing outcomes and training have become increasingly important in HNC rehabilitation. Functional success is best achieved with a multidisciplinary team including SLPs, who play an indispensable role in (preventive) dysphagia rehabilitation[1, 4, 8, 16, 21, 29].

Optimizing swallowing outcomes begins with comprehensive baseline assessments, since HNC patients comprise already pre-treatment an elevated risk for dysphagia[37], and should be continued per/post-treatment. Validated measures from instrumental examinations are considered gold-standard, because these are not confounded by subjective factors inherent to patient-reported metrics[1]. However, FEES and VFS studies contain some subjectivity as well because clinicians apply personal interpretations of various criteria. The inter-observer variation in interpreting these studies in quite high. Therefore, instrumental, clinician-reported examinations always should be combined with complementary patient-reported outcomes[21, 29].

Furthermore, this review confirms the low degree of standardized outcomes in HNC treatment. Three RCTs coupling prophylactic swallowing therapy with avoidance of NPO intervals demonstrated positive effects on important functional endpoints[13, 22, 38]. Van der Molen e.a. in the first RCT on this topic demonstrated that compliance was quite good, with a majority of patients (69%) being able to perform the exercises during treatment[38], which resulted in limited functional problems at one- and two-years post-treatment[12]. In their study on this topic, Carnaby-Mann e.a., randomizing patients to standard care, sham-, and active exercises, demonstrated the effectiveness of initiating preventive therapy pre-treatment, in terms of superior muscle maintenance and functional swallowing ability[13]. Similarly, Kotz e.a. performed a RCT on multiple prophylactic swallowing exercises, one of the first examining the super-supraglottic swallow. Significantly better scores were found in the experimental arm three- and six-months post-treatment (although this effect was not seen immediately or at nine- and 12-months post-treatment), which provides additional evidence that patients should adhere to the exercises – especially during treatment[22]. Unfortunately, there is lack of consensus regarding time, type, frequency, or intensity of exercises, which suggests further research by RCTs assessing optimal treatment strategies. Also longer follow-up with continuation of exercises is needed, given the potential for long-term sequels, even in absence of swallowing disorders pre- or shortly post-treatment. Compliance might improve when patients are counselled more intensively, as was demonstrated by van der Molen e.a.[38]. Besides, maintenance of oral intake during treatment seems to be associated with better long-term swallowing outcomes, as well[32]. Hutcheson e.a. found an independent, positive association for eating during treatment in approximately 500 patients, who had complete response to definitive (C)RT for pharyngeal cancers. However, the retrospective dataset did not control for acute toxic effects such as mucositis or odynophagia, which both can affect patients' ability to eat (and exercise) during treatment. Therefore, there might have been selection bias in the groups that either did or did not need a feeding tube. Future prospective studies should examine these factors, to ensure the observed effects are not merely a reflection of severe changes from treatment, that preclude swallowing activity during (C)RT. Interestingly, only few studies about (prolonged) tube placement and dependency per-/post-treatment, and its negative impact on swallowing, were identified in our search. In order to limit the rate of tube placement during treatment (to improve long-term swallowing function), further research on this topic is required. Furthermore, there is room for improvement in delineating radiation fields and adjustments during treatment, to better spare salivary glands and pharyngeal muscle/mucosa structures, and to further reduce dosage to functionally important structures.

Finally, this literature review clearly demonstrates the increasing interest in and awareness about this topic, considering the numerous reviews about various assessment and treatment strategies for dysphagia – which all stress the importance of further longitudinal studies.

However, data from prospective studies, which actually evaluated these topics (especially from RCTs), and data on dysphagia in patients who underwent a laryngectomy or other surgical treatments, are still limited.

CONCLUSION

Over the last years, functional swallowing assessment and treatment have become standard of care in head and neck cancer patients, given the serious impact of dysphagia on quality of life. However, there is still no uniform 'gold-standard' for either assessment or treatment strategies. More high quality data, adequately controlled, adequately powered and randomized, on prophylactic and therapeutic swallowing exercises are needed, with longer follow-up and optimal adherence to treatment, in order to better reduce toxicity of chemo- and radiotherapy, and possibly modify surgical resections and reconstructions. In addition, frequency, timing and duration of therapy need further studies to improve swallowing function and optimize quality of life.

KEY-POINTS

- Xerostomia, fibrosis, mucositis, and anatomical changes (neuropathies) are the major sequels affecting swallowing function following head and neck cancer treatment;
- Swallowing function has a major impact on quality of life during head and neck cancer survivorship;
- Pre-, per- and post-treatment functional swallowing assessment is an important short- and long-term component of comprehensive care in head and neck cancer patients;
- Head and neck cancer patients benefit from pre-, per- and post-treatment swallow exercises that address all structures involved in swallowing (the 'use it or lose it' concept);
- There is a lack of consensus regarding dysphagia therapy, despite growing evidence supporting the benefits of preventive swallowing therapy.

ACKNOWLEDGEMENTS

The department of Head and Neck Oncology and Surgery receives an unrestricted research grant of Atos Medical AB, Sweden.

REFERENCES

Papers of particular interest, published within the annual period of review, have been highlighted as special (*) or outstanding (**) interest.

1. Hutcheson KA, Lewin JS. Functional outcomes after chemoradiotherapy of laryngeal and pharyngeal cancers. Curr Oncol Rep. 2012;14:158-65.
2. Kreeft AM, van der Molen L, Hilgers FJ, Balm AJ. Speech and swallowing after surgical treatment of advanced oral and oropharyngeal carcinoma: a systematic review of the literature. Eur Arch Otorhinolaryngol. 2009;266:1687-98.
3. Ellabban MA, Shoaib T, Devine J, McMahon J, Morley S, Adly OA, et al. The functional intraoral Glasgow scale in floor of mouth carcinoma: longitudinal assessment of 62 consecutive patients. Eur Arch Otorhinolaryngol. 2013;270:1055-66.
4. Russi. Swallowing dysfunction in head and neck cancer patients treated by radiotherapy: Review and recommendations of the supportive task group of the Italian Association of Radiation Oncology. Cancer Treatment Reviews. 2012;38:1033-49.
5. Langendijk JA, Doornaert P, Verdonck-de Leeuw IM, Leemans CR, Aaronson NK, Slotman BJ. Impact of late treatment-related toxicity on quality of life among patients with head and neck cancer treated with radiotherapy. J Clin Oncol. 2008;26:3770-6.
6. Mowry SE, Tang C, Sadeghi A, Wang MB. Standard chemoradiation versus intensity-modulated chemoradiation: a quality of life assessment in oropharyngeal cancer patients. Eur Arch Otorhinolaryngol. 2010;267:1111-6.
7. Roe JW, Carding PN, Dwivedi RC, Kazi RA, Rhys-Evans PH, Harrington KJ, et al. Swallowing outcomes following Intensity Modulated Radiation Therapy (IMRT) for head & neck cancer - a systematic review. Oral Oncol. 2010;46:727-33.
8. Tippett DC, Webster KT. Rehabilitation needs of patients with oropharyngeal cancer. Otolaryngol Clin North Am. 2012;45:863-78.
9. Dwivedi. Evaluation of swallowing by Sydney swallow questionnaire (SSQ) in oral and oropharyngeal cancer patients treated with primary surgery. Dysphagia. 2012;27:491-7.
10. Batth SS, Caudell JJ, Chen AM. Practical considerations in reducing swallowing dysfunction following concurrent chemoradiotherapy with intensity-modulated radiotherapy for head and neck cancer. Head Neck. 2014 Feb;36(2):291-8.
11. Higgins JP, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration; 2011. Available from www.cochrane-handbook.org. [Assessed 8 november 2013].
12. (**) van der Molen L, van Rossum MA, Rasch CR, Smeele LE, Hilgers FJ. Two-year results of a prospective preventive swallowing rehabilitation trial in patients treated with chemoradiation for advanced head and neck cancer. Eur Arch Otorhinolaryngol. 2014 May;271(5):1257-70.

    This first prospective RCT on preventive (standard or experimental) swallowing rehabilitation for advanced head and neck cancer patients treated with chemoradiotherapy, showing quite good compliance and limited functional problems at 1- and 2-years post-treatment.
13. Carnaby-Mann G, Crary MA, Schmalfuss I, Amdur R. "Pharyngocise": randomized controlled trial of preventative exercises to maintain muscle structure and swallowing function during head-and-neck chemoradiotherapy. Int J Radiat Oncol Biol Phys. 2012;83:210-9.
14. Cartmill B, Cornwell P, Ward E, Davidson W, Porceddu S. Long-term functional outcomes and patient perspective following altered fractionation radiotherapy with concomitant boost for oropharyngeal cancer. Dysphagia. 2012;27:481-90.
15. Cnossen IC, de Bree R, Rinkel RN, Eerenstein SE, Rietveld DH, Doornaert P, et al. Computerized monitoring of patient-reported speech and swallowing problems in head and neck cancer patients in clinical practice. Support Care Cancer. 2012;20:2925-31.

16. (*) Cousins. A systematic review of interventions for eating and drinking problems following treatment for head and neck cancer suggests a need to look beyond swallowing and trismus. Oral Oncology. 2013;49:387-400.

This review evaluates several rehabilitation interventions (swallowing exercises alone/ combined with other interventions, jaw mobility exercises with/without medical devices, mechanical devices alone, and swallowing interventions combined with jaw mobility interventions) in order to improve the physical difficulties (swallowing and jaw mobility), but also the functional and psychosocial difficulties with eating and drinking following HNC treatment.

17. Crary. Functional and physiological outcomes from an exercise-based dysphagia therapy: A pilot investigation of the mcneill dysphagia therapy program. Archives of Physical Medicine and Rehabilitation. 2012;93:1173-8.

18. Deutschmann. Fiber-optic endoscopic evaluation of swallowing (FEES): Predictor of swallowing-related complications in the head and neck cancer population. Head and Neck. 2013;35:974-9.

19. Ghazali N, Kanatas A, Scott B, Lowe D, Zuydam A, Rogers SN. Use of the Patient Concerns Inventory to identify speech and swallowing concerns following treatment for oral and oropharyngeal cancer. J Laryngol Otol. 2012;126:800-8.

20. Hunter KU, Schipper M, Feng FY, Lyden T, Haxer M, Murdoch-Kinch CA, et al. Toxicities affecting quality of life after chemo-IMRT of oropharyngeal cancer: prospective study of patient-reported, observer-rated, and objective outcomes. Int J Radiat Oncol Biol Phys. 2013;85:935-40.

21. (**)Hutcheson KA, Lewin JS. Functional assessment and rehabilitation: how to maximize outcomes. Otolaryngol Clin North Am. 2013;46:657-70.

This review correctly underscores the need for both standardized, comprehensive baseline assessments (speech and swallowing outcomes) as functional, individualized rehabilitation post-treatment in oral cavity/ oropharyngeal cancer patients.

22. Kotz T, Federman AD, Kao J, Milman L, Packer S, Lopez-Prieto C, et al. Prophylactic swallowing exercises in patients with head and neck cancer undergoing chemoradiation: a randomized trial. Arch Otolaryngol Head Neck Surg. 2012;138:376-82.

23. Kreeft AM, Rasch CR, Muller SH, Pameijer FA, Hallo E, Balm AJ. Cine MRI of swallowing in patients with advanced oral or oropharyngeal carcinoma: a feasibility study. Eur Arch Otorhinolaryngol. 2012;269:1703-11.

24. Krisciunas. Survey of usual practice: Dysphagia therapy in head and neck cancer patients. Dysphagia. 2012;27:538-49.

25. Long YB, Wu XP. A randomized controlled trail of combination therapy of neuromuscular electrical stimulation and balloon dilatation in the treatment of radiation-induced dysphagia in nasopharyngeal carcinoma patients. Disabil Rehabil. 2013;35:450-4.

26. More YI, Tsue TT, Girod DA, Harbison J, Sykes KJ, Williams C, et al. Functional swallowing outcomes following transoral robotic surgery vs primary chemoradiotherapy in patients with advanced-stage oropharynx and supraglottis cancers. JAMA Otolaryngol Head Neck Surg. 2013;139:43-8.

27. (**)Paleri V, Roe JW, Strojan P, Corry J, Gregoire V, Hamoir M, et al. Strategies to reduce long-term postchemoradiation dysphagia in patients with head and neck cancer: An evidence-based review. Head Neck. 2014 Mar;36(3):431-43.

This review discusses the evidence for three important strategies to improve swallowing function after chemoradiation: preventative swallowing exercises, maintenance of oral intake (continued oral swallowing), and radiation dose restriction to swallowing structures by using IMRT.

28. Pauloski BR, Logemann JA, Rademaker AW, Lundy D, Sullivan PA, Newman LA, et al. Effects of enhanced bolus flavors on oropharyngeal swallow in patients treated for head and neck cancer. Head Neck. 2013;35:1124-31.

29. Raber-Durlacher JE, Brennan MT, Verdonck-de Leeuw IM, Gibson RJ, Eilers JG, Waltimo T, et al. Swallowing dysfunction in cancer patients. Support Care Cancer. 2012;20:433-43.

30. Roe JW, Carding PN, Rhys-Evans PH, Newbold KL, Harrington KJ, Nutting CM. Assessment and management of dysphagia in patients with head and neck cancer who receive radiotherapy in the United Kingdom - a web-based survey. Oral Oncol. 2012;48:343-8.

31. Zhen Y, Wang JG, Tao D, Wang HJ, Chen WL. Efficacy survey of swallowing function and quality of life in response to therapeutic intervention following rehabilitation treatment in dysphagic tongue cancer patients. Eur J Oncol Nurs. 2012;16:54-8.

32. (*) Hutcheson KA, Bhayani MK, Beadle BM, Gold KA, Shinn EH, Lai SY, et al. Eat and exercise during radiotherapy or chemoradiotherapy for pharyngeal cancers: use it or lose it. JAMA Otolaryngol Head Neck Surg. 2013;139:1127-34.

Data from almost 500 patients from this retrospective observational study show independent positive associations of both maintaining oral intake throughout (chemo-) radiotherapy treatment and adherence to preventive swallowing exercises with better long-term swallowing outcomes.

33. Chen AY, Frankowski R, Bishop-Leone J, Hebert T, Leyk S, Lewin J, et al. The development and validation of a dysphagia-specific quality-of-life questionnaire for patients with head and neck cancer: the M. D. Anderson dysphagia inventory. Arch Otolaryngol Head Neck Surg. 2001;127:870-6.

34. McHorney CA, Robbins J, Lomax K, Rosenbek JC, Chignell K, Kramer AE, et al. The SWAL-QOL and SWAL-CARE outcomes tool for oropharyngeal dysphagia in adults: III. Documentation of reliability and validity. Dysphagia. 2002;17:97-114.

35. List MA, Ritter-Sterr C, Lansky SB. A performance status scale for head and neck cancer patients. Cancer. 1990;66:564-9.

36. O'Neil KH, Purdy M, Falk J, Gallo L. The Dysphagia Outcome and Severity Scale. Dysphagia. 1999;14:139-45.

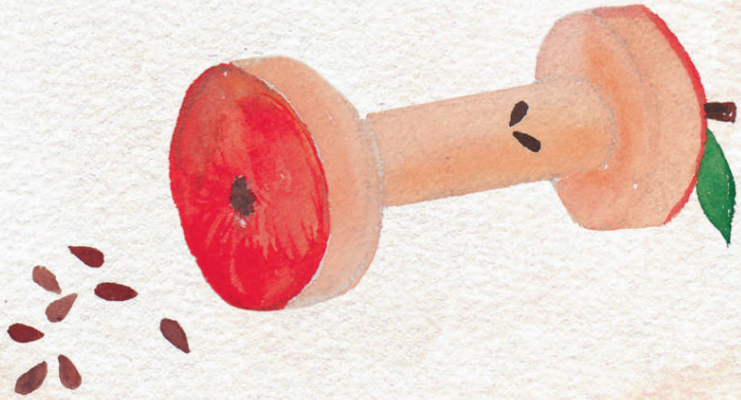
37. van der Molen L, van Rossum MA, Ackerstaff AH, Smeele LE, Rasch CR, Hilgers FJ. Pretreatment organ function in patients with advanced head and neck cancer: clinical outcome measures and patients' views. BMC Ear Nose Throat Disord. 2009;9:10.

38. van der Molen L, van Rossum MA, Burkhead LM, Smeele LE, Rasch CR, Hilgers FJ. A randomized preventive rehabilitation trial in advanced head and neck cancer patients treated with chemoradiotherapy: feasibility, compliance, and short-term effects. Dysphagia. 2011;26:155-70.39.39.

39. van der Molen L, Heemsbergen WD, de Jong R, van Rossum MA, Smeele LE, Rasch CR, et al. Dysphagia and trismus after concomitant chemo-Intensity-Modulated Radiation Therapy (chemo-IMRT) in advanced head and neck cancer; dose-effect relationships for swallowing and mastication structures.

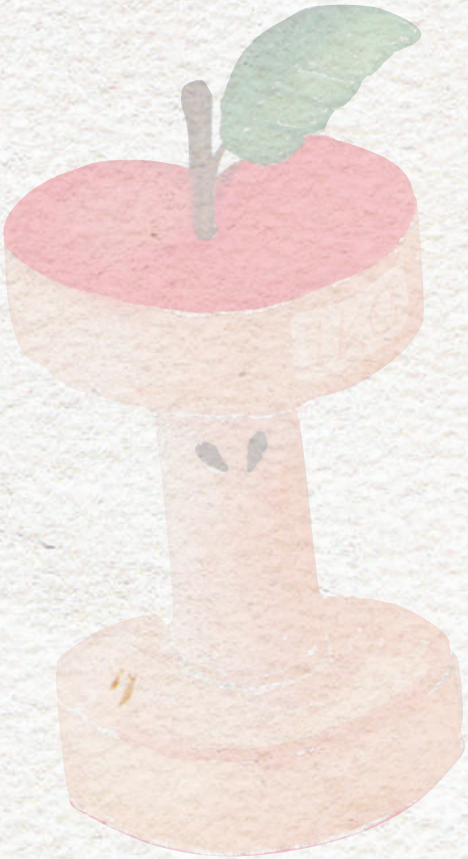
PART 1

LONG-TERM EVALUATION



CHAPTER 3

Evaluation of long-term (10-years+) dysphagia and trismus in patients treated with concurrent chemoradiotherapy for advanced head and neck cancer



S.A.C. Kraaijenga
I.M. Oskam
L. van der Molen
O. Hamming-Vrieze
F.J.M. Hilgers
M.W.M. van den Brekel

Oral Oncol. 2015; 51: 787-794.

ABSTRACT

Objectives: Assessment of long term (10-years+) swallowing function, mouth opening, and quality of life (QOL) in head and neck cancer (HNC) patients treated with chemo-radiotherapy (CRT) for advanced stage IV disease.

Materials and Methods: Twenty-two disease-free survivors, participating in a multicenter randomized clinical trial for inoperable HNC (1999-2004), were evaluated to assess long-term morbidity. The prospective assessment protocol consisted of videofluoroscopy (VFS) for obtaining Penetration Aspiration Scale (PAS) and presence of residue scores, Functional Oral Intake Scale (FOIS) scores, maximum mouth opening measurements, and (SWAL-QOL and study-specific) questionnaires.

Results: At a median follow-up of 11-years, 22 patients were evaluable for analysis. Ten patients (45%) were able to consume a normal oral diet without restrictions (FOIS score 7), whereas 12 patients (55%) had moderate to serious swallowing issues, of whom 3 (14%) were feeding tube dependent. VFS evaluation showed 15/22 patients (68%) with penetration and/or aspiration (PAS ≥3). Fifty-five percent of patients (12/22) had developed trismus (mouth opening ≤35 mm), which was significantly associated with aspiration (p =.011). Subjective swallowing function (SWAL-QOL score) was impaired across almost all QOL domains in the majority of patients. Patients treated with IMRT showed significantly less aspiration (p =.011), less trismus (p =.035), and less subjective swallowing problems than those treated with conventional radiotherapy.

Conclusion: Functional swallowing and mouth opening problems are substantial in this patient cohort more than 10-years after organ-preservation CRT. Patients treated with IMRT had less impairment than those treated with conventional radiotherapy.

KEY WORDS

Head and Neck Cancer – Chemoradiotherapy – Dysphagia – Swallowing – Mouth Opening – IMRT

INTRODUCTION

Head and neck cancer (HNC) patients are at risk to develop substantial functional impairments after organ-preserving treatment with chemoradiotherapy (CRT)[1]. Dysphagia is commonly the most severe functional impairment following this treatment. Given its serious impact on quality of life (QOL), assessment of deglutition disorders has become an important functional endpoint measure[2]. It is therefore not surprising that prevention of dysphagia has become a major focus point in HNC research. In the past decade, improved radiotherapy protocols with intensity modulated radiotherapy (IMRT) have been introduced to reduce radiation dosage to swallowing musculature and structures, with the intention to decrease post-treatment dysphagia[3, 4]. More recently, the prevalence of dysphagia also has led to the development of preventive exercise programs. These exercise programs are associated with better post-treatment swallowing function, in particular on the short-term[5-10], and probably also longer-term[11]. However, since dysphagia can develop and/or progress years after CRT[12, 13], long term (10-years+) prospectively collected swallowing and mouth opening data are of great importance to assess deglutition in HNC survivors[14]. In this study the prospectively collected objective and subjective functional results at 10-years+ post-treatment will be reported in a patient cohort treated with CRT for advanced, anatomical and functional inoperable HNC.

MATERIAL AND METHODS

This study concerns the long term follow-up of all disease-free and evaluable patients, who participated in a randomized clinical trial (M99RAD) on two different cisplatin-based chemoradiation treatment protocols for advanced HNC[15]. The original cohort consisted of 237 patients diagnosed with advanced (stage IV), anatomical or functional[16] inoperable squamous cell carcinoma of the oral cavity, oropharynx, or hypopharynx. Patients were included between December 1999 and November 2004. The chemotherapy protocol consisted either of 100 mg/m^2 cisplatin in a 40 minutes intravenous (IV) infusion on days 1, 22, and 43, or of a weekly high-dose intra-arterial (IA) injection of 150 mg/m^2 cisplatin in combination with intravenous sodium thiosulphate rescue in weeks 1, 2, 3, and 4. Radiotherapy (70 Gy in 35 fractions) was administered over seven weeks, starting concurrently with chemotherapy. Since IMRT had been gradually introduced in our Institute during the trial period, roughly one fourth of the original patient population was treated with IMRT[4, 17], while the remaining patients were treated with conventional radiotherapy (RT). During treatment, patients were encouraged to maintain an oral diet for as long as possible and prophylactic tube feeding was not applied. A (nasogastric or gastric) feeding tube only was given when the carefully monitored intake became troublesome. In the period the trial was conducted (1999-2004),

the concept of standard preventive swallowing rehabilitation was not yet developed, and swallowing exercises were given post-treatment 'on demand', when removal of a feeding tube appeared troublesome because of aspiration and/or when sufficient oral intake could not be regained.

The original (phase III) trial compared standard IV with IA cisplatin infusion on oncological outcomes in 237 patients[17] and QOL in 207 patients[18, 19]. Regarding oncological outcomes and toxicities, results showed that CRT with IA infusion is not superior to CRT with IV infusion. Toxicity results were comparable in both arms, although site and degree of toxicity differed. In short, renal toxicity was significantly lower in the IA treatment arm, and neurological toxicity was significantly more prevalent in the IA arm[17]. Regarding QOL results, no statistically significant differences between the groups (IA, IV) were found, and no statistically significant changes over time (1-year versus 5-years post-treatment) were observed for the total patient group during follow-up assessments[19]. Therefore, in the present study, functional swallowing and mouth opening results are reported for the combined patient cohort still alive and evaluable at 10-years+ post-treatment. All patient data and reasons for exclusion after 5-years and 10-years+ follow-up are provided in a consort flow-chart (Figure 1). As can be seen, at 10-years+ post-treatment, besides the 20 evaluable patients from the 5-year cohort, 4 additional survivors, who had been unresponsive or refused to participate at the 5-years evaluation point, were also willing to participate. Two patients had major salvage surgery for recurrent disease during follow-up, and were excluded from swallowing/mouth opening analysis, since the functional outcomes in these patients were no longer (only) attributable to the CRT. Furthermore, two patients had minor (laser) surgery for a second primary at the oropharynx (pharyngeal arch and alveolar process, respectively) at 10-years and 11-years post-treatment. Subsequently, due to a recurrence the alveolar process patient two years later additionally required local resection with bone grafting. These latter two patients were kept in the functional analysis of in total 22 patients.

Multidimensional assessment

Assessment of functional sequels was performed with standard, multidimensional objective and subjective outcome-measures[20, 21]. First, the protocol included standard videofluoroscopy (VFS) to determine swallowing function. All VFS studies were carried out by an experienced speech language pathologist. Patients were seated upright and were asked to swallow different consistencies of varying amounts twice (1, 3, 5 and 10 cc thin liquid; 3 and 5 cc paste; as well as solid [Omnipaque coated cake]). Testing was discontinued if the clinicians judged the swallowing potentially harmful to the patient. All VFS studies were reviewed in real-time, slow motion, and frame-by-frame, and rated in consensus by two experienced researchers (authors SK and LM). Results were expressed in terms of the Penetration and Aspiration Scale (PAS), as well as an overall 'presence of residue' score. The PAS, a tool with an acceptable

reliability, consists of a 8-points scale, ranging from 1–8 (score 1: material does not enter the airway; score 2: material enters the airway, remains above the vocal folds, and is ejected from the airway; score 3: material enters the airway, remains above the vocal folds, and is not ejected from the airway; score 4: material enters the airway, contacts the vocal folds, and is ejected from the airway; score 5: material enters the airway, contacts the vocal folds, and is not ejected from the airway; score 6: material enters the airway, passes below the vocal folds, and is ejected into the larynx or out of the airway; score 7: material enters the airway, passes below the vocal folds, and is not ejected from the trachea despite effort; score 8: material enters the airway, passes below the vocal folds, and no effort is made to eject)[22]. The overall 'presence of residue' score ranges from 0–3 (score 0: no residue, to score 3: residue above and below the vallecula, with minimal residue judged as normal). To interpret and compare results, individual test results were clustered with the highest score representing the total PAS or residue score per patient. The PAS was also simplified by dividing it into three categories (1: normal; 2–5: penetration; 6–8: aspiration), which roughly corresponds to normal, mild-to-moderate, and severe performance[23].

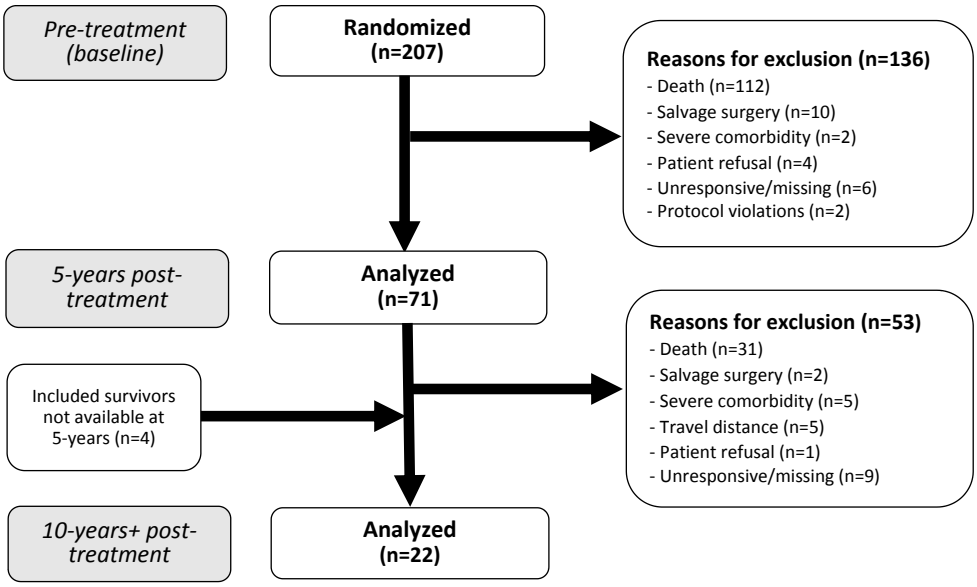


Figure 1. Consort flowchart showing the number of patients participating at 10-years+ post-treatment and previous QOL assessments (baseline and 5-years post-treatment), including reasons for exclusion after 5-years and 10-years+ follow-up. At 10-years+ post-treatment, 4 additional survivors were willing to participate, who were unresponsive or refused to participate at 5-years post-treatment.

Secondly, oral intake/nutritional status was assessed with the Functional Oral Intake Scale (FOIS; range from 1–7 with score 1: nothing by mouth, score 2: tube dependent with minimal/inconsistent oral intake, score 3: tube dependent with consistent oral intake, score 4: total oral diet of a single consistency, score 5: total oral intake of multiple consistencies requiring special preparation or compensations, score 6: total oral intake of multiple consistencies without special preparation but with specific food limitations, and score 7: total oral diet without restrictions), and with data on oral nutritional supplements, tube feeding dependency, weight changes, and Body Mass Index (BMI).

Furthermore, maximum interincisor (mouth) opening (MIO) was measured in mm to determine trismus. MIO was measured using disposable TheraBite range of motion scales (Atos Medical, Sweden), and trismus was defined as a MIO of ≤ 35 mm[24].

Patients' subjective swallowing and mouth opening impairment was assessed with quality of life (QOL) questionnaires. The first questionnaire was the Swallowing Quality of Life Questionnaire (SWAL-QOL), which was administered to assess patients' perceived swallowing disorder. The SWAL-QOL has been translated and validated for use with Dutch oral, oropharyngeal, and laryngeal cancer patients [25, 26]. The SWAL-QOL consists of 44-items that assess the effects of swallowing difficulties on 10 QOL domains (30 items), including food selection, eating duration, eating desire, fear, burden, mental health, social functioning, communication, sleep, and fatigue. Each domain ranges from 0–100 with a higher score indicating more impairment. Also a symptom scale (14 additional items) and a total SWAL-QOL score (the 23 items of the first seven scales listed above) can be calculated. Finally, the questionnaire includes three separate questions regarding nutrition intake, liquids intake, and general health [27]. A cut-off score of 14 points (or higher) has been established for identifying HNC patients with clinically relevant swallowing problems[25, 26]. Additionally, a Dutch structured study-specific questionnaire was used, which aimed at assessing in more detail complaints during the last week concerning diet/swallowing and concerning mastication/mouth opening, in part based on the EORTC C30/HN35, as described earlier (Appendix I)[20]. There were 6 questions in each category with mostly 4 possible, structured answers. For diet and swallowing these questions were: "What is the consistency of your diet?" "Do you have problems with swallowing solid food?" "Do you have problems with swallowing soft/minced food?" "Do you have problems with swallowing liquid food?" "Do you have to swallow repeatedly to get rid of the food?" "Is it painful to swallow?" For mastication and mouth opening these questions were: "Do you still have your own (set of) teeth?" "How often do you clean your teeth/dentures?" "How do you experience your mouth opening?" "Do you experience problems with eating, because of a limited mouth opening?" "Do you experience problems with speech, because of a limited mouth opening?" "Do you have problems with chewing your food?".

Statistical analysis

Descriptive statistics were generated for all continuous outcome measures (i.e. MIO, SWAL-QOL) at the 10-years+ assessment point. Data were summarised as medians with associated range. Spearman's rank correlation was used to determine significant associations between objective and subjective outcome variables (e.g. FOIS with SWAL-QOL score). The Mann-Whitney U test was used to compare outcome variables between two unpaired groups (IMRT vs. conventional RT). Percentages of reported/measured disorders were calculated for categorical outcome parameters, comparable to the methods described by Logemann et al.[28]. Pearson's Chi-Square test was used to test associations/differences in proportion between two or more groups. All data were collected and analyzed in SPSS (Chicago, Illinois; version 22.0), and a significance level of $p < 0.05$ was used.

RESULTS

Patients' characteristics

At 10-years+ post-treatment (median 134 months; range 109–165 months), 22 patients (13 male, 9 female; current mean age: 62 years, range 42–74) were evaluable All patients were in complete remission. The majority of patients (82%) had a primary tumor located at the oropharynx. All patients were curatively treated with CRT for advanced (stage IV) HNC. Eight patients (36%) were treated with standard IV cisplatin infusion and 14 patients (64%) with high-dose IA cisplatin infusion. Ten patients (45%; IA/IV: 6/4) were treated with IMRT and 12 patients (55%; IA/IV: 8/4) with conventional RT. Regarding nutrition and oral intake, during treatment ultimately 19 of 22 patients (86%) needed nasogastric/gastric tube feeding (including 5 patients who already had a feeding tube at baseline), which was discontinued/ended after treatment as soon as nutritional requirements could be maintained orally again (see Table 1 for the number of patients with a feeding tube at the various assessment points).

The clinical patients' and tumor characteristics of the analyzed patient cohort at 10-years+ post-treatment (n=22) and the original patient cohort at baseline (n=207) are listed in Table 2. There were no significant differences in proportion between these two groups with respect to gender, tumor site, stage, or treatment ($p > .05$).

Table 1. Number of patients with nasogastric or gastric feeding per assessment.

	Baseline Pre-CRT	7-weeks During CRT	12-weeks Post-CRT	1-year Post-CRT	5-years Post-CRT	10-years Post-CRT
Yes	5	19	12	5	3	3
No	17	3	10	17	19	19

Abbreviations: CRT = chemo-radiotherapy

Table 2. Clinical patient-, tumor- and treatment characteristics for the long term analysed patient cohort (n=22) and the original patient cohort (n=207).

Characteristic	207 patients at baseline n (%)	22 patients 10-years+ n (%)	Statistics Chi-Square	*P* value
Mean age, y (range)	55 (24-81)	62 (42-74)	NA	NA
Gender				
Male	153 (74%)	13 (59%)	2.191	.139
Female	54 (26%)	9 (41%)		
Tumor site				
Oral cavity	33 (16%)	1 (4.5%)	2.755	.252
Oropharynx	136 (66%)	18 (82%)		
Hypopharynx	38 (18%)	3 (14%)		
T stage				
T2	4 (2%)	1 (4.5%)	3.291	.193
T3	61 (29%)	10 (45%)		
T4	142 (69%)	11 (50%)		
N stage				
N0	37 (18%)	9 (41%)	8.177	.147
N1	25 (12%)	3 (14%)		
N2a	10 (5%)	0 (0%)		
N2b	55 (27%)	5 (23%)		
N2c	60 (29%)	3 (14%)		
N3	20 (10%)	2 (9%)		
Chemotherapy				
IV	103 (50%)	8 (36%)	1.429	.232
IA	104 (50%)	14 (64%)		
Radiotherapy				
IMRT	(± 25%)	10 (45%)	NA	NA
CONV	(± 75%)	12 (55%)		

Abbreviations: y = years; IV = intravenous; IA = intra-arterial; IMRT = Intensity-Modulated Radiotherapy; CONV = conventional radiotherapy

Functional results

Swallowing and mouth opening results per patient (n=22) are summarized in Table 3.

Table 3. Swallowing and mouth opening data collection per patient.

	PATIENT			TUMOR		TREATMENT			OBJECTIVE OUTCOMES 10-YEARS							SUBJECTIVE OUTCOMES 10-YEARS				
	Sex	Age	Baseline weight	Site	Stage TNM	CTx	RTx	Feeding tube	Nutrition / Intake			VFS		Mouth opening		Swallowing		Mastication		Pneumonia (≥2 half yr)
									Weight	FOIS	Tube	PAS	Residue	MIO	Trismus	Difficulty	Pain	Difficulty	Pain	
1	M	70	106 kg	oroph	T3N0	IV	IMRT	yes	105 kg	7	no	1	yes	46 mm	no	no	no	no	no	no
2	M	65	95 kg	oroph	T4N2c	IV	IMRT	yes	80 kg	7	no	5	yes	58 mm	no	yes	no	yes	no	no
3	M	64	75 kg	oroph	T3N0	IA	IMRT	yes	68 kg	6	no	3	yes	41 mm	no	no	no	no	no	no
4	M	64	79 kg	oroph	T4N2b	IA	IMRT	yes	80 kg	7	no	1	yes	10 mm	yes	no	no	no	no	no
5	M	63	93 kg	oroph	T3N2b	IV	IMRT	yes	96 kg	6	no	1	yes	40 mm	no	no	no	no	no	no
6	F	58	66 kg	oroph	T3N2c	IV	IMRT	yes	65 kg	2	yes	6	yes	10 mm	yes	yes	no	yes	no	yes
7	M	58	70 kg	hypo	T3N1	IA	IMRT	yes	78 kg	6	no	8	yes	52 mm	no	yes	no	no	no	no
8	M	57	89 kg	hypo	T2N0	IA	IMRT	yes	102 kg	7	no	8	yes	40 mm	no	no	no	no	no	no
9	M	56	88 kg	oroph	T3N2b	IA	IMRT	no	90 kg	7	no	1	yes	40 mm	no	yes	yes	yes	yes	no
10	F	42	65 kg	oral	T3N0	IA	IMRT	yes	67 kg	7	no	1	yes	21 mm	yes	no	no	no	no	no
11	F	67	83 kg	oroph	T4N0	IA	CONV	yes	60 kg	6	no	8	yes	32 mm	yes	no	no	no	no	no
12	M	64	68 kg	oroph	T4N1	IA	CONV	yes	69 kg	7	no	8	yes	25 mm	yes	yes	yes	yes	yes	no
13	F	67	62 kg	oroph	T4N2b	IA	CONV	yes	64 kg	7	no	8	yes	23 mm	yes	no	no	no	no	no
14	M	69	64 kg	oroph	T4N0	IV*	CONV	yes	78 kg	1	yes	8	yes	15 mm	yes	yes	yes	yes	yes	no
15	F	63	43 kg	oroph	T3N0	IA	CONV	yes	44 kg	6	no	8	yes	34 mm	yes	yes	yes	yes	yes	no
16	F	62	45 kg	oroph	T4N1	IV	CONV	yes	45 kg	5	no	6	yes	23 mm	yes	yes	no	no	no	no
17	F	62	54 kg	oroph	T4N3	IV	CONV	yes	56 kg	2	yes	7	yes	40 mm	no	yes	no	no	no	yes
18	M	70	90 kg	oroph	T3N0	IA**	CONV	yes	92 kg	6	no	8	yes	27 mm	yes	yes	no	yes	no	no
19	F	60	54 kg	oroph	T3N2c	IV	CONV	yes	54 kg	5	no	8	yes	8 mm	yes	yes	no	yes	no	no
20	F	60	62 kg	oroph	T4N2b	IA	CONV	yes	63 kg	5	no	8	yes	23 mm	yes	yes	no	yes	no	yes
21	M	74	78 kg	hypo	T4N0	IA	CONV	no	77 kg	7	no	1	yes	46 mm	no	no	no	no	no	no
22	M	50	84 kg	oroph	T4N3	IA	CONV	yes	84 kg	7	no	1	yes	45 mm	no	yes	no	yes	no	no

* This patient had required laser surgery for second primary at the pharyngeal arch at 10-years post-treatment. ** This patient had required laser surgery for second primary at the alveolar process at 11-years post-treatment, subsequently followed by local resection with bone grafting due to recurrent disease at 13-years post-treatment. Abbreviations: TNM = Tumor Node Metastasis; CTx = chemotherapy treatment; RTx = radiotherapy treatment; FOIS = Functional Oral Intake Scale; VFS = Videofluoroscopy; PAS = Penetration and Aspiration Scale; MIO = Maximal Interincisor Opening; M = male; F = female; hypo = hypopharynx; oroph = oropharynx; oral = oral cavity; IA = intra-arterial; IV = intravenous; IMRT = Intensity-Modulated Radiotherapy; CONV = conventional radiotherapy; kg = kilograms; mm = millimetres; NA = not applicable.

Swallowing function and dietary intake

VFS evaluation of swallowing function showed more than normal post-swallow contrast residue in all patients, mainly at the vallecula and piriform sinus and already occurring after 1cc sips of thin liquid. Safe oral intake was demonstrated in 7 patients (32%), whereas penetration and/or aspiration occurred in 15 patients (68%). Specifically, penetration (PAS score 2–5) was demonstrated in 2 patients (9%), and aspiration (PAS score 6–8) was shown in 13 patients (59%), with 10 of 13 patients making no effort to eject (silent aspiration). Aspiration (PAS ≥6) occurred significantly less in patients treated with IMRT (3 of 10 patients) compared to patients treated with conventional RT (10 of 12 patients; p=.011; Chi-Square test).

Regarding oral intake, 10 patients (45%) were able to consume a normal oral diet without restrictions (FOIS score 7), whereas 12 patients (55%) had restrictions: 10 patients were only able to consume an oral diet with specific food limitations (FOIS score 6; n=6) or with special preparation (FOIS score 5; n=3), and 3 patients were feeding-tube dependent (FOIS score 1–3). Three patients (2 of 3 with a feeding tube) had a history of repeated (≥2) aspiration pneumonia and/or other recurring pulmonary problems in the last 6 months. Moreover, according to the study-specific questionnaire, 13 patients (59%) reported swallowing difficulties, of whom 4 patients also reported painful swallowing.

Results of the SWAL-QOL questionnaire (n=22) are described in Table 4. Signs of impaired swallowing function (score >14) were found across all QOL domains with exception of the domains sleep and mental health. Especially eating duration was severely impaired (median score = 63; mean score ± SD = 58±32), and significantly associated with lower FOIS scores (r_s= -.61, p=.002). Similarly, social functioning (r_s=-.50, p=.019) and fear of eating (r_s=-.48, p=.025) were associated with restricted oral intake (FOIS score). General burden (r_s= -.54, p=.010), and fear of eating (r_s= -.58, p=.005) correlated with repeated pneumonia. Patients treated with IMRT showed significant better scores on the domains food selection, eating desire, communication, mental health, and social functioning (Mann-Whitney U test; see Figure 2 and Table 5). No associations between swallowing outcomes and tumor site or stage were found.

Mouth opening and mastication

Mean maximum mouth opening at 10-years+ post-treatment (n=22) was 32 mm (median 33 mm, range 8–58 mm) with 12 patients (55%; CONV/IMRT: 9/3) showing trismus (as defined as a MIO ≤35 mm) at this assessment point. This concerned mainly oropharyngeal cancer patients (n=11; CONV/IMRT: 9/2). Ten patients (45%) reported besides swallowing problems also difficulties with mastication and 4 patients (18%) reported also pain during mastication. There was a significant lower incidence of trismus in patients treated with IMRT (3/10) versus patients treated with conventional RT (9/12; p=.035; Chi-Square test). Trismus was significantly associated with aspiration (p=.011).

Table 4. Distribution of domains by SWAL-QOL questionnaire variables in 22 HNC patients at 10-years+ post-treatment.

Variable	N valid	Min- Max	Median	Mean ± SD
General burden	22	0 – 100	31.5	36 ± 33
Food selection	22	0 – 75	25	27 ± 24
Eating duration	22	0 – 100	63	58 ± 32
Eating desire	22	0 – 42	29	25 ± 15
Fear of eating	22	0 – 100	56.5	44 ± 36
Sleep	22	0 – 75	13	19 ± 22
Fatigue	22	0 – 67	21	25 ± 22
Communication	22	0 – 88	25	34 ± 27
Mental Health	22	0 – 55	10	20 ± 19
Social Function	22	0 – 65	25	23 ± 19
Symptom score	22	0 – 75	41	41 ± 23

Abbreviations: Min = minimum; Max = maximum; SD = standard deviation.

Table 5. Distribution of domains by SWAL-QOL questionnaire variables in 22 HNC patients at 10-years+ post-treatment, divided by radiotherapy treatment (Intensity-Modulated Radiotherapy [IMRT] versus conventional radiotherapy [CONV])

Variable	RTx	N valid	Min- Max	Median	Mean ± SD	Statistic
General burden	IMRT	10	0 – 75	19	26.4 ± 28.6	*p* = .203
	CONV	12	0 – 100	44	44.1 ± 34.6	
Food selection	IMRT	10	0 – 50	12.5	16.3 ± 18.7	***p* = .043***
	CONV	12	0 – 75	31.5	36.6 ± 24.6	
Eating duration	IMRT	10	0 – 100	50	41.3 ± 39.2	*p* = .059
	CONV	12	50 – 100	69	72.1 ± 16.9	
Eating desire	IMRT	10	0 – 42	21	17.5 ± 16.4	***p* = .050***
	CONV	12	17 – 42	33	31.3 ± 10.1	
Fear of eating	IMRT	10	0 – 100	25	35.1 ± 39.1	*p* = .314
	CONV	12	0 – 94	63	50.8 ± 33.0	
Sleep	IMRT	10	0 – 63	6.5	18.9 ± 23.9	*p* = .923
	CONV	12	0 – 75	19	18.8 ± 22.3	
Fatigue	IMRT	10	0 – 67	17	24.2 ± 24.8	*p* = .821
	CONV	12	0 – 67	25	25.0 ± 21.4	
Communication	IMRT	10	0 – 50	6.5	18.8 ± 23.0	***p* = .014***
	CONV	12	25 – 88	50	46.9 ± 22.8	
Mental Health	IMRT	10	0 – 40	2.5	10 ± 13.9	***p* = .014***
	CONV	12	5 – 55	30	27.9 ± 20.1	
Social Function	IMRT	10	0 – 45	7.5	13 ± 15.7	***p* = .017***
	CONV	12	0 – 65	27.5	31.3 ± 18.0	
Symptom score	IMRT	10	0 – 75	28.5	31.1 ± 28.1	*p* = .123
	CONV	12	21 – 68	46.5	48.8 ± 14.8	

Abbreviations: RTx = radiotherapy treatment; Min = minimum; Max = maximum; SD = standard deviation; IMRT = Intensity–Modulated Radiotherapy; CONV = conventional radiotherapy.
* p-value according to Mann-Whitney U test; significance level at $p < 0.05$.

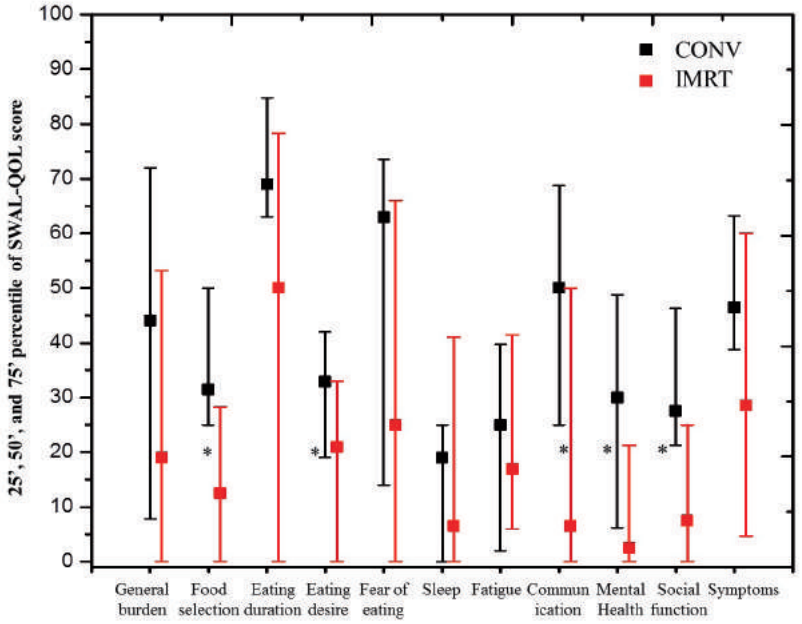


Figure 2. Distribution of domains by SWAL-QOL questionnaire variables in 22 HNC patients at 10-years+ post-treatment, associated by radiotherapy treatment protocol (Intensity-Modulated Radiotherapy [IMRT] versus conventional radiotherapy [CONV]). Asterisk means statistical difference based on a *p* value < 0.05 according to Mann-Whitney U test.

DISCUSSION

This is one of the first studies prospectively investigating long term (10-years+) QOL, swallowing function, and mouth opening in HNC patients treated with CRT for advanced disease. Regarding swallowing function, both observer-rated and patient-reported severe functional disorders and related morbidity problems were common in this patient cohort. Results showed occurrence of penetration and/or aspiration in almost 70% of patients and profound pharyngeal residue in all patients. Moreover, four patients were still feeding tube dependent and/or had developed frequent aspiration pneumonias and/or other recurring pulmonary problems. Forty-six percent of patients were able to consume a normal oral diet without restrictions, but four of them still reported having swallowing difficulties. Patients' perceived swallowing function, as assessed with the SWAL-QOL questionnaire, was impaired across most QOL domains (score >14) too, indicating clinically relevant swallowing problems with significant impact on QOL[25, 26]. We did not find an association between site of disease and dysphagia severity. However, all patients had advanced (stage IV) disease and were predominantly treated with large radiation fields, encompassing several organs at risk involved in swallowing, regardless of disease site.

On a positive note, impairments were significantly less profound in patients treated with IMRT – a treatment modality that during the trial period had gradually been introduced in our Institute. Although the patient population was rather small in the current study, results are in concordance with a previous, larger-scale study from our Institute, that also showed better xerostomia related QOL 2-3-years post-treatment in patients treated with IMRT compared to conventional RT[4]. Interestingly, another article from our Institute on late efficacy/toxicity in the same patient population recently reported that treatment protocol (IV versus IA cisplatin infusion) might also play a role in this. After a median follow-up of 7.5 years, dysphagia according to the RTOG toxicity criteria was reported to be worse in the IV arm[29]. However, the present and previous studies on swallowing function and dietary intake did not reveal any significant differences between the two IA and IV chemotherapy protocols in this respect[18, 19]. The authors in the '7.5-years study' did not take into account the effects of the changes in radiation treatment (IMRT versus conventional RT) during the trial. Having those IMRT–conventional RT data taken into consideration now[30], it therefore seems more likely that treatment with IMRT instead of the IV cisplatin infusion has been causing the more favourable swallowing outcomes in this patient cohort.

Regarding mouth opening problems, trismus was observed in more than fifty percent of patients. This is substantially higher than the weighted prevalence of 31% following conventional RT with chemotherapy, as recently determined in a review of several studies where trismus was appropriately assessed[31]. The population of this study, with mainly advanced primaries located at the oropharynx[32], might be a reason for this difference. Limited mouth opening may make proper mastication of food more difficult, which is in accordance with half of our patients complaining about mastication difficulty. Furthermore, trismus may result in compromised airway clearance with poor bolus organization that – together with increased pharyngeal residue – has the potential to lead to aspiration problems[31]. Also in our patient cohort a relationship between trismus and aspiration was found. An explanation might be that the patients who developed both functional deficits (trismus and aspiration) received higher RT doses on the muscles critical to mastication and swallowing[33]. The fact that trismus occurred significantly more in patients treated with conventional RT compared to patients treated with IMRT confirms such a dose-effect relationship.

To prevent CRT-induced swallowing disorders, maintenance of oral intake throughout CRT treatment and/or preventive swallowing exercises ("eat or exercise" principle) have independently been associated with better post-treatment swallowing outcomes directly after treatment and at short-term follow-up[34, 35]. Also in a recent prospective clinical trial from our institute, with a cisplatin-based CRT with IMRT therapy protocol, results showed minimal swallowing disorders at 6-years follow-up in patients, who were treated with preventive swallowing exercises[11]. In that study cohort, none of the twenty-two patients was dependent on tube feeding at 6-years post-treatment, and it is likely that the favourable

swallowing outcomes can be attributed both to the organ-sparing IMRT and to the preventive and continued post-treatment rehabilitation programs which were applied. It is not clear whether the poor outcome in the current cohort is mainly caused by the lack of preventive rehabilitation, the larger radiation fields, or the progressive fibrosis at long term following RT. However, results probably would have been even more dismal if not 45% of these long term survivors had received IMRT.

Regarding oral intake during treatment, the usefulness of prophylactic gastric tube placement to maintain weight and nutrition during treatment is currently under debate[36]. The controversy is mainly about maintaining weight during treatment versus maintaining swallowing function by training oral intake[37]. As supported by several studies[28, 35, 38, 39], it seems reasonable to assume that prophylactic gastric tube placement leads to worse post-treatment swallowing and diet outcomes, since the swallowing muscles are no longer actively used and may atrophy (the "use it or lose it" principle)[39]. Weight loss during treatment is associated with worse oncological outcome[37], but it is not clear what loss is acceptable. However, initial body mass index (BMI) may play a role in that, since oropharyngeal cancer patients with a BMI >25 at the start of treatment may have a better overall survival[37].

CONCLUSION

Functional problems in this patient cohort at 10-years+ post CRT treatment are substantial, with noticeable occurrence of dysphagia, recurrent aspiration pneumonia, feeding tube dependency, and trismus. IMRT patients showed less swallowing impairment and trismus, though, than patients treated with conventional RT.

ACKNOWLEDGEMENTS

Wilma van Heemsbergen, epidemiologist and clinical researcher at the Department of Epidemiology & Biostatistics at the Netherlands Cancer Institute, is greatly acknowledged for her support and advice in the statistical analysis. This study was made possible by grants provided by "Stichting de Hoop" and the "Verwelius Foundation".

REFERENCES

1. van der Molen L, van Rossum MA, Burkhead LM, Smeele LE, Hilgers FJ. Functional outcomes and rehabilitation strategies in patients treated with chemoradiotherapy for advanced head and neck cancer: a systematic review. Eur Arch Otorhinolaryngol. 2009;266:889-900.
2. Kraaijenga SA, van der Molen L, van den Brekel MW, Hilgers FJ. Current assessment and treatment strategies of dysphagia in head and neck cancer patients: a systematic review of the 2012/13 literature. Curr Opin Support Palliat Care. 2014;8:152-63.
3. Eisbruch A, Kim HM, Feng FY, Lyden TH, Haxer MJ, Feng M, et al. Chemo-IMRT of oropharyngeal cancer aiming to reduce dysphagia: swallowing organs late complication probabilities and dosimetric correlates. Int J Radiat Oncol Biol Phys. 2011;81:e93-9.
4. van Rij CM, Oughlane-Heemsbergen WD, Ackerstaff AH, Lamers EA, Balm AJ, Rasch CR. Parotid gland sparing IMRT for head and neck cancer improves xerostomia related quality of life. Radiat Oncol. 2008;3:41.
5. Kulbersh BD, Rosenthal EL, McGrew BM, Duncan RD, McColloch NL, Carroll WR, et al. Pretreatment, preoperative swallowing exercises may improve dysphagia quality of life. Laryngoscope. 2006;116:883-6.
6. Carroll WR, Locher JL, Canon CL, Bohannon IA, McColloch NL, Magnuson JS. Pretreatment swallowing exercises improve swallow function after chemoradiation. Laryngoscope. 2008;118:39-43.
7. van der Molen L, van Rossum MA, Burkhead LM, Smeele LE, Rasch CR, Hilgers FJ. A randomized preventive rehabilitation trial in advanced head and neck cancer patients treated with chemoradiotherapy: feasibility, compliance, and short-term effects. Dysphagia. 2011;26:155-70.
8. Carnaby-Mann G, Crary MA, Schmalfuss I, Amdur R. "Pharyngocise": randomized controlled trial of preventative exercises to maintain muscle structure and swallowing function during head-and-neck chemoradiotherapy. Int J Radiat Oncol Biol Phys. 2012;83:210-9.
9. Kotz T, Federman AD, Kao J, Milman L, Packer S, Lopez-Prieto C, et al. Prophylactic swallowing exercises in patients with head and neck cancer undergoing chemoradiation: a randomized trial. Arch Otolaryngol Head Neck Surg. 2012;138:376-82.
10. van der Molen L, van Rossum MA, Rasch CR, Smeele LE, Hilgers FJ. Two-year results of a prospective preventive swallowing rehabilitation trial in patients treated with chemoradiation for advanced head and neck cancer. neck cancer. Eur Arch Otorhinolaryngol. 2014;271(5):1257–70.
11. Kraaijenga SA, van der Molen L, Jacobi I, Hamming-Vrieze O, Hilgers FJ, van den Brekel MW. Prospective clinical study on long-term swallowing function and voice quality in advanced head and neck cancer patients treated with concurrent chemoradiotherapy and preventive swallowing exercises. Eur Arch Otorhinolaryngol. 2015 (Epub)
12. Rutten H, Pop LA, Janssens GO, Takes RP, Knuijt S, Rooijakkers AF, et al. Long-term outcome and morbidity after treatment with accelerated radiotherapy and weekly cisplatin for locally advanced head-and-neck cancer: results of a multidisciplinary late morbidity clinic. Int J Radiat Oncol Biol Phys. 2011;81:923-9.
13. Hutcheson KA, Lewin JS, Barringer DA, Lisec A, Gunn GB, Moore MW, et al. Late dysphagia after radiotherapy-based treatment of head and neck cancer. Cancer. 2012;118:5793-9.
14. Hutcheson KA, Lewin JS, Holsinger FC, Steinhaus G, Lisec A, Barringer DA, et al. Long-term functional and survival outcomes after induction chemotherapy and risk-based definitive therapy for locally advanced squamous cell carcinoma of the head and neck. Head Neck. 2014;36:474-80.
15. Balm AJ, Rasch CR, Schornagel JH, Hilgers FJ, Keus RB, Schultze-Kool L, et al. High-dose superselective intra-arterial cisplatin and concomitant radiation (RADPLAT) for advanced head and neck cancer. Head Neck. 2004;26:485-93.

16. Kreeft AM, van der Molen L, Hilgers FJ, Balm AJ. Speech and swallowing after surgical treatment of advanced oral and oropharyngeal carcinoma: a systematic review of the literature. Eur Arch Otorhinolaryngol. 2009;266:1687-98.

17. Rasch CR, Hauptmann M, Schornagel J, Wijers O, Buter J, Gregor T, et al. Intra-arterial versus intravenous chemoradiation for advanced head and neck cancer: Results of a randomized phase 3 trial. Cancer. 2010;116:2159-65.

18. Ackerstaff AH, Balm AJ, Rasch CR, de Boer JP, Wiggenraad R, Rietveld DH, et al. First-year quality of life assessment of an intra-arterial (RADPLAT) versus intravenous chemoradiation phase III trial. Head Neck. 2009;31:77-84.

19. Ackerstaff AH, Rasch CR, Balm AJ, de Boer JP, Wiggenraad R, Rietveld DH, et al. Five-year quality of life results of the randomized clinical phase III (RADPLAT) trial, comparing concomitant intra-arterial versus intravenous chemoradiotherapy in locally advanced head and neck cancer. Head Neck. 2012;34:974-80.

20. van der Molen L, van Rossum MA, Ackerstaff AH, Smeele LE, Rasch CR, Hilgers FJ. Pretreatment organ function in patients with advanced head and neck cancer: clinical outcome measures and patients' views. BMC Ear Nose Throat Disord. 2009;9:10.

21. van der Molen L, van Rossum MA, Jacobi I, van Son RJ, Smeele LE, Rasch CR, et al. Pre- and posttreatment voice and speech outcomes in patients with advanced head and neck cancer treated with chemoradiotherapy: expert listeners' and patient's perception. J Voice. 2012;26:664.e25-33.

22. Rosenbek JC, Robbins JA, Roecker EB, Coyle JL, Wood JL. A penetration-aspiration scale. Dysphagia. 1996;11:93-8.

23. McHorney CA, Martin-Harris B, Robbins J, Rosenbek J. Clinical validity of the SWAL-QOL and SWAL-CARE outcome tools with respect to bolus flow measures. Dysphagia. 2006;21:141-8.

24. Dijkstra PU, Huisman PM, Roodenburg JL. Criteria for trismus in head and neck oncology. Int J Oral Maxillofac Surg. 2006;35:337-42.

25. Rinkel RN, Verdonck-de Leeuw IM, Langendijk JA, van Reij EJ, Aaronson NK, Leemans CR. The psychometric and clinical validity of the SWAL-QOL questionnaire in evaluating swallowing problems experienced by patients with oral and oropharyngeal cancer. Oral Oncol. 2009;45:e67-71.

26. Rinkel RN, Verdonck-de Leeuw IM, van den Brakel N, de Bree R, Eerenstein SE, Aaronson N, et al. Patient-reported symptom questionnaires in laryngeal cancer: voice, speech and swallowing. Oral Oncol. 2014;50:759-64.

27. McHorney CA, Robbins J, Lomax K, Rosenbek JC, Chignell K, Kramer AE, et al. The SWAL-QOL and SWAL-CARE outcomes tool for oropharyngeal dysphagia in adults: III. Documentation of reliability and validity. Dysphagia. 2002;17:97-114.

28. Logemann JA, Pauloski BR, Rademaker AW, Lazarus CL, Gaziano J, Stachowiak L, et al. Swallowing disorders in the first year after radiation and chemoradiation. Head Neck. 2008;30:148-58.

29. Heukelom J, Lopez-Yurda M, Balm AJ, Wijers OB, Buter J, Gregor T, et al. Late follow-up of the randomized radiation and concomitant high-dose intra-arterial or intravenous cisplatin (RADPLAT) trial for advanced head and neck cancer. Head Neck. 2015 (Epub).

30. Gupta T, Agarwal J, Jain S, Phurailatpam R, Kannan S, Ghosh-Laskar S, et al. Three-dimensional conformal radiotherapy (3D-CRT) versus intensity modulated radiation therapy (IMRT) in squamous cell carcinoma of the head and neck: a randomized controlled trial. Radiother Oncol. 2012;104:343-8.

31. Bensadoun RJ, Riesenbeck D, Lockhart PB, Elting LS, Spijkervet FK, Brennan MT. A systematic review of trismus induced by cancer therapies in head and neck cancer patients. Support Care Cancer. 2010;18:1033-8.

32. Kamstra JI, Dijkstra PU, van Leeuwen M, Roodenburg JL, Langendijk JA. Mouth opening in patients irradiated for head and neck cancer: A prospective repeated measures study. Oral Oncol. 2015 (Epub).

33. van der Molen L, Heemsbergen WD, de Jong R, van Rossum MA, Smeele LE, Rasch CR, et al. Dysphagia and trismus after concomitant chemo-Intensity-Modulated Radiation

Therapy (chemo-IMRT) in advanced head and neck cancer; dose-effect relationships for swallowing and mastication structures. Radiother Oncol. 2013;106:364-9.

34. Langmore S, Krisciunas GP, Miloro KV, Evans SR, Cheng DM. Does PEG use cause dysphagia in head and neck cancer patients? Dysphagia. 2012;27:251-9.

35. Hutcheson KA, Bhayani MK, Beadle BM, Gold KA, Shinn EH, Lai SY, et al. Eat and exercise during radiotherapy or chemoradiotherapy for pharyngeal cancers: use it or lose it. JAMA Otolaryngol Head Neck Surg. 2013;139:1127-34.

36. Wopken K, Bijl HP, van der Schaaf A, van der Laan HP, Chouvalova O, Steenbakkers RJ, et al. Development of a multivariable normal tissue complication probability (NTCP) model for tube feeding dependence after curative radiotherapy/chemo-radiotherapy in head and neck cancer. Radiother Oncol. 2014;113:95-101.

37. Ottosson S, Soderstrom K, Kjellen E, Nilsson P, Zackrisson B, Laurell G. Weight and body mass index in relation to irradiated volume and to overall survival in patients with oropharyngeal cancer: a retrospective cohort study. Radiat Oncol. 2014;9:160.

38. Mekhail TM, Adelstein DJ, Rybicki LA, Larto MA, Saxton JP, Lavertu P. Enteral nutrition during the treatment of head and neck carcinoma: is a percutaneous endoscopic gastrostomy tube preferable to a nasogastric tube? Cancer. 2001;91:1785-90.

39. Chen AM, Li BQ, Lau DH, Farwell DG, Luu Q, Stuart K, et al. Evaluating the role of prophylactic gastrostomy tube placement prior to definitive chemoradiotherapy for head and neck cancer. Int J Radiat Oncol Biol Phys. 2010;78:1026-32.

Appendix I. The translated Dutch study specific questionnaire.

Study specific questionnaire

A. Socio-demographic data (12 questions)

B. Complaints over the last week (12 questions)

a. Diet and swallowing

1. What is your diet like?
   1 = I eat solid food 2 = I only eat soft (minced) food
   3 = I only eat liquid food 4 = I only have tube feeding
   5 = combination soft diet and tube feeding
2. Do you have problems with swallowing solid food?
   1 = not at all 2 = a little
   3 = rather 4 = quite a lot
3. Do you have problems with swallowing soft/minced food?
   1 = not at all 2 = a little
   3 = rather 4 = quite a lot
4. Do you have problems with swallowing liquid food?
   1 = not at all 2 = a little
   3 = rather 4 = quite a lot
5. Do you have to swallow repeatedly to get rid of food?
   1 = yes 2 = no
   3 = sometimes
6. Is it painful to swallow?
   1 = yes 2 = no
   3 = sometimes

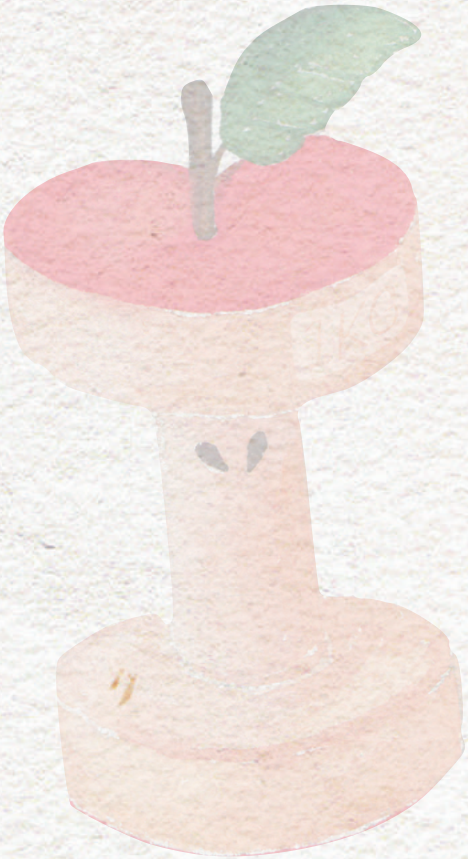
b. Mastication and mouth opening

1. Do you still have your own teeth?
   1 = yes 2 = yes, partially
   3 = no, I have a prosthesis 4 = no, and I don't wear a prosthesis
2. How often do you clean your teeth?
   1 = a couple of times a day 2 = once a day
   3 = less than once a day 4 = not at all
3. How do you experience your mouth opening?
   1 = normal 2 = a little bit limited
   3 = very limited 4 = I cannot open my mouth

4. Do you experience problems with eating, because of a limited mouth opening?
   1 = not at all 2 = a little
   3 = rather 4 = quite a lot
5. Do you experience problems with speech, because of a limited mouth opening?
   1 = not at all 2 = a little
   3 = rather 4 = quite a lot
6. Do you have problems with chewing your food?
   1 = not at all 2 = a little
   3 = rather 4 = quite a lot

CHAPTER 4

Assessment of voice, speech, and related quality of life in advanced head and neck cancer patients 10-years+ after chemoradiotherapy



S.A.C. Kraaijenga
I.M. Oskam
O. Hamming-Vrieze
F.J.M. Hilgers
M.W.M. van den Brekel
R.J.J.H. van Son
L. van der Molen

Oral Oncol. Online 2016 Feb 10.

ABSTRACT

Objectives: Assessment of long-term objective and subjective voice, speech, articulation, and quality of life in patients with head and neck cancer (HNC) treated with concurrent chemoradiotherapy (CRT) for advanced, stage IV disease.

Materials and methods: Twenty-two disease-free survivors, treated with cisplatin-based CRT for inoperable HNC (1999–2004), were evaluated at 10-years post-treatment. A standard Dutch text was recorded. Perceptual analysis of voice, speech, and articulation was conducted by two expert listeners (SLPs). Also an experimental expert system based on automatic speech recognition was used. Patients' perception of voice and speech and related quality of life was assessed with the Voice Handicap Index (VHI) and Speech Handicap Index (SHI) questionnaires.

Results: At a median follow-up of 11-years, perceptual evaluation showed abnormal scores in up to 64% of cases, depending on the outcome parameter analyzed. Automatic assessment of voice and speech parameters correlated moderate to strong with perceptual outcome scores. Patient-reported problems with voice (VHI >15) and speech (SHI >6) in daily life were present in 68% and 77% of patients, respectively. Patients treated with IMRT showed significantly less impairment compared to those treated with conventional radiotherapy.

Conclusion: More than 10-years after organ-preservation treatment, voice and speech problems are common in this patient cohort, as assessed with perceptual evaluation, automatic speech recognition, and with validated structured questionnaires. There were fewer complaints in patients treated with IMRT than with conventional radiotherapy.

KEY WORDS

Head and Neck Cancer – Chemoradiotherapy – Voice Quality – Speech Intelligibility – GRBAS – Perceptual Evaluation – Automatic Speech Recognition – Long-term effects – IMRT

INTRODUCTION

In patients with advanced head and neck cancer (HNC), both the tumor and its treatment with combined chemoradiotherapy (CRT) can adversely impact voice and speech outcomes. In patients with cancers of the oral cavity and oropharynx, destructive effects of the tumor will mainly affect patients' articulation and/or speech, whereas in laryngeal cancer patients, the tumor often has negative effects on voice quality[1,2]. Treatment effects of (chemo-) radiotherapy on voice quality and speech predominantly depend on radiation doses to the organs at risk surrounding the primary tumor and lymph nodes. When the larynx is included in the radiation field, decreased voice quality may be attributed to impaired vocal fold vibration, incomplete glottic closure, insufficient lubrication/dryness of the laryngeal mucosa, muscle atrophy, fibrosis, hyperaemia, and/or erythema[3]. Patients often complain about increased vocal effort, breathiness, and hoarseness[2]. Radiation treatment for non-laryngeal cancer may also influence voice and speech, even at long-term[4], due to radiation-induced anatomical changes of the vocal tract, e.g. scarring, edema and/or fibrosis of structures in/around the oral cavity or oropharynx[5,6][1]. Consequently, reduced speech intelligibility and impaired articulation may affect patients' daily life activities and interactions, which can be associated with severe functional and psychosocial problems, and reduced quality of life[7,8].

Previous literature on voice quality and speech following CRT for advanced HNC has proposed the use of prospective, standardised multidimensional voice and speech assessment protocols, based on adequate scientific background with long-term follow-up[1,7,9]. In 2009, Dwivedi and colleagues studied speech outcomes following oral cavity and/or oropharyngeal cancer, and recommended speech evaluation by various modalities, i.e. perceptual evaluation, acoustic evaluation, and structured questionnaires[9]. Also Jacobi et al. (2010) and Schuster et al. (2012) clarified in their reviews in this area the need for structured, standardised protocols, including baseline assessments and long-term follow-up[1,7].

Despite these recommendations, prospectively collected voice and speech data still are scarce[4,10,11], especially at long-term[2]. At the same time, technology is improving, and automated methods of voice and speech evaluation are under development as an alternative and/or adjunct to traditional, time-consuming perceptual evaluation of voice quality and speech[7,12,13]. In particular in research setting, automatic speech recognition is already used, to provide global measures of speech intelligibility and (to a lesser extent) of voice quality[14,15]. However, also in clinical settings automatic speech evaluation can be used to ensure multidimensional assessments, which can be time efficient and fast. The aim of the current study was to report on the long-term objective and subjective voice and speech outcomes, including perceptual evaluation, automatic evaluation, and patient-reported outcomes.

MATERIAL AND METHODS

Patient and treatment characteristics

As part of a randomized controlled clinical trial between 1999 and 2004 at the Netherlands Cancer Institute[16], twenty-two HNC survivors treated with concurrent cisplatin-based radiotherapy were disease-free, evaluable, and willing to participate at long-term (10-years+) post-treatment evaluation. For patients' and treatment characteristics and reasons for exclusion at the long-term assessment point we refer to the recently published paper on dysphagia in the same patient cohort[17]. In summary, the original patient cohort consisted of patients diagnosed with stage IV cancer of the oral cavity, oropharynx, or hypopharynx. Patients were treated with cisplatin as either a standard 100 mg/m^2 intravenous (IV) 40 min infusion on days 1, 22, and 43, or a high-dose, targeted and rapid 150 mg/m^2 intra-arterial (IA) cisplatin injection with intravenous sodium thiosulphate rescue in weeks 1, 2, 3, and 4. The primary tumor area and neck nodes were irradiated with 2 Gy per fraction, in 35 fractions over 7 weeks, starting concurrently with chemotherapy. Ten patients (45%) were treated with intensity-modulated radiotherapy (IMRT), and 12 patients (55%) with conventional radiotherapy. Based on perceptual categorization, three patients were categorized as audibly non-native speakers, whereas the other nineteen were categorized as native (with/without audible regional or dialect variants).

Data collection

Voice, speech, and articulation outcomes were collected at 10-years+ post-treatment from speech recordings consisting of a 189-word Dutch fairy tale with neutral content containing almost all Dutch phonemes (similar to earlier studies in our Institute[10,12]; Appendix I). Patients were asked to read the text aloud at a comfortable loudness and pitch level. All recordings were made in a sound-treated room using a Sennheiser MD421 Dynamic Microphone and an Edirol (Roland) R-1 portable 16-bit (44.1 kHz) digital wave recorder. The mouth-to-microphone distance was kept constant at approximately 30 cm.

Perceptual evaluation

The stimuli for the listening experiment consisted of two fragments, the first 70 words (A) and the following 68 words (B), from the original 189-word passage read by the patients[12,13]. Thus, each patient was rated twice by each SLP, once on fragment A and once on fragment B. Stimulus material was manually selected by an independent expert, excised, and equalized at 70 decibel with the PRAAT program[18]. Four practice items, a list of words, and sustained /a/ vowels were also recorded but not used for the current analysis. During the listening experiment, all recordings were presented over a Sennheiser HD418 headphone.

Perceptual rating

Two experienced speech language pathologists (SLPs), both Dutch native speakers, were asked as expert listeners to rate voice, speech, and articulation parameters independently. The listeners were blinded to patient information. Recordings were presented for evaluation using the Open Source program TEVA[19]{, #2}{TEVA, #2}, which runs as a PRAAT extension[10,15,20]. Semantic scales were used to rate voice quality on computerized Visual Analogue Scales (VAS). Included scales were overall grade of voice quality, roughness, breathiness, asthenia, and strain (GRBAS)[21]. Also a number of additional semantic scales were included to rate overall speech intelligibility, the precision of articulation, nasality, and prosody. The GRBAS scale was not used in its standardized form (rating on 0–3), but the descriptors of the GRBAS scale were used to computerize and digitize VAS ratings to scores ranging from 0 ('least similar to normal') to 1000 ('most similar to normal'). The listeners discussed and adjusted scale definitions during the evaluation of 10 practice sessions, with the same recorded text available from a different patient population[10]. The final/experiment recordings were presented in identical order to both listeners one week later. The expert listeners could repeat the stimuli as often as necessary. Approximately 3 minutes per patient were necessary to complete the full experiment.

Reliability and agreement

Supplement Table 1 lists the intrarater (exact and close) agreement and disagreement for each listener separated per variable converted into ordinal categories, by dividing the visual analog scale into four equal parts labelled 'good' (normal), 'fair', 'moderate', and 'poor' (abnormal)[15]. Agreement occurred in >73% per rater. The strength of the correlation between the individual judgments (test-retest reliability of fragment A compared to fragment B) of each rater on a 0–1000 scale was also quite high (single-measure Intraclass Correlation Coefficient (ICC(3,1)) for [consistency] using a two-way mixed model; see supplement Table 1 for the corresponding ICC(3,1) values and confidence intervals per variable). Therefore, for further analysis the mean opinion scores were used to define the agreement and disagreement between the two listeners. Supplement Table 2 provides the interrater reliability and agreement of the raters' mean opinion scores. As can be seen, scores were in exact agreement (difference ≤125 points) in 6 to 21 cases (27–96%), in close agreement (difference ≤250 points) in 1 to 12 cases (5–55%), and in disagreement in 1 to 9 cases (5–41%), depending on the variable analyzed. Except for prosody, all variables demonstrated ICC(3,1) values of 0.75 or higher, indicating good reliability. For prosody the ICC(3,1) was 0.60, indicating acceptable reliability[22,23]. Hence, for overall analysis of perceptual evaluation, average scores between the two raters' mean opinion scores were used to evaluate perceptual voice and speech parameters.

Automatic speech recognition

Automatic assessment of voice quality and speech was conducted with the Automatic Speech analysis In Speech Therapy for Oncology (ASISTO) expert system [12, 13, 24]. The assessment models used in this paper have been developed and tested on speech recordings of a similar group of Dutch speakers with HNC before and after CRT [12, 13]. Perceptual variables analyzed were Automatic Voice Quality Index (AVQI) and two different systems for determining Running Speech Intelligibility. These latter two expert systems are developed by the Department of Electronics and Information Systems, University of Gent, Belgium; one for text-aligned (ELIS [25]) and one for alignment-free (ELISALF) evaluation [12, 13]. AVQI results ranged from 1–8 with 1 meaning 'most similar to normal' and 8 meaning 'least similar to normal'. Similarly, Running Speech Intelligibility results ranged from 0–100 with 0 meaning 'no phonemes recognized' and 100 meaning 'all phonemes recognized'.

Patient-reported outcomes

Patients' perceived voice and speech impairment and related quality of life was assessed with two validated specific voice and speech related quality of life questionnaires: the Voice Handicap Index (VHI) and the Speech Handicap Index (SHI).

The VHI is a 30-item questionnaire scored on a 0–4 point scale for measuring patients' suffering caused by dysphonia, specified into 3 subscales (physical, functional, emotional) identified with 10 items each. The total VHI score can range from 0–120 with a higher score corresponding to a higher degree of patient-reported vocal handicap (VHI score 0–30: minimal handicap; 31–60: moderate handicap; 60–120: significant and serious handicap) [26, 27]. A cut-off score of 15 points (97% sensitivity and 86% specificity) has been established to identify patients with HNC and voice problems in daily life [28].

Based on the VHI, the SHI has been developed as a valid speech assessment tool for patients with HNC, to provide insight into the nature and severity of patients' speech complaints. Instructions and grading are identical to the VHI, but now adapted to speech-related problems in daily life [29, 30]. The total SHI score is calculated by summing the scores on all 30 items (score range 0–120), with a higher score indicating a higher level of speech-related problems. A cut-off score of 6 or higher (95% sensitivity and 90% specificity) has been established for speech problems in daily life, and a difference score of 12 points or higher has been proposed as criterion for clinically significance in-group comparisons [31]. Furthermore, there are two SHI subscales: psychosocial function (14 items, score range 0–56) and speech function (14 items, score range 0–56). The questionnaire also includes a global question "how is your speech today", with 4 response categories ('good', 'reasonable', 'poor', and 'severe').

Statistical Analysis

Descriptive statistics were generated for all continuous outcome measures at the 10-years+-assessment point. Data were summarised as medians with associated range. Spearman's rank correlation was used to determine significant associations between perceptual, automatic and/or patient-reported outcome variables. The Mann-Whitney U test was used to compare outcome variables between two unpaired groups (i.e. IMRT vs. conventional radiotherapy). Pearson's Chi-Square test was used to test associations or differences in proportion between two or more groups. All data were collected and analyzed in SPSS (Chicago, Illinois; version 23.0), and a significance level of $p < 0.05$ was used.

RESULTS

At 10-years+ post-treatment (median 134 months; range 109–165 months), 22 patients (13 male, 9 female; current mean age: 62 years, range 42–74) were evaluable. All patients were in complete remission. The majority of patients (82%) had a primary tumor located in the oropharynx. The clinical patients' and tumor characteristics of the analyzed cohort at 10-years+ post-treatment (n=22) and the original patient cohort at baseline (n=207) recently have been extensively described[17]. There were no significant differences in proportion between these two groups with respect to gender, tumor site, stage, or treatment (p >.05). In Table 1 the perceptual, automatic, and patient-reported voice and speech outcome parameters in 22 patients with HNC at 10-years+ post-treatment are demonstrated.

Perceptual evaluation

For perceptual evaluation by the SLPs, mean scores (Table 1) were also converted into a four-point ordinal scale 'good', 'fair', 'moderate', and 'poor', whereby the top 25% was labelled as 'normal', and the remainder as 'deviant' (Figure 1). As can be seen, prosody was most frequently judged as deviant (in 64% of cases), followed by intelligibility (46%), articulation (36%), and voice quality (one or more deviant parameter(s) of the GRBAS; 32%). In total 18/22 patients (82%) showed impairments (deviant scores) on one or more of the outcome parameters. Except for overall grade of voice quality and breathiness, which were significantly more deviant in patients with hypopharyngeal tumors (Mann-Whitney U test; grade: p =.040; breathiness: p =.005), no correlations between perceptual outcome variables and tumor characteristics were found. Speech intelligibility strongly correlated with articulation (r = 0.93; p <.001), and nasality (r=0.67, p=.001), whereas overall grade of voice quality significantly correlated with roughness (r = 0.94; p =.000), and strain (r = 0.89; p =.000). Patients treated with IMRT (45%) showed significant better intelligibility scores compared to patients treated with conventional radiotherapy (55%; see Table 2).

Table 1. Descriptive statistics and distribution by domain of perceptual, automatic, and patient-reported voice and speech variables in 22 head and neck cancer patients at 10-years+ post-treatment.

Variable (score)	Min–Max	Median	Mean ± SD
Perceptual evaluation			
Grade	105 – 993	832	743 ± 245
Roughness	179 – 995	936	822 ± 223
Breathiness	387 – 999	995	934 ± 145
Asthenia	687 – 999	987	961 ± 71
Strain	360 – 998	969	888 ± 186
Nasality	6 – 991	877	794 ± 284
Prosody	293 – 998	721	693 ± 214
Speech intelligibility	113 – 987	771	689 ± 256
Articulation	94 – 983	842	722 ± 270
Automatic evaluation			
Voice quality (AVQI)	3.7 – 6.1	4.7	4.9 ± 0.6
Intelligibility (ELIS)	62 – 94	83	82 ± 9
Intelligibility (ELISALF)	67 – 92	85	82 ± 8
Subjective evaluation			
Voice Handicap Index	0 – 57	21	22 ± 18
Physical domain	0 – 22	10	10 ± 8
Functional domain	0 – 19	6,5	7 ± 6
Emotional domain	0 – 18	3	5 ± 5
Speech Handicap Index	0 – 65	21.5	24 ± 20
Speech domain	0 – 38	13.5	16 ± 12
Psychosocial domain	0 – 26	5	7 ± 8

Abbreviations: Min = minimum; Max = maximum; SD = standard deviation; AVQI = Automatic Voice Quality Index; ELIS: text-aligned Running Speech Intelligibility[25]; ELISALF: alignment-free Running Speech Intelligibility.

Automatic evaluation

Table 1 shows the descriptive statistics at 10-years+ post-treatment for automatic assessment of voice quality (AVQI) and speech intelligibility. AVQI scores ranged from 3.66 to 6.08 (with 1 meaning 'most similar to normal' and 8 meaning 'least similar to normal'). A trend was seen for a moderate correlation between AVQI and perceptual voice quality scores by the SLPs (r=0.42; *p* =.051; see Figure 2). Patients with a tumor located in the hypopharynx showed significantly worse AVQI scores (n=3; mean 5.77; range 5.47–6.08) compared to the patients with a tumor located in the oral cavity/oropharynx (n=19; mean 4.72; range 3.66–5.95; Mann-Whitney U test; *p* =.009). Regarding (ELIS) speech intelligibility, scores ranged from 62.21 to 93.87 (Table 1). There was a significant correlation with perceptual scores of speech intelligibility (r = 0.74; *p* =.000; see Figure 2).

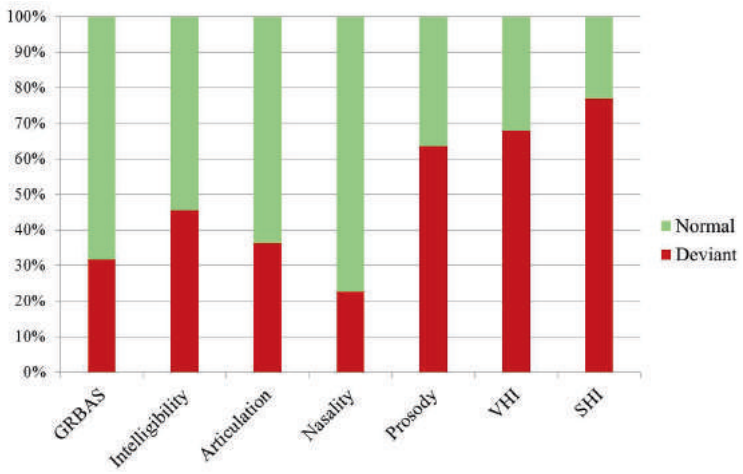


Figure 1. Percentages of patients (n=22) with 'normal' or 'deviant' perceptual and patient-reported voice and speech parameters. Note: for perceptual scores the top 25% was labelled as 'normal', and the remainder as 'deviant'. For patient-reported outcome parameters 'deviant' scores were based on validated cut-offs[28, 31].

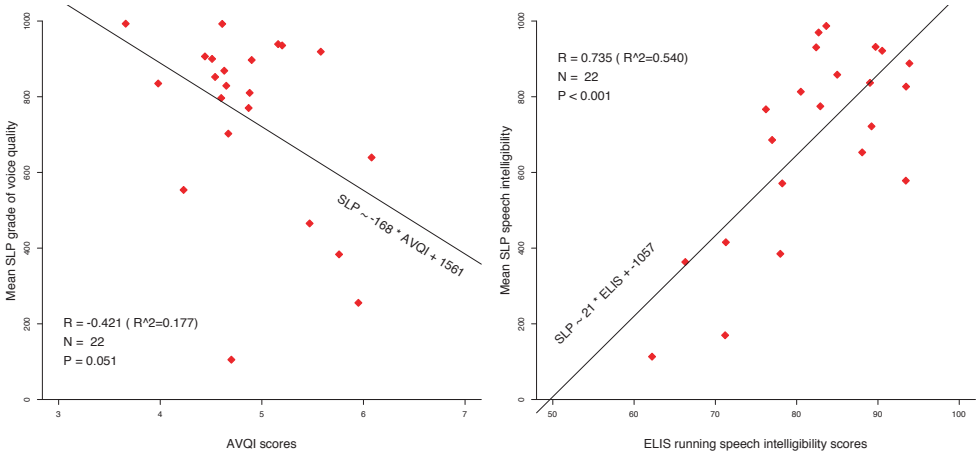


Figure 2. Relationship between automatic evaluation of voice quality (AVQI scores) and perceptual evaluation of voice quality by the SLPs (left), and between automatic text-aligned evaluation of running speech intelligibility (ELIS scores) and perceptual evaluation of speech intelligibility by the SLPs (right).

Patient-reported outcomes

Voice Handicap Index (VHI) and Speech Handicap Index (SHI) scores were used to assess patients' perspective and related quality of life of voice and speech dysfunction. In Table 1 the distribution of the various subdomains at 10-years+ post-treatment are shown. Patients with a physical voice disability mainly reported problems such as increased vocal effort, breathiness, and unpredictable/varying clarity of voice, resulting in functional disabilities

such as poor understandability by others, in particular during phone calls or in noisy rooms. Patients with speech problems instead more often complained about unpredictably/varying intelligibility and unclear articulation. Overall, deviant SHI scores (SHI >6) were present in 77% of patients (17/22), whereas 68% (15/22) showed voice problems (VHI >15). In the psychosocial voice and speech domains hardly any disabilities were reported (median scores 3 and 5, respectively; see Table 1). Patients treated with IMRT (45%) showed significant better scores on all domains compared to patients treated with conventional radiotherapy (55%; see Table 2). Correlation with perceptual and automatic outcome measures (i.e. overall grade of voice quality, speech intelligibility) was poor (r <0.4), except for the question "how is your speech today", which significantly but moderately correlated with automatically assessed speech intelligibility (r = 0.46, *p* =.032).

Table 2. Perceptual, automatic, and patient-reported voice and speech variables in 22 patients with HNC at 10-years+ post-treatment, divided by radiotherapy treatment (Intensity-Modulated Radiotherapy [IMRT] versus conventional radiotherapy [CONV]).

Variable (score)	RTx	N valid	Min- Max	Median	Mean ± SD	Statistic
Perceptual voice quality (Grade)	IMRT	10	465 – 993	875	797 ± 180	*p* =.38
	CONV	12	105 – 993	813	698 ± 288	
Automatic voice quality (AVQI)	IMRT	10	3.7 – 6.1	4.9	4.9 ± 0.7	*p* =.82
	CONV	12	4.0 – 6.0	4.7	4.8 ± 0.5	
Voice Handicap Index	IMRT	10	0 – 49	2	12.5 ± 17.1	***p* =.021**
	CONV	12	9 – 57	26	30.2 ± 14.3	
Physical domain	IMRT	10	0 – 22	1.5	6.6 ± 8.6	***p* =.050**
	CONV	12	3 – 22	16	13.7 ± 6.3	
Functional domain	IMRT	10	0 – 16	0.5	3.5 ± 5.2	***p* =.007**
	CONV	12	0 – 19	8.5	9.6 ± 5.3	
Emotional domain	IMRT	10	0 – 14	0	2.4 ± 4.5	***p* =.011**
	CONV	12	0 – 18	6.5	6.9 ± 5.4	
Perceptual speech intelligibility	IMRT	10	416 – 987	873	828 ± 171	***p* =.006**
	CONV	12	113 – 922	616	574 ± 263	
Running speech intelligibility (ELIS)	IMRT	10	71 – 94	83	84 ± 6.4	*p* =.82
	CONV	12	62 – 93	79	81 ± 10.5	
Running speech intelligibility (ELISALF)	IMRT	10	69 – 92	86	83 ± 8.4	*p* =.50
	CONV	12	67 – 91	82	81 ± 8.7	
Speech Handicap Index	IMRT	10	0 – 53	5.5	14.0 ± 18.5	***p* =.021**
	CONV	12	10 – 65	27.5	31.4 ± 18.2	
Speech domain	IMRT	10	0 – 33	5.5	9.9 ± 11.7	***p* =.030**
	CONV	12	7 – 38	21	20.8 ± 10.6	
Psychosocial domain	IMRT	10	0 – 20	0	4.0 ± 7.0	***p* =.017**
	CONV	12	1 – 26	6	10.3 ± 8.5	

Abbreviations: RTx = radiotherapy treatment; Min = minimum; Max = maximum; SD = standard deviation; IMRT = Intensity–Modulated Radiotherapy; CONV = conventional radiotherapy.
* p-value according to Mann-Whitney U test; significance level at p < 0.05.

DISCUSSION

This study assessed long-term (10-years+) objective and subjective voice and speech outcomes following organ-preservation treatment for advanced HNC. Results of the 22 evaluable patients showed considerable functional deficits in this respect. Perceptual evaluation by the SLPs, rating overall speech intelligibility, the precision of articulation, the GRBAS criteria, prosody, and nasality, revealed that 86% of patients showed impairments on one or more of the outcome parameters. The automatic expert system ASISTO, rating automatic voice quality index (AVQI) and running speech intelligibility, seemed to support the perceptual evaluation results of the SLPs, since there were significant, moderate to strong correlations with overall grade of voice quality and with speech intelligibility. Subjective voice and speech complaints were evaluated in the present patient cohort with (sub) total VHI and SHI scores, and revealed moderate but clinically relevant disabilities, that were present in 68% and 77% of patients, respectively.

Other studies evaluating patient-reported voice and speech outcomes after treatment for HNC also demonstrated decreased voice quality following CRT[11,32], with impact on quality of life and psychosocial function[33]. One of the first VHI evaluations after CRT for stage III-IV HNC was performed by Keereweer and colleagues. Mild to severe voice impairment was found in all of the 20 participating patients, who were at least 2.5 years after treatment[32]. In the study of Vainshtein and colleagues, almost 20% of patients reported further voice worsening at 18- and 24-months follow-up after chemo-IMRT for stage III-IV oropharyngeal cancer, most commonly due to worsening vocal clarity[11]. Speech problems were also found in recent studies that evaluated post-treatment SHI scores[8,31]. Rinkel at al. reported impaired speech in daily life (SHI >6) in 55% of patients with primary HNC (all subsites and stages included), whereas in our study this was 77%. The higher prevalence of disabilities in the current study might be attributable to the more advanced tumor stage with only stage IV tumors included. Furthermore, the follow-up time in the current study was considerably longer (11 years versus a maximum of 5 years in the other studies), which might reflect a further deterioration post CRT over time, as recently also was found for dysphagia issues[17,34].

Interestingly, the problems were predominantly related to radiation technique, because patients treated with IMRT showed significantly less voice and speech problems on the various domains compared to patients treated with conventional radiotherapy. This is in line with other studies that found correlations between radiation dose to the glottis and voice quality worsening or speech impairment after IMRT[11,35]. In the literature, it has been found that radiation dose to the larynx correlates with laryngeal edema severity, resulting in vocal cord dysfunction and thus poor voice quality[5,6]. This might explain why the patients with a hypopharynx tumor in the current cohort showed more voice problems compared to the others, because high doses to the larynx are unavoidable in these patients, although this

concerned only three patients. For non-laryngeal HNC, IMRT may reduce the radiation dose to the pharynx[36], resulting in less edema, fibrosis, and structural alteration of the vocal tract, and thus better speech intelligibility[35]. Ongoing clinical trials in HNC are currently trying to optimize the IMRT process to further improve outcomes[37].

Relation to radiation technique was previously also found for dysphagia and quality of life issues[17,38]. It is therefore not unlikely that the patients who developed both functional deficits (dysphagia and voice/speech problems were significantly correlated in the current cohort; results not published) received higher radiotherapy doses on the muscles or structures critical to these functions. Besides, none of the patients had participated in a preventive rehabilitation program, which has been associated with better post-treatment functional outcomes[2].

Although perceptual evaluation is currently a widely used assessment tool for voice and speech evaluation, we also performed automatic assessment of voice quality and speech intelligibility with the expert system ASISTO[24]. This system has previously been shown to be as accurate as SLPs (n=13) for evaluation of patients treated for HNC[12]. To our knowledge, this is the first practical/clinical application of automatic assessment of voice quality and speech in a HNC patient population with considerable functional deficits following organ-preservation treatment. Additionally, the system was used to evaluate possible bias/subjectivity within perceptual evaluation. The ASISTO scores for speech intelligibility correlated strongly with perceptual mean opinion scores of speech intelligibility, while this correlation was only moderate and borderline significant for voice quality. Possibly, some bias can be blamed here, since only two SLPs participated as listeners in the present study, and they rated voice quality as less severe compared to the system in 15/22 (68%) of patients (Figure 2). This indicates that their judgement might have been somewhat 'coloured' and thus overrated by their extensive experience with patients with HNC. Intelligibility results correlated well, and thus were probably not overrated, which is conceivable because it is easier to score whether one understands something than to rate voice quality, as was found in previous studies[12,39].

Despite the acceptable correlations, it is obvious that perceptual evaluation by SLPs is still not identical to that of a computer program. With regards to radiation technique, minor differences between groups can be statistically significant in one evaluation and just not anymore in the other, especially when numbers are small as in the current study. Moreover, our ASR has not been trained/calibrated on the severest pathological voices in HNC patients, and earlier research with this tool has shown that very low perceptual scores are somewhat more difficult to predict[12,39]. This might have obscured the RT-induced perceptual difference found for SLP assessment. Nevertheless, these differences in outcomes between the two evaluation methods thus have to be interpreted with caution.

We did not measure other acoustic voice parameters (e.g. voicedness, fundamental frequency), since multiple studies have demonstrated that these modalities (independently)

have no clear role in the management of patients with cancers of the oral cavity and oropharynx, due to lack of reproducible results, poor correlation with other speech assessment methods (e.g. perceptive or subjective evaluation), and absence of standard protocols[40,41]. In fact, automatic evaluation with ASISTO could also apply as such 'acoustic' parameter, since AVQI is a weighted combination of acoustic parameters[42], and running speech intelligibility is the recognition result of a phoneme recognizer based on the audio signal[12]. Unfortunately, because standardized procedures of objective voice and speech assessments do not exist, yet, results are difficult to compare with other studies performed at different clinics or centres[7].

CONCLUSION

Ten years after organ-preservation treatment, functional voice and speech problems are common in this patient cohort, as assessed with perceptual evaluation, automatic speech recognition, and with validated structured questionnaires. There were fewer complaints in patients treated with IMRT than with conventional radiotherapy.

ACKNOWLEDGEMENTS

Catherine Middag and Jean-Pierre Martens (Department of Electronics and Information Systems, University of Gent, Belgium) are greatly acknowledged for their collaboration regarding ASISTO; Irene Jacobi (PhD, The Netherlands Cancer Institute) is acknowledged for her help with the speech recordings; Klaske van Sluis (SLP, The Netherlands Cancer Institute) is acknowledged for her collaboration with the perceptual analysis. This study was made possible by grants provided by Atos Medical (Sweden), "Stichting de Hoop" (The Netherlands), and the "Verwelius Foundation" (the Netherlands).

REFERENCES

1. Jacobi I, van der Molen L, Huiskens H, van Rossum MA, Hilgers FJ. Voice and speech outcomes of chemoradiation for advanced head and neck cancer: a systematic review. Eur Arch Otorhinolaryngol. 2010;267:1495-505.
2. Kraaijenga SA, van der Molen L, Jacobi I, Hamming-Vrieze O, Hilgers FJ, van den Brekel MW. Prospective clinical study on long-term swallowing function and voice quality in advanced head and neck cancer patients treated with concurrent chemoradiotherapy and preventive swallowing exercises. Eur Arch Otorhinolaryngol. 2015;272(11):3521-31.
3. Lazarus CL. Effects of chemoradiotherapy on voice and swallowing. Curr Opin Otolaryngol Head Neck Surg. 2009;17:172-8.
4. Paleri V, Carding P, Chatterjee S, Kelly C, Wilson JA, Welch A, et al. Voice outcomes after concurrent chemoradiotherapy for advanced nonlaryngeal head and neck cancer: a prospective study. Head Neck. 2012;34:1747-52.
5. Fung K, Yoo J, Leeper HA, Hawkins S, Heeneman H, Doyle PC, et al. Vocal function following radiation for non-laryngeal versus laryngeal tumors of the head and neck. Laryngoscope. 2001;111:1920-4.
6. Hamdan AL, Geara F, Rameh C, Husseini ST, Eid T, Fuleihan N. Vocal changes following radiotherapy to the head and neck for non-laryngeal tumors. Eur Arch Otorhinolaryngol. 2009;266:1435-9.
7. Schuster M, Stelzle F. Outcome measurements after oral cancer treatment: speech and speech-related aspects--an overview. Oral Maxillofac Surg. 2012;16:291-8.
8. Lazarus CL, Husaini H, Hu K, Culliney B, Li Z, Urken M, et al. Functional outcomes and quality of life after chemoradiotherapy: baseline and 3 and 6 months post-treatment. Dysphagia. 2014;29:365-75.
9. Dwivedi RC, Kazi RA, Agrawal N, Nutting CM, Clarke PM, Kerawala CJ, et al. Evaluation of speech outcomes following treatment of oral and oropharyngeal cancers. Cancer Treat Rev. 2009;35:417-24.
10. van der Molen L, van Rossum MA, Jacobi I, van Son RJ, Smeele LE, Rasch CR, et al. Pre- and posttreatment voice and speech outcomes in patients with advanced head and neck cancer treated with chemoradiotherapy: expert listeners' and patient's perception. J Voice. 2012;26:664 e25-33.
11. Vainshtein JM, Griffith KA, Feng FY, Vineberg KA, Chepeha DB, Eisbruch A. Patient-Reported Voice and Speech Outcomes After Whole-Neck Intensity Modulated Radiation Therapy and Chemotherapy for Oropharyngeal Cancer: Prospective Longitudinal Study. Int J Radiat Oncol Biol Phys. 2014;89(5):973-80.
12. Clapham R, Middag C, Hilgers F, Martens J-P, Brekel Mvd, Son Rv. Developing automatic articulation, phonation and accent assessment techniques for speakers treated for advanced head and neck cancer. Speech Communication. 2014;59:44-54.
13. Middag CC, R; van Son, R; Martens, JP. Robust automatic intelligibility assessment techniques evaluated on speakers treated for head and neck cancer. Computer Speech and Language. 2014;28:467-82.
14. Kitzing P, Maier A, Ahlander VL. Automatic speech recognition (ASR) and its use as a tool for assessment or therapy of voice, speech, and language disorders. Logoped Phoniatr Vocol. 2009;34:91-6.
15. Clapham RP, van As-Brooks CJ, van Son RJ, Hilgers FJ, van den Brekel MW. The Relationship Between Acoustic Signal Typing and Perceptual Evaluation of Tracheoesophageal Voice Quality for Sustained Vowels. J Voice. 2015;29(4):23-29.
16. Rasch CR, Hauptmann M, Schornagel J, Wijers O, Buter J, Gregor T, et al. Intra-arterial versus intravenous chemoradiation for advanced head and neck cancer: Results of a randomized phase 3 trial. Cancer. 2010;116:2159-65.
17. Kraaijenga SA, Oskam IM, van der Molen L, Hamming-Vrieze O, Hilgers FJ, van den Brekel MW. Evaluation of long term (10-years+) dysphagia and trismus in patients treated with concurrent chemo-radiotherapy for advanced head and neck cancer. Oral Oncol. 2015;51(8):787-94.

18. Free downloadable at http://www.praat.org.

19. Open Source program TEVA; available at http://www.fon.hum.uva.nl/IFASpokenLanguageCorpora/NKIcorpora/NKI_TEVA/.

20. Boersma P, Weenink D. Praat: doing phonetics by computer [Computer program].Version 6.0.05.

21. Hirano M. Clinical Examination of Voice. New York: Springer-Verlag. 1981.

22. Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. Psychol Bull. 1979;86:420-8.

23. Portney LG; Watkins MP. Foundations of Clinical Research: Applications to Practice; Appleton & Lange; 1993.

24. ASISTO expert system; available at http://asisto.elis.ugent.be/.

25. ELIS: 'ELektronica en Informatie Systemen'; available at https://elis.ugent.be/.

26. Jacobsen B JA, Grywalski C, Silbergleit A, Jacobsen G, Benninger M. The Voice Handicap Index (VHI): Development and Validation. American Journal of Speech-Language Pathology. 1997;6:66-70.

27. Verdonck-de Leeuw IM, Kuik DJ, De Bodt M, Guimaraes I, Holmberg EB, Nawka T, et al. Validation of the voice handicap index by assessing equivalence of European translations. Folia Phoniatr Logop. 2008;60:173-8.

28. Van Gogh CD, Mahieu HF, Kuik DJ, Rinkel RN, Langendijk JA, Verdonck-de Leeuw IM. Voice in early glottic cancer compared to benign voice pathology. Eur Arch Otorhinolaryngol. 2007;264:1033-8.

29. Rinkel RN, Verdonck-de Leeuw IM, van Reij EJ, Aaronson NK, Leemans CR. Speech Handicap Index in patients with oral and pharyngeal cancer: better understanding of patients' complaints. Head Neck. 2008;30:868-74.

30. Dwivedi RC, St Rose S, Roe JW, Chisholm E, Elmiyeh B, Nutting CM, et al. First report on the reliability and validity of speech handicap index in native English-speaking patients with head and neck cancer. Head Neck. 2011;33:341-8.

31. Rinkel RN, Verdonck-de Leeuw IM, Doornaert P, Buter J, de Bree R, Langendijk JA, et al. Prevalence of swallowing and speech problems in daily life after chemoradiation for head and neck cancer based on cut-off scores of the patient-reported outcome measures SWAL-QOL and SHI. Eur Arch Otorhinolaryngol. 2015 June 14 [Epub ahead of print].

32. Keereweer S, Kerrebijn JD, Al-Mamgani A, Sewnaik A, Baatenburg de Jong RJ, van Meerten E. Chemoradiation for advanced hypopharyngeal carcinoma: a retrospective study on efficacy, morbidity and quality of life. Eur Arch Otorhinolaryngol. 2012;269:939-46.

33. Rinkel RN, Verdonck-de Leeuw IM, van den Brakel N, de Bree R, Eerenstein SE, Aaronson N, et al. Patient-reported symptom questionnaires in laryngeal cancer: voice, speech and swallowing. Oral Oncol. 2014;50:759-64.

34. Hutcheson KA, Lewin JS, Barringer DA, Lisec A, Gunn GB, Moore MW, et al. Late dysphagia after radiotherapy-based treatment of head and neck cancer. Cancer. 2012;118:5793-9.

35. Nguyen NP, Abraham D, Desai A, Betz M, Davis R, Sroka T, et al. Impact of image-guided radiotherapy to reduce laryngeal edema following treatment for non-laryngeal and non-hypopharyngeal head and neck cancers. Oral Oncol 2011;47(9):900–904.

36. Roe JW, Carding PN, Dwivedi RC, Kazi RA, Rhys-Evans PH, Harrington KJ, et al. Swallowing outcomes following Intensity Modulated Radiation Therapy (IMRT) for head & neck cancer - a systematic review. Oral Oncol. 2010;46:727-33.

37. Tejpal G, Jaiprakash A, Susovan B, Ghosh-Laskar S, Murthy V, Budrukkar A. IMRT and IGRT in head and neck cancer: Have we delivered what we promised? Indian J Surg Oncol. 2010;1:166-85.

38. Rathod S, Gupta T, Ghosh-Laskar S, Murthy V, Budrukkar A, Agarwal J. Quality-of-life (QOL) outcomes in patients with head and neck squamous cell carcinoma (HNSCC) treated with intensity-modulated radiation therapy (IMRT) compared to three-dimensional conformal radiotherapy (3D-CRT): evidence from a prospective randomized study. Oral Oncol. 2013;49:634-42.

39. Van Nuffelen G, Middag C, De Bodt M, Martens JP. Speech technology-based assessment of phoneme intelligibility in dysarthria. Int J Lang Commun Disord. 2009;44:716-30.

40. Finizia C, Dotevall H, Lundstrom E, Lindstrom J. Acoustic and perceptual evaluation of voice and speech quality: a study of patients with laryngeal cancer treated with laryngectomy vs irradiation. Arch Otolaryngol Head Neck Surg. 1999;125:157-63.

41. Dwivedi RC, St Rose S, Chisholm EJ, Clarke PM, Kerawala CJ, Nutting CM, et al. Acoustic parameters of speech: Lack of correlation with perceptual and questionnaire-based speech evaluation in patients with oral and oropharyngeal cancer treated with primary surgery. Head Neck. 2014 Dec 18 [Epub ahead of print].

42. Maryn Y, de Bodt M, Roy N. The Acoustic Voice Quality Index: Toward improved treatment outcomes assessment in voice disorders Journal of Communication Disorders 2010;43:161–74.

Supplement Table 1. Intrarater agreement and disagreement for voice and speech parameters between mean opinion scores (converted into ordinal categories).

		Rater 1					Rater 2				
Speech / voice parameter	n	Exact agreement (%)	Close agreement (%)	Dis-agreement (%)	Intrarater reliability ICC(3,1)		n	Exact agreement (%)	Close agreement (%)	Dis-agreement (%)	Intrarater reliability ICC(3,1)	
Intelligibility	22	13 (59)	5 (23)	4 (18)	0.86	(0.69-0.94)	22	18 (82)	2 (9)	2 (9)	0.78	(0.54-0.90)
Articulation	22	12 (54)	6 (27)	4 (18)	0.80	(0.58-0.91)	22	18 (82)	3 (14)	1 (4.5)	0.92	(0.81-0.96)
Grade	22	15 (68)	7 (32)	0 (0)	0.91	(0.80-0.96)	22	15 (68)	5 (23)	2 (9)	0.77	(0.51-0.90)
Roughness	22	17 (77)	4 (18)	1 (4.5)	0.89	(0.76-0.95)	22	17 (77)	4 (18)	1 (4.5)	0.80	(0.59-0.91)
Breathiness	22	22 (100)	0 (0)	0 (0)	0.99	(0.99-1.00)	22	18 (82)	1 (4.5)	3 (14)	0.30	(-0.13-0.64)
Asthenia	22	19 (86)	2 (9)	1 (4.5)	NA	NA	22	19 (86)	2 (9)	1 (4.5)	NA	NA
Strain	22	15 (68)	6 (27)	1 (4.5)	0.83	(0.64-0.93)	21	19 (90.5)	1 (5)	1 (5)	0.54	(0.16-0.79)
Nasality	22	15 (68)	4 (18)	3 (14)	0.84	(0.64-0.93)	22	13 (59)	6 (27)	3 (14)	0.85	(0.67-0.94)
Prosody	22	14 (64)	5 (23)	3 (14)	0.83	(0.64-0.93)	22	10 (45.5)	6 (27)	6 (27)	0.52	(0.14-0.77)
Accent	22	13 (59)	4 (18)	5 (23)	0.87	(0.72-0.95)	22	16 (73)	3 (14)	3 (14)	0.88	(0.74-0.95)

Abbreviations: ICC = Intraclass Correlation Coefficient.
Notes: Agreement split into exact agreement (two scores ± 125), close agreement (two scores ± 250), and disagreement (two scores differ by >250).

Supplement Table 2. Interrater agreement and disagreement for voice and speech parameters between mean opinion scores (converted into ordinal categories).

Speech / voice parameter	n	Exact agreement (%)	Close agreement (%)	Dis-agreement (%)	Interrater reliability ICC(3,1)
Intelligibility	22	10 (46)	5 (23)	7 (32)	0.88 (0.71-0.95)
Articulation	22	13 (59)	5 (23)	4 (18)	0.89 (0.73-0.95)
Grade	22	16 (73)	3 (14)	3 (14)	0.90 (0.77-0.96)
Roughness	22	17 (77)	3 (14)	2 (9)	0.90 (0.75-0.96)
Breathiness	22	17 (77)	1 (4.5)	4 (18)	0.79 (0.49-0.91)
Asthenia	22	21 (96)	1 (4.5)	0 (0)	0.87 (0.68-0.94)
Strain	21	17 (77)	1 (4.5)	4 (18)	0.76 (0.41-0.90)
Nasality	22	14 (64)	6 (27)	2 (9)	0.93 (0.83-0.97)
Prosody	22	8 (36)	5 (23)	9 (41)	0.60 (0.05-0.84)
Accent	22	6 (27)	12 (55)	4 (18)	0.89 (0.74-0.96)

Abbreviations: ICC = Intraclass Correlation Coefficient. Notes: Agreement split into exact agreement (two scores ± 125), close agreement (two scores ± 250), and disagreement (two scores differ by >250).

Appendix I. Excerpt from 'De vijvervrouw' by Godfried Bomans (in Dutch).

Fragment A (70 words)

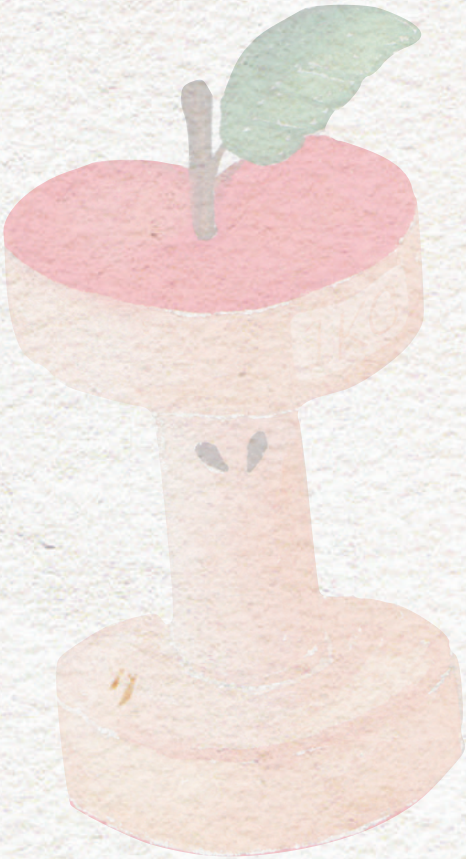
Er leefden eens een koning en een koningin en die hadden maar één kind. Dat was de prins. De prins was erg verwend. Toen hij nog in de wieg lag, kreeg hij al een gouden rammelaar. Hij at van een gouden bordje en hij dronk uit een gouden bekertje. Al zijn speelgoed was van goud, en het werd steeds moeilijker om hem iets te geven, wat hij al niet had.

Fragment B (68 words)

En toen hij achttien jaar werd, had hij alles wat hij maar bedenken kon en het was allemaal van zuiver goud. Maar hij was toch jarig en er moest hem iets gegeven worden. De prins stond bij het raam, toen zijn ooms en tantes binnenkwamen. Zij hadden ieder een cadeautje in de hand, maar ze waren erg verlegen, want ze begrepen wel dat de prins het al had.

CHAPTER 5

Prospective clinical study on long-term swallowing function and voice quality in advanced head and neck cancer patients treated with concurrent chemoradiotherapy and preventive swallowing exercises



S.A.C. Kraaijenga
L. van der Molen
I. Jacobi
O. Hamming-Vrieze
F.J.M. Hilgers
M.W.M. van den Brekel

Eur Arch Otorhinolaryngol. 2015; 272: 3521-3531.

ABSTRACT

Importance: Concurrent chemoradiotherapy (CRT) for advanced head and neck cancer (HNC) is associated with substantial early and late side effects, most notably regarding swallowing function, but also regarding voice quality and quality of life (QOL). Despite increased awareness/knowledge on acute dysphagia in HNC survivors, long-term (i.e. beyond five years) prospectively collected data on objective and subjective treatment-induced functional outcomes (and their impact on QOL) still are scarce.

Objectives: Assessment of long-term CRT-induced results on swallowing function and voice quality in advanced HNC patients.

Design: A randomized controlled trial on preventive swallowing rehabilitation (2006 – 2008).
Setting: Tertiary comprehensive HNC centre.
Participants: Twenty-two disease-free and evaluable HNC patients.

Main Outcomes and Measures: Multidimensional assessment of functional sequels was performed with videofluoroscopy, mouth opening measurements, Functional Oral Intake Scale, acoustic voice parameters, and (study-specific, SWAL-QOL, and VHI) questionnaires. Outcome-measures at 6-years post-treatment were compared with results at baseline and at 2-years post-treatment.

Results: At a mean follow-up of 6.1 years most initial tumor-, and treatment-related problems remained similarly low to those observed after 2-years follow-up, except increased xerostomia (68%) and increased (mild) pain (32%). Acoustic voice analysis showed less voicedness, increased fundamental frequency, and more vocal effort for the tumors located below the hyoid bone (n=12), without recovery to baseline values. Patients' subjective vocal function (VHI score) was good.

Conclusions and Relevance: Functional swallowing and voice problems at 6-years post-treatment are minimal in this patient cohort, originating from preventive and continued post-treatment rehabilitation programs.

KEY WORDS
Head and Neck Cancer – Chemoradiotherapy – Dysphagia – Swallowing – Voice – Preventive Rehabilitation

INTRODUCTION

Organ preservation protocols with concurrent chemo-radiotherapy (CRT) are increasingly used for primary treatment of locally advanced head and neck cancer (HNC). Meta-analytic data from randomized controlled trials (RCTs) show improved loco-regional control and overall survival advantages for these protocols as compared to radiotherapy (RT) alone[1], but also higher incidence of dysphagia secondary to CRT-induced tissue reactions such as mucositis, fibrosis, neuropathies, and especially xerostomia[2, 3]. Both acute and long-term swallowing problems can result in decreased oral intake and eventually may lead to weight loss and (prolonged) nasogastric or percutaneous feeding tube dependency. Furthermore, dysphagia can adversely affect compliance to treatment and post-treatment recovery (e.g. because of aspiration problems), and can deteriorate patient's social contacts and quality of life (QOL)[3]. Since radiation fields frequently encompass the larynx, also substantial effects on voice quality have been noted, which are correlated to the RT dose to the larynx[4-6]. Combination with chemotherapy aggravates these negative effects on patients' speech, daily life activities, and again QOL[7-13].

Regarding dysphagia in the HNC field, many centers have made attempts to prevent or reduce swallowing sequels following CRT. So far, focus primarily has been on reduction of the dose on pharyngeal musculature with advanced RT treatment planning techniques such as intensity modulated radiation therapy (IMRT)[14-18]. More recently, pre-, per- and post-treatment interventions ensuring continued use of swallowing musculature by adherence to targeted swallowing exercises (the 'use it or lose it' concept) are increasingly suggested in the literature to benefit HNC survivors[19]. Preventive rehabilitation programs have been associated with a long list of positive effects: improved QOL[20], better base of tongue retraction and better maintained epiglottic inversion[21], superior muscle maintenance and functional swallowing ability[22], better oral intake and clinician-rated swallowing function at three and six months[23], reduced extent and severity of penetration and/or aspiration, less trismus, less weight loss, and less pain (both short term[24] and at one- and two-years post-treatment[25]), and better oral intake and shorter duration of feeding tube dependency[26] post-treatment. Also maintained oral intake (no feeding tube dependency) has been shown to lead to better swallowing function after CRT, possibly due to continued use of the swallowing musculature[26-28]. Benefits from preventive (swallowing) exercises have been reported in particular on the short-term (up to two years)[19]. Eisbruch et al. were among the first prospectively evaluating swallowing function in HNC survivors, and these authors found objective swallowing dysfunction (high incidence of silent aspiration) 6–12 months after RT[29]. Also Goguen et al. described dysphagia to be only partly resolved 6–12 months following RT treatment[30]. Nguyen et al. reported on somewhat longer-term dysphagia severity following CRT. After a median post-treatment follow-up of 17 months, severe dysphagia was found in 45% of patients[31], whereas after

more than two years post-treatment (median follow-up 26 months), it worsened in 20% of patients[32]. More recently, Hutcheson et al. retrospectively evaluated dysphagia in HNC patients, who were treated more than five years ago. Aspiration and pharyngeal residue were the norm in all patients. Eighty-six percent had developed aspiration pneumonia and 66% were tube feeding dependent as a consequence of their dysphagia[33]. Ackerstaff et al., and Metreau et al., evaluated long-term (5-years) results in advanced (stage IV) HNC patients following CRT too. While Metreau et al. retrospectively assessed a high rate of dysphagia-related morbidity (feeding tube, oral supplements, and pneumonia) and QOL alterations, the prospective study of Ackerstaff et al. found QOL issues after 5-years follow-up to be similar to those at 1-year. A limitation of these latter two studies is that no objective evaluation of swallowing function was performed in these studies regarding long-term functional/QOL evaluation following CRT. Moreover, none of these patient groups was treated with preventive (swallowing) exercises before, during, and/or after the course of treatment, whereas especially a prospective evaluation of swallowing therapy in the HNC population would be valuable/informative[3].

Regarding voice problems following (C)RT for HNC, efforts to prevent or reduce sequels following treatment are scarcer. Furthermore, only few studies with adequate pre-treatment data collection prospectively investigated changes in patient- and observer-rated voice quality[6, 9-11, 34-36]. Longest follow-up was a year in all. Adequately controlled and randomized data on voice outcomes are scarce anyway, and the available studies often used different diagnostic tests to assess voice quality. Voice problems after (C)RT treatment may be attributed to impaired vocal fold vibration with incomplete closure, as a result of dryness of the laryngeal mucosa, muscle atrophy, fibrosis, hyperemia, and erythema[8, 37]. As a result, abnormal acoustic and aerodynamic measures (harmonics-to-noise-ratio, fundamental frequency, measures of jitter, shimmer, and spectral tilt) have been demonstrated in irradiated HNC patients. Also subjective voice problems, often assessed with the Voice Handicap Index (VHI), are reported in the available but limited literature on this topic[6, 38-42].

Earlier, we reported about the one- and two-year CRT-related functional outcomes from a previous prospective RCT, comparing two preventive swallowing rehabilitation regimens[25]. In comparison with the literature, swallowing problems were limited in both treatment arms. Here, the prospectively collected objective and subjective functional swallowing and voice outcomes of this study in the combined patient cohort still alive at 6-years will be reported.

MATERIAL AND METHODS

This study concerns the long-term follow-up of all disease-free and evaluable patients from an original cohort of 55 patients with advanced (stage III and IV), functionally[43] or anatomically

inoperable squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, larynx, or nasopharynx, who were treated with concurrent chemo-radiotherapy (CRT)[24, 25, 44]. Of the original patient cohort of 55 patients, 49 patients actually completed treatment. Each patient received 100 mg/m^2 Cisplatin as a 40 min IV infusion on days 1, 22, and 43. Intensity-modulated RT (IMRT) of 70 Gy in 35 fractions was administered over seven weeks starting concurrently with chemotherapy. Of the 22 evaluable patients (see below) 20 (91%) received a radiation dose of 43.5 Gy or higher to the larynx, because of advanced stage of the tumors and/or positive lymph nodes[45].

The original study compared two preventive rehabilitation programs (consisting of standard logopaedic swallowing exercises or an experimental swallowing rehabilitation program, based on the TheraBite® Jaw Motion Rehabilitation System™)[23]. Patients were instructed to practice daily from the start of treatment until 1-year post-treatment. Since both treatment groups showed more or less similar results, except for a slight but significant weight increase at 2-years with the experimental program[28], here the 6-years data of all disease-free and evaluable patients (n=22) are combined. Of the additional seven patients included in the 2-years assessment (n=29), in the meantime three had died, three suffered from severe unrelated disease precluding their participation in this long-term evaluation (Alzheimer's disease, primary liver cancer, progressive obstructive pulmonary disease) and one patient refused to participate. Although during a telephone interview with this last patient no swallowing and/or voice complaints were revealed, he was excluded because most multidimensional assessment data were missing. All patient data and reasons for exclusion at the various assessment points are provided in the consort flowchart (Figure 1).

Multidimensional assessment

As previously published[34, 44], assessment of functional (voice and swallowing) sequels was performed with multidimensional objective and subjective outcome-measures. In short, the protocol included standard videofluoroscopy (VFS) to determine swallowing function, the Penetration and Aspiration Scale (PAS; score 1: material does not enter the airway, to 8: material enters the airway, passes below the vocal folds, and no effort is made to eject[46]), and an overall 'presence of residue' score (score 0: no residue, to score 3: residue above and below the vallecula, with minimal residue judged as normal). Maximum interincisor (mouth) opening (MIO) was measured in mm using the disposable TheraBite range of motion scale, and trismus was defined as a MIO of ≤ 35 mm[47]. Oral intake/nutritional status was assessed with the Functional Oral Intake Scale (FOIS; range from 1–7 with 1: nothing by mouth to 7: no oral restrictions), and with data on tube feeding dependency, weight change, and Body Mass Index (BMI). Pain was assessed with a visual analog scale (VAS) of 0–100 mm with zero being no pain and 100 being the worst possible pain (VAS; score 0–4 mm: no pain, to score 75–100: severe pain)[48].

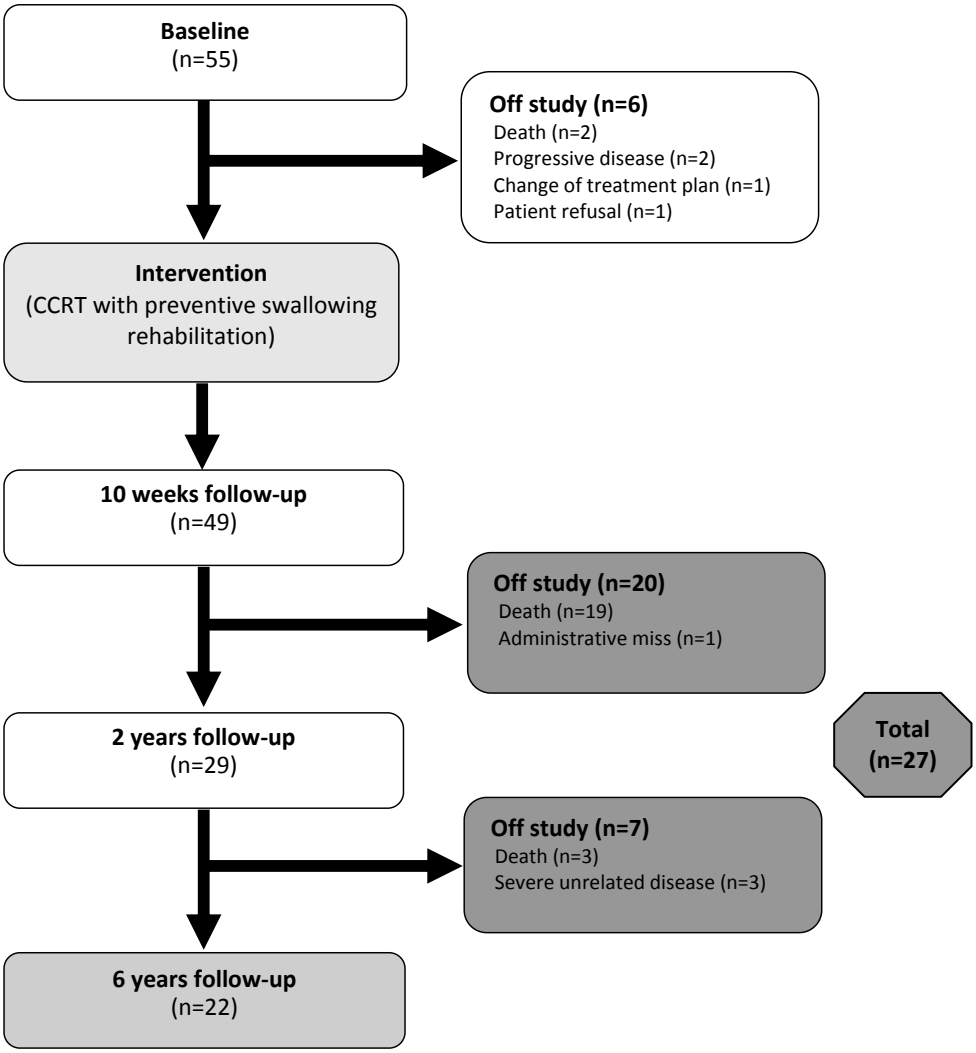


Figure 1. Consort flowchart with patient data and reasons for exclusion at the various assessment points.

Acoustic voice parameters (voicedness, fundamental frequency, harmonics-to-noise ratio, measures of spectral tilt, jitter and shimmer measures, and nasality) were derived from recordings in a quiet room of a standard Dutch text and sustained /a/. Acoustic analysis was performed with the program PRAAT (www.praat.org).

A study-specific questionnaire, in part based on the EORTC-HN and EORTC-C30, was used to evaluate patients' perception of swallowing function, mouth opening and voice quality, several QOL aspects, and compliance with the exercises[44]. Additionally, at the 6-years

assessment point, the SWAL-QOL and the Voice Handicap Index (VHI) questionnaires were administered. The SWAL-QOL is one of the validated questionnaires for assessing patients' swallowing impairment (44-items that assess 10 QOL domains, each ranging from 0–100 with a higher score indicating more impairment)[49, 50]. The VHI is a validated 30-item questionnaire scored on a 0–4 point scale for measuring patients' subjective suffering caused by dysphonia, specified into 3 subscales (physical, functional, emotional) identified with 10 items each. The total VHI score can range from 0–120 with a higher score corresponding to a higher degree of patient-reported vocal handicap (VHI score 0–30: minimal handicap; 31–60: moderate handicap; 60–120: significant and serious handicap)[51, 52]. At the start of the original RCT (2006) these questionnaires were not yet validated into Dutch, and thus these data are only available at the 6-years assessment point. All (other) outcome-measures at 6-years post-treatment were compared with results at baseline and at 2-years post-treatment.

Statistical Analysis

All data were collected and analyzed in a specially developed Statistical Package of Social Sciences database (SPSS, Inc, Chicago, Illinois; version 20.0). Concerning the functional outcome parameters, percentages of reported/measured disorders were calculated at each assessment point, comparable to the methods described by Logemann et al.[53]. McNemar's test with Bonferroni correction was used for pairwise comparisons among the various assessment points (baseline, 2-years- and 6-years post-treatment). Continuous variables (i.e. weight and MIO) were compared by means of paired *t* tests. For acoustic voice analysis, patients were divided into several subgroups according to tumor site. Independent sample *t* tests were used for comparisons between groups and paired *t* test were used for pairwise (subgroup) comparisons over time. For all analyses, a p value of ≤ 0.05 was considered to be statistically significant. Overall survival (OS) was calculated from randomization until death or last time of assessment. Survival curves were generated with the Kaplan–Meier method. The log-rank test was used to examine the difference in OS between subgroups.

RESULTS

Patients' characteristics

At approximately 6 years (median follow-up 74 months, range 67–83 months) 22 patients (17 males and 5 females, mean age: 63 years; range 45–79 years) were disease-free and evaluable. Three patients (all stage IV; 14%), who had required a salvage neck dissection for residual regional disease, were kept in the analysis. Patients' and tumor characteristics of the total patient group that started and completed treatment (n=49), of the evaluated patients (n=22), and of those who were not evaluable (n=27), are given in Table 1. Except for T-stage,

there were no significant differences between the groups with respect to gender, mean age, tumor site, or general tumor stage (stage III or IV).

Table 1. Clinical characteristics of patients at baseline (n=55), patients at the 6-years assessment point (n=22), and patients, who went off study (n=27). For acoustic analyses, tumor sites were grouped as *above hyoid bone** and *below hyoid bone***, and according to velopharyngeal tumor extension (*NT group* = *N*asopharyngeal and *T*onsil tumors; *LHBT group* = *L*aryngeal, *H*ypopharyngeal, and *B*ase of *T*ongue tumors).

	Baseline	Patients who started treatment	
	Pre-treatment n=55 (%)	6-yrs evaluated patientsn=22 (%)	Not evaluated patientsn=27 (%)
Gender			
Male (%)	44 (80)	19 (86)	22 (82)
Female (%)	11 (20)	3 (14)	5 (18)
Age at baseline (range)	58 (32–79)	57 (39–73)	56 (32–78)
Tumor site			
* Nasopharynx (%)	7 (13)	4 (18)	3 (11)
* Oral / Oropharynx (%)	29 (53)	10 (46)	14 (52)
** Hypopharynx/ Larynx (%)	19 (35)	8 (36)	10 (37)
NT group (%)	13 (24)	6 (27)	5 (19)
LHBT group (%)	42 (76)	16 (73)	22 (81)
Tumor stage			
Stage III (%)	17 (31)	10 (45)	6 (22)
Stage IV (%)	38 (69)	12 (55)	21 (78)
T stage			
T1 (%)	8 (15)	5 (23)	3 (11)
T2 (%)	15 (27)	9 (41)	6 (33)
T3 (%)	21 (38)	7 (32)	12 (44)
T4 (%)	11 (20	1 (5)	6 (22)
N stage			
N0 (%)	6 (11)	2 (9)	2 (7)
N1 (%)	15 (27)	8 (36)	6 (22)
N2 (%)	28 (51)	8 (36)	18 (67)
N3 (%)	6 (11)	4 (18)	1 (4)
Exercise group			
Standard group (%)	28 (51)	10 (45)	12 (44)
Experimental group (%)	27 (49)	12 (55)	15 (56)

Swallowing function

Table 2 shows overall percentages of laryngeal penetration and/or aspiration, contrast residue, tube feeding, abnormal FOIS score, trismus, patients' perceived swallowing and mouth opening issues (e.g. xerostomia), pain (VAS), mean mouth opening (MIO) and mean weight. As can be seen, some functional problems were already present at baseline, related to tumor site and/or extension. Furthermore, Table 2 shows that many functional and QOL aspects had not significantly changed over the various assessment points, except increased xerostomia (baseline vs. 6-years; p=.003), ultimately reported by two thirds of the patients. Despite the non-significant differences over time, some trends will be discussed.

Regarding swallowing function, the percentages of laryngeal penetration and/or aspiration and the frequency of more than normal residue above and below the hyoid bone on VFS (n=18) remained more or less stable over time (this concerned mainly patients with a tumor located at the larynx or hypopharynx). None of the patients was dependent on tube feeding or on nutritional oral supplements at 6-years post-treatment. Regarding mouth opening, only 1 patient (5%), who had been treated for a tumor located at the oropharynx (tonsillar carcinoma), showed trismus at the 6-years assessment point. Patients' perceived trismus was higher, and was reported by 6 patients (27%), of whom 4 actually showed a measurable decreased MIO (mean decrease 8 mm; range 3–15 mm) compared to baseline values. Pain in the head and neck region was already present in 36% of patients before treatment onset, decreased below baseline levels at 2-years post-treatment, and tended to increase again at 6-years post-treatment (32%; p=.06). With respect to QOL issues related to swallowing function at 6-years post-treatment, xerostomia (n=15; 68%; especially in oropharyngeal cancer (n=9) patients), and problems with swallowing solids (50%) were most frequently reported.

Voice quality

Table 3 shows the subjective and objective voice parameters divided into subgroups according to tumor site above/below the hyoid bone (HB), and for the parameter nasality according to velopharyngeal tumor extension (nasopharyngeal and tonsil tumors) or not (laryngeal, hypopharyngeal, and base of tongue tumors). See table 3 for the number of patients per subgroup. For subjective voice analysis (n=22), mean VHI scores, as assessed at 6-years post-treatment, are shown. For acoustic voice analysis (n=19), three patients were excluded due to missing data or poor quality of the voice recordings. For these parameters mean differences between measures at baseline and measures at 6-years are shown.

Table 2. Percentages of disorders and other measures observed at the various assessment points after concurrent chemoradiotherapy in 22 advanced head and neck cancer patients.

Description of disorder	Pre-treatment		Post-treatment				McNemar's *p* value	
n = 22	*Baseline*		*2-years*		*6-years*		pre vs.	2 yrs vs.
	n (%)		n (%)		n (%)		6 yrs	6 yrs
Videofluoroscopy (n=18)								
Aspiration or penetration	3	(17)	3	(18)	4	(22)	1.0	1.0
Residue above and below hyoid	17	(94)	11	(65)	14	(78)	.38	.25
Feeding tube	0	(0)	0	(0)	0	(0)	x	x
Abnormal diet (FOIS score 1–6)	3	(14)	2	(9)	0	(0)	.25	.50
Pain (VAS)	8	(36)	2	(9)	7	(32)	1.0	.06
Trismus	2	(9)	2	(9)	1	(5)	1.0	1.0
QOL aspect / issue								
Perceived decreased mouth opening	1	(5)	5	(23)	6	(27)	.06	1.0
Xerostomia	4	(18)	13	(59)	15	(68)	**.003**	.63
Oral transport with solids	3	(14)	5	(23)	3	(14)	1.0	.63
Oral transport with paste	2	(9)	1	(5)	1	(5)	1.0	1.0
Oral transport with liquids	0	(0)	1	(5)	1	(5)	1.0	1.0
Swallowing problems with solids	8	(36)	11	(50)	11	(50)	.51	1.0
Swallowing problems with paste	2	(9)	1	(5)	2	(9)	1.0	1.0
Swallowing problems with liquids	1	(5)	0	(0)	2	(9)	1.0	.50
Perceived different voice	8	(37)	14	(64)	11	(50)	1.0	.51
Weight in kg (range)	82 (51–106)		80 (56–105)		81 (57–110)		.61*	.54*
Mouth opening in mm (range)	52 (26–69)		52 (20–70)		53 (21–70)		.87*	.40*

Values marked by asterisks (*) mean compared mean p values; x means no statistical analyses possible. Videofluoroscopy records at 6-years post-treatment were available for 18 patients. If patients needed tube feeding, the QOL questions about oral transport and swallowing problems were not filled in. CRT: Concurrent chemo-radiotherapy; HNC: Head and Neck Cancer; FOIS: Functional Oral Intake Scale; QOL: Quality of Life.

Table 3. Subjective and objective voice parameters divided according to tumor site. For subjective voice analysis (n=22), mean Voice Handicap Index (VHI) scores, as assessed at 6-years post-treatment, are shown. For acoustic voice analysis (n=19), mean differences between measures at baseline and measures at 6-years are shown. For all acoustic voice parameters except voicedness and fundamental frequency, 1 patient with a tumor below the hyoid bone was excluded because of the presence of a nasogastric feeding tube at baseline. *Above hyoid bone group* = Oral cavity, Oropharyngeal (tonsil and base of tongue), and Nasopharyngeal tumors; *Below hyoid bone group* = Laryngeal and Hypopharyngeal tumors; *NT group* = *N*asopharyngeal and *T*onsil tumors; *LHBT group* = *L*aryngeal, *H*ypopharyngeal, and *B*ase of *T*ongue tumors.

	Above hyoid bone group			Below hyoid bone group			Total		
	N	*Mean*	*SD*	*N*	*Mean*	*SD*	*N*	*Mean*	*SD*
Voice Handicap Index (VHI) score	14	6,86	14,13	8	21,00	29,80	22	12.00	21,64
VHI physical domain	14	2,86	5,91	8	10,13	10,11	22	5,50	8,27
VHI functional domain	14	2,71	5,18	8	5,88	8,97	22	3,86	6,76
VHI emotional domain	14	1,29	3,12	8	5,00	11,81	22	2,64	7,47
Voicedness /text/	12	-1,50	8,19	7	0,14	7,38	19	-0,89	7,73
Fundamental frequency /text/	12	-2,92	23,20	7	-12,71	13,24	19	-6,53	20,27
Harmonics-to-noise ratio /a/	12	-1,81	4,72	6	-0,52	3,55	18	-1,38	4,30
Measures of spectral tilt /a/	12	-2,91	4,63	6	-4,88	7,91	18	-3,57	5,76
Jitter /a/	12	-0,00	0,65	6	-0,21	0,47	18	-0,07	0,59
Shimmer /a/	12	2,60	3,28	6	-0,37	4,54	18	1,61	3,88
		NT group			LHTB group			Total	
	N	Mean	SD	N	Mean	SD	N	Mean	SD
Nasality /a/	6	-3,59	6,61	12	0,72	6,04	18	-2,15	6,59

Regarding subjective voice outcomes at the 6-years assessment point, half of the patients (n=11; 50%) perceived their voice as different from baseline. The median total VHI score at 6-years post-treatment was 3 (mean=12; range 0–91; n=22). Patients with a tumor located below the HB ('below HB group') reported higher total VHI scores (mean=21, median=11, range 0–91), indicating more voice problems, in comparison with those with a tumor above the hyoid bone ('above HB group'; mean=7, median=1, range 0–47). In particular the physical and functional subscales of the VHI predicted the total VHI scores. Emotional voice problems were reported by 7 patients, who all had high physical and functional VHI sub scores. Five were laryngeal cancer patients and 2 were oropharyngeal cancer patients. The latter two received a high radiation dose (>55 Gy) to the larynx and both parotid glands.

For acoustic analysis of all voice parameters except voicedness and fundamental frequency (indicating pitch), 1 patient with a tumor below the HB was excluded because of the presence of a nasogastric feeding tube at baseline. It has to be noted that none of the patients suffered from a cold during voice recordings. Acoustic analysis of the read aloud text at baseline (n=19) showed that patients in the 'below HB group' (n=7) presented with significantly less voicedness than the patients in the 'above HB group' (n=12; independent sample *t* test; p=.011). Over time, there was no improvement in both groups, and the difference was still significant at 6-years post-treatment (p=.016). There was also no significant improvement in the harmonics-to-noise ratio from baseline to 6-years post-treatment in both groups. Mean fundamental frequency during text aloud reading at 6-years post-treatment had not changed much for the 'above HB group', while it had significantly increased in the 'below HB group' (p=.044; see Figure 2). Jitter measures had increased as well in the 'below HB group', while shimmer measures were stable over time. In contrast, in the 'above HB group' shimmer had improved while jitter was stable. Measures of spectral tilt (indicating vocal effort) on sustained /a/ at baseline showed more effort in the 'below HB group' (p=.231). At 6-years post-treatment, results had improved up to the level of the 'above HB group' (see Figure 3). Velopharyngeal function was analyzed by nasality (antiformants) in sustained /a/. The patients were divided into subgroups according to velopharyngeal tumor extension ('NT group': *N*asopharyngeal and *T*onsil tumors; n=6) or not ('LHBT group': *L*aryngeal, *H*ypopharyngeal, and Base of *T*ongue tumors; n=12). While the 'NT group' showed improvements after 2-years compared to baseline, at 6-years post-treatment the measures had worsened again. Also in the 'LHBT group' there was a trend that the measures had worsened compared to baseline values (paired *t* test p=.087).

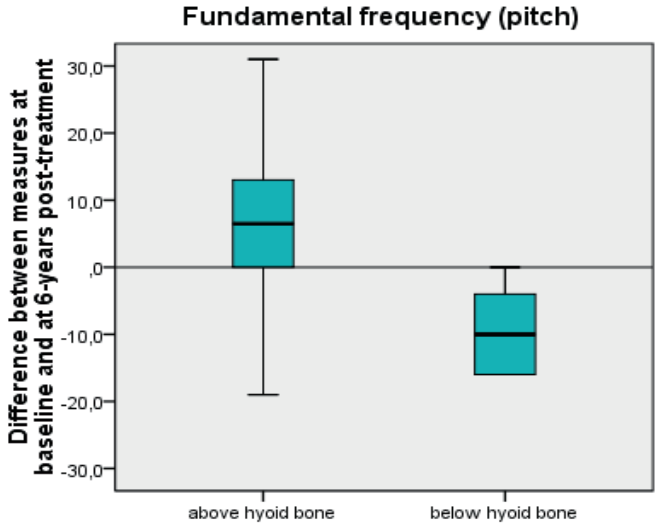


Figure 2. Change in fundamental frequency ("pitch") between measures at baseline and at 6-years post-treatment among patients with a tumor above the hyoid bone (n=12) and below the hyoid bone (n=7). Negative values mean increased pitch between the two assessment points.

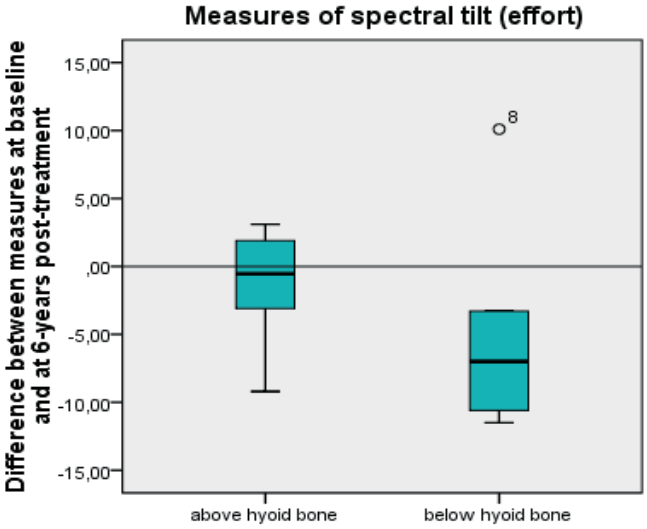


Figure 3. Change in measures of spectral tilt ("vocal effort") between baseline and 6-years post-treatment among patients with a tumor above the hyoid bone (n=12) and below the hyoid bone (n=6). Negative values show a decrease in vocal effort between the two assessment points.

General treatment outcomes

Beyond 6-years of treatment, 24 of the included 55 patients (44%) had died; 14 patients had died of progressive (recurrent or residual) disease, two patients had died of a second primary malignancy (lung and liver) and 8 patients had died due to other/unknown causes. The 6-year overall survival (OS) rate, based on the original cohort of 55 patients, was 60%. Both tumor stage and site (stage IV, oral cavity) were found to be associated with poorer OS in this patient cohort. Patients with a tumor located at the nasopharynx (n=7) showed the best OS. See Figure 4 for the Kaplan-Meier curves for OS per tumor stage.

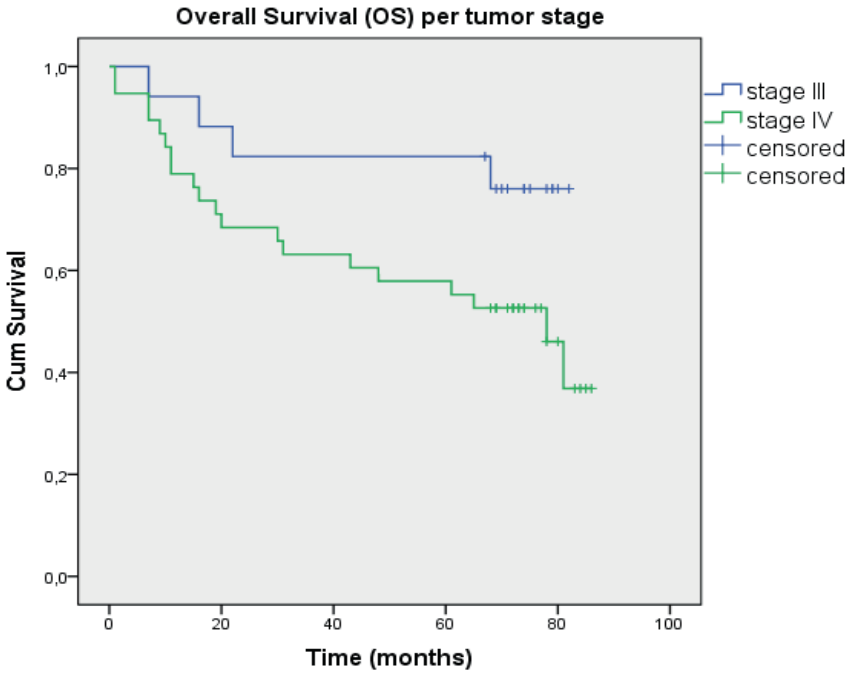


Figure 4. Kaplan-Meier curve for overall survival (OS) per tumor stage with poorer OS (p=.067) for stage IV tumors compared to stage III tumors.

DISCUSSION

This prospective clinical study on swallowing function and voice quality in advanced head and neck cancer (HNC) patients treated with concurrent chemoradiotherapy (CRT) and preventive swallowing exercises shows that functional swallowing and voice problems at 6-years post-treatment are minimal. Moreover, no significant changes since the one-year (voice quality[34]) or two-years (swallowing function[25]) assessment points are found.

Swallowing function

In the earlier reports on this CRT-preventive swallowing rehabilitation trial, outcomes were compared with an in-house preceding RCT on CRT with a similar (IMRT) therapy protocol, except for the application of this preventive swallowing rehabilitation protocol. Since the 5-years results of this latter trial are published as well[54], and data from prospective studies with longer follow-up after preventive swallowing rehabilitation still are scarce[19], it is again possible and interesting to also compare the more long-term results of both trials. Regarding swallowing function and oral intake, in that earlier study it was found that 7/71 patients (10%) still required tube feeding at 5-years post-treatment, whereas in the present study all patients were able to consume a normal oral diet at the 6-years assessment point. In the preceding CRT study, no objective evaluation of swallowing function was performed, which precludes comparison of those data available for the present study. Comparison to some extent is possible with the study of Hutcheson et al.[33], which evaluated late dysphagia (dysphagic patients with a median of 9-years post-treatment), and included videofluoroscopic studies. Pharyngeal residue and aspiration was found in all patients, with silent aspiration occurring in 23/28 patients (82%). Six patients (21%) were feeding tube dependent and 11 patients (38%) had developed trismus. However, only symptomatic dysphagic patients were evaluated in that study, precluding estimate of the prevalence of late dysphagia, and in depths comparison with our findings.

It's not unlikely that the favorable swallowing outcomes in the present study can be attributed to the preventive and continued post-treatment rehabilitation programs, which were applied in this patient cohort. Preventive rehabilitation programs have been associated with better post-treatment swallowing outcomes before[20-26], especially on the short-term[19], and probably, the exercises applied are associated with better long-term results as well.

Patients' perceived functional changes correlated only weakly with objective outcome measures. Regarding swallowing function, only one of the four patients who showed laryngeal penetration or aspiration on VFS, actually reported of swallowing problems. With regards to trismus, there was only one patient (5%) who actually fulfilled the criterion for an objective trismus (MIO ≤ 35 mm). Interestingly, however, patients' perceived trismus was higher (n=6, including the objective trismus patient; 27%), and in 4 of these 6 patients the MIO did show a measurable decrease (mean 8 mm) compared to baseline values. Therefore, clinical outcome measures should always be combined with patients' views, in order to gain best insight in the extent of the functional problems.

Voice quality

Since combined CRT regimens can have adverse effects on voice quality as well, assessment of functional sequels of CRT should include patients' voice quality, e.g. by calculating means of acoustic parameters at the various assessment points. In the present cohort, due to positive

lymph nodes, the vast majority of patients (20/22) received a radiation dose of 43.5 Gy and higher to the larynx, which has been described in the literature as cut-off value for developing voice problems or chronic edema[4, 5]. Voice problems can also occur due to changes in saliva production and lubrication, mainly as a result of radiation dose to the parotid gland and the laryngeal mucosa, which can lead to insufficient lubrication/dryness of the vocal folds[37, 55]. Hence, the fact that generally all patients with a tumor located at the larynx or hypopharynx (still) demonstrated less voicedness and increased fundamental frequency at voice recordings at 6-years post-treatment is understandable. Interestingly, although this concerned only six patients, patients with a tumor located at the tonsil or nasopharynx, who had shown improvements in nasality at the 2-years assessment point, showed increased nasality again at the 6-years assessment point. Previously, only few studies with adequate pre-treatment data prospectively investigated effects of CRT on voice quality, and the available studies often used different diagnostic tests[9-11, 34, 36]. Longest follow-up was a year in all, except for the study of Vainshtein et. al. that evaluated voice changes up to two years following CRT[6]. However, only patient-reported voice quality was assessed in that study, while especially acoustic voice parameters at long-term follow-up would be informative, since changes in voice quality (i.e. more nasality) after 6-years follow-up are demonstrable in our study.

Subjective voice complaints were evaluated in the present patient cohort with some study-specific questions ("do you perceive your voice as different from baseline"?) and with (sub)total VHI scores. Previously, subjective voice outcomes showed that 70% of patients reported their voice as different from baseline to one year post-treatment[56]. Besides, most of the laryngeal and hypopharyngeal cancer patients already presented with voice problems at the time of diagnosis. At 6-years post-treatment, (still) half of the patients (50%) perceived their voice as different from baseline. Patients with a functional and/or physical voice disability (based on VHI sub scores[51]) reported of problems such as increased vocal effort, breathiness, and hoarseness. To date, there are little studies that evaluated VHI scores after CRT treatment for HNC, especially at long-term. In recent studies that evaluated voice quality, results showed decreases in voice quality following CRT[6, 40], with an impact on QOL and emotional distress[42]. Though almost the whole VHI range (0–91) was covered in our patient population (with various tumor sites included) at 6-years post-treatment, the median total VHI score was only three. Apparently, the subjectively perceived and acoustically measured changes in voice quality were not considered a handicap for the vast majority of our patients.

Limitations

In prospective trials, patients are lost to follow-up because of death, or of progressive, residual or recurrent disease, which always forms a limitation in long-term evaluation of functional treatment results. Moreover, there might be a survival bias towards patients with good functional outcomes. Longer-term severe unrelated disease and patient refusal are further

decreasing the sample on which conclusions have to be based upon. And obviously, as can be seen in Table 1, more stage III than stage IV patients are surviving/evaluable (originally 33-66, and at 6-years almost 50-50). As a result, some selection bias cannot be excluded in the present study, which might as well in part explain the limited functional problems in the analyzed patient cohort. However, except for initial T-stage, the patient group at 6-years post-treatment (n=22) still is comparable to the group at baseline (n=49) concerning most patient and tumor characteristics (age, gender, tumor site and stage etc.). Also the patients who went "off-study" after initial treatment (n=27) did not differ significantly on most of these parameters from the currently analyzed patients (n=22).

CONCLUSION

This is one of the first studies investigating CRT-induced effects on swallowing function and voice quality in HNC patients 6-years after treatment. Overall, functional problems at 6-years post-treatment are minimal in this patient cohort, possibly due to the preventive and continued post-treatment swallowing rehabilitation programs applied.

ACKNOWLEDGEMENTS

This study was made possible by grants provided by "Stichting de Hoop" and the "Verwelius Foundation".

REFERENCES

1. Pignon JP, le Maitre A, Maillard E, Bourhis J. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol. 2009;92:4-14.
2. Hutcheson KA, Lewin JS. Functional outcomes after chemoradiotherapy of laryngeal and pharyngeal cancers. Curr Oncol Rep. 2012;14:158-65.
3. Metreau A, Louvel G, Godey B, Le Clech G, Jegoux F. Long-term functional and quality of life evaluation after treatment for advanced pharyngolaryngeal carcinoma. Head Neck. 2013;Epub.
4. Sanguineti G, Adapala P, Endres EJ, Brack C, Fiorino C, Sormani MP, et al. Dosimetric predictors of laryngeal edema. Int J Radiat Oncol Biol Phys. 2007;68:741-9.
5. Nguyen NP, Abraham D, Desai A, Betz M, Davis R, Sroka T, et al. Impact of image-guided radiotherapy to reduce laryngeal edema following treatment for non-laryngeal and non-hypopharyngeal head and neck cancers. Oral Oncol. 2011;47:900-4.
6. Vainshtein JM, Griffith KA, Feng FY, Vineberg KA, Chepeha DB, Eisbruch A. Patient-Reported Voice and Speech Outcomes After Whole-Neck Intensity Modulated Radiation Therapy and Chemotherapy for Oropharyngeal Cancer: Prospective Longitudinal Study. Int J Radiat Oncol Biol Phys. 2014.
7. Fung K, Yoo J, Leeper HA, Bogue B, Hawkins S, Hammond JA, et al. Effects of head and neck radiation therapy on vocal function. J Otolaryngol. 2001;30:133-9.
8. Starmer HM, Tippett DC, Webster KT. Effects of laryngeal cancer on voice and swallowing. Otolaryngol Clin North Am. 2008;41:793-818, vii.
9. Bibby JR, Cotton SM, Perry A, Corry JF. Voice outcomes after radiotherapy treatment for early glottic cancer: assessment using multidimensional tools. Head Neck. 2008;30:600-10.
10. Kazi R, Venkitaraman R, Johnson C, Prasad V, Clarke P, Newbold K, et al. Prospective, longitudinal electroglottographic study of voice recovery following accelerated hypofractionated radiotherapy for T1/T2 larynx cancer. Radiother Oncol. 2008;87:230-6.
11. Agarwal JP, Baccher GK, Waghmare CM, Mallick I, Ghosh-Laskar S, Budrukkar A, et al. Factors affecting the quality of voice in the early glottic cancer treated with radiotherapy. Radiother Oncol. 2009;90:177-82.
12. Jacobi I, van der Molen L, Huiskens H, van Rossum MA, Hilgers FJ. Voice and speech outcomes of chemoradiation for advanced head and neck cancer: a systematic review. Eur Arch Otorhinolaryngol. 2010;267:1495-505.
13. Lazarus CL, Husaini H, Hu K, Culliney B, Li Z, Urken M, et al. Functional Outcomes and Quality of Life After Chemoradiotherapy: Baseline and 3 and 6 Months Post-Treatment. Dysphagia. 2014.
14. Feng FY, Kim HM, Lyden TH, Haxer MJ, Worden FP, Feng M, et al. Intensity-modulated chemoradiotherapy aiming to reduce dysphagia in patients with oropharyngeal cancer: clinical and functional results. J Clin Oncol. 2010;28:2732-8.
15. Mowry SE, Tang C, Sadeghi A, Wang MB. Standard chemoradiation versus intensity-modulated chemoradiation: a quality of life assessment in oropharyngeal cancer patients. Eur Arch Otorhinolaryngol. 2010;267:1111-6.
16. Roe JW, Carding PN, Dwivedi RC, Kazi RA, Rhys-Evans PH, Harrington KJ, et al. Swallowing outcomes following Intensity Modulated Radiation Therapy (IMRT) for head & neck cancer - a systematic review. Oral Oncol. 2010;46:727-33.
17. Eisbruch A, Kim HM, Feng FY, Lyden TH, Haxer MJ, Feng M, et al. Chemo-IMRT of oropharyngeal cancer aiming to reduce dysphagia: swallowing organs late complication probabilities and dosimetric correlates. Int J Radiat Oncol Biol Phys. 2011;81:e93-9.
18. Peponi E, Glanzmann C, Willi B, Huber G, Studer G. Dysphagia in head and neck cancer

patients following intensity modulated radiotherapy (IMRT). Radiat Oncol. 2011;6:1.

19. Kraaijenga SA, van der Molen L, van den Brekel MW, Hilgers FJ. Current assessment and treatment strategies of dysphagia in head and neck cancer patients: a systematic review of the 2012/13 literature. Curr Opin Support Palliat Care. 2014;8:152-63.

20. Kulbersh BD, Rosenthal EL, McGrew BM, Duncan RD, McColloch NL, Carroll WR, et al. Pretreatment, preoperative swallowing exercises may improve dysphagia quality of life. Laryngoscope. 2006;116:883-6.

21. Carroll WR, Locher JL, Canon CL, Bohannon IA, McColloch NL, Magnuson JS. Pretreatment swallowing exercises improve swallow function after chemoradiation. Laryngoscope. 2008;118:39-43.

22. Carnaby-Mann G, Crary MA, Schmalfuss I, Amdur R. "Pharyngocise": randomized controlled trial of preventative exercises to maintain muscle structure and swallowing function during head-and-neck chemoradiotherapy. Int J Radiat Oncol Biol Phys. 2012;83:210-9.

23. Kotz T, Federman AD, Kao J, Milman L, Packer S, Lopez-Prieto C, et al. Prophylactic swallowing exercises in patients with head and neck cancer undergoing chemoradiation: a randomized trial. Arch Otolaryngol Head Neck Surg. 2012;138:376-82.

24. van der Molen L, van Rossum MA, Burkhead LM, Smeele LE, Rasch CR, Hilgers FJ. A randomized preventive rehabilitation trial in advanced head and neck cancer patients treated with chemoradiotherapy: feasibility, compliance, and short-term effects. Dysphagia. 2011;26:155-70.

25. van der Molen L, van Rossum MA, Rasch CR, Smeele LE, Hilgers FJ. Two-year results of a prospective preventive swallowing rehabilitation trial in patients treated with chemoradiation for advanced head and neck cancer. Eur Arch Otorhinolaryngol. 2013.

26. Hutcheson KA, Bhayani MK, Beadle BM, Gold KA, Shinn EH, Lai SY, et al. Eat and exercise during radiotherapy or chemoradiotherapy for pharyngeal cancers: use it or lose it. JAMA Otolaryngol Head Neck Surg. 2013;139:1127-34.

27. Chen AM, Li BQ, Lau DH, Farwell DG, Luu Q, Stuart K, et al. Evaluating the role of prophylactic gastrostomy tube placement prior to definitive chemoradiotherapy for head and neck cancer. Int J Radiat Oncol Biol Phys. 2010;78:1026-32.

28. Langmore S, Krisciunas GP, Miloro KV, Evans SR, Cheng DM. Does PEG use cause dysphagia in head and neck cancer patients? Dysphagia. 2012;27:251-9.

29. Eisbruch A, Lyden T, Bradford CR, Dawson LA, Haxer MJ, Miller AE, et al. Objective assessment of swallowing dysfunction and aspiration after radiation concurrent with chemotherapy for head-and-neck cancer. Int J Radiat Oncol Biol Phys. 2002;53:23-8.

30. Goguen LA, Posner MR, Norris CM, Tishler RB, Wirth LJ, Annino DJ, et al. Dysphagia after sequential chemoradiation therapy for advanced head and neck cancer. Otolaryngol Head Neck Surg. 2006;134:916-22.

31. Nguyen NP, Moltz CC, Frank C, Vos P, Smith HJ, Karlsson U, et al. Dysphagia following chemoradiation for locally advanced head and neck cancer. Ann Oncol. 2004;15:383-8.

32. Nguyen NP, Moltz CC, Frank C, Vos P, Smith HJ, Karlsson U, et al. Evolution of chronic dysphagia following treatment for head and neck cancer. Oral Oncol. 2006;42:374-80.

33. Hutcheson KA, Lewin JS, Barringer DA, Lisec A, Gunn GB, Moore MW, et al. Late dysphagia after radiotherapy-based treatment of head and neck cancer. Cancer. 2012;118:5793-9.

34. Jacobi I vdML, van Rossum M, Hilgers FJ. Pre- and Short-term Posttreatment Vocal Functioning in Patients with Advanced Head and Neck Cancer Treated with Concomitant Chemoradiotherapy. Interspeech. 2010:2582-85.

35. Adams G, Burnett R, Mills E, Penniment M. Objective and subjective changes in voice quality after radiotherapy for early (T1 or T2, N0) laryngeal cancer: a pilot prospective cohort study. Head Neck. 2013;35:376-80.

36. Jacobi I, van Rossum MA, van der Molen L, Hilgers FJ, van den Brekel MW. Acoustic analysis of changes in articulation proficiency in patients with advanced head and neck cancer treated with chemoradiotherapy. Ann Otol Rhinol Laryngol. 2013;122:754-62.

37. Lazarus CL. Effects of chemoradiotherapy on voice and swallowing. Curr Opin Otolaryngol Head Neck Surg. 2009;17:172-8.

38. Oridate N, Homma A, Suzuki S, Nakamaru Y, Suzuki F, Hatakeyama H, et al. Voice-related quality of life after treatment of laryngeal cancer. Arch Otolaryngol Head Neck Surg. 2009;135:363-8.

39. Thomas L, Jones TM, Tandon S, Carding P, Lowe D, Rogers S. Speech and voice outcomes in oropharyngeal cancer and evaluation of the University of Washington Quality of Life speech domain. Clin Otolaryngol. 2009;34:34-42.

40. Keereweer S, Kerrebijn JD, Al-Mamgani A, Sewnaik A, Baatenburg de Jong RJ, van Meerten E. Chemoradiation for advanced hypopharyngeal carcinoma: a retrospective study on efficacy, morbidity and quality of life. Eur Arch Otorhinolaryngol. 2012;269:939-46.

41. Myers C, Kerr P, Cooke A, Bammeke F, Butler J, Lambert P. Functional outcomes after treatment of advanced oropharyngeal carcinoma with radiation or chemoradiation. J Otolaryngol Head Neck Surg. 2012;41:108-18.

42. Rinkel RN, Verdonck-de Leeuw IM, van den Brakel N, de Bree R, Eerenstein SE, Aaronson N, et al. Patient-reported symptom questionnaires in laryngeal cancer: voice, speech and swallowing. Oral Oncol. 2014;50:759-64.

43. Kreeft AM, van der Molen L, Hilgers FJ, Balm AJ. Speech and swallowing after surgical treatment of advanced oral and oropharyngeal carcinoma: a systematic review of the literature. Eur Arch Otorhinolaryngol. 2009;266:1687-98.

44. van der Molen L, van Rossum MA, Ackerstaff AH, Smeele LE, Rasch CR, Hilgers FJ. Pretreatment organ function in patients with advanced head and neck cancer: clinical outcome measures and patients' views. BMC Ear Nose Throat Disord. 2009;9:10.

45. van der Molen L, Heemsbergen WD, de Jong R, van Rossum MA, Smeele LE, Rasch CR, et al. Dysphagia and trismus after concomitant chemo-Intensity-Modulated Radiation Therapy (chemo-IMRT) in advanced head and neck cancer; dose-effect relationships for swallowing and mastication structures. Radiother Oncol. 2013;106:364-9.

46. Rosenbek JC, Robbins JA, Roecker EB, Coyle JL, Wood JL. A penetration-aspiration scale. Dysphagia. 1996;11:93-8.

47. Dijkstra PU, Huisman PM, Roodenburg JL. Criteria for trismus in head and neck oncology. Int J Oral Maxillofac Surg. 2006;35:337-42.

48. Jensen MP, Chen C, Brugger AM. Interpretation of visual analog scale ratings and change scores: a reanalysis of two clinical trials of postoperative pain. J Pain. 2003;4:407-14.

49. Rinkel RN, Verdonck-de Leeuw IM, Langendijk JA, van Reij EJ, Aaronson NK, Leemans CR. The psychometric and clinical validity of the SWAL-QOL questionnaire in evaluating swallowing problems experienced by patients with oral and oropharyngeal cancer. Oral Oncol. 2009;45:e67-71.

50. Lemmens J, Bours GJ, Limburg M, Beurskens AJ. The feasibility and test-retest reliability of the Dutch SWAL-QOL adapted interview version for dysphagic patients with communicative and/or cognitive problems. Qual Life Res. 2013;22:891-5.

51. Jacobsen B JA, Grywalski C, Silbergleit A, Jacobsen G, Benninger M. The Voice Handicap Index (VHI): Development and Validation. American Journal of Speech-Language Pathology. 1997;6:66-70.

52. Verdonck-de Leeuw IM, Kuik DJ, De Bodt M, Guimaraes I, Holmberg EB, Nawka T, et al. Validation of the voice handicap index by assessing equivalence of European translations. Folia Phoniatr Logop. 2008;60:173-8.

53. Logemann JA, Pauloski BR, Rademaker AW, Lazarus CL, Gaziano J, Stachowiak L, et al. Swallowing disorders in the first year after radiation and chemoradiation. Head Neck. 2008;30:148-58.

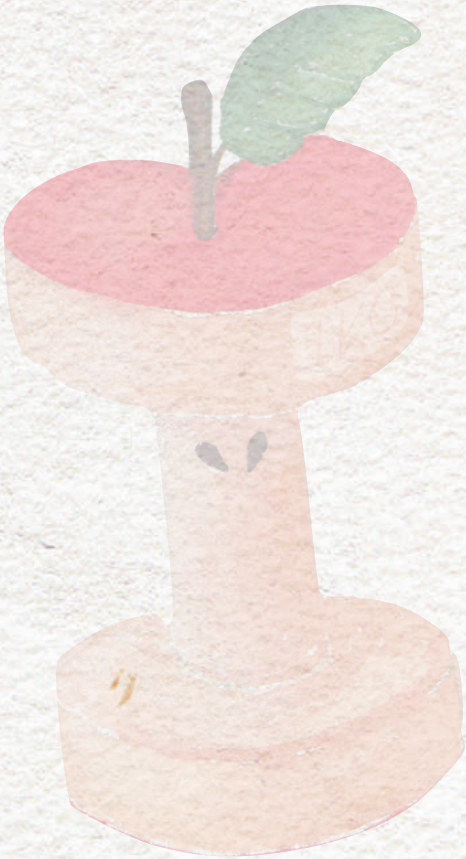
54. Ackerstaff AH, Rasch CR, Balm AJ, de Boer JP, Wiggenraad R, Rietveld DH, et al. Five-year quality of life results of the randomized clinical phase III (RADPLAT) trial, comparing concomitant intra-arterial versus intravenous chemoradiotherapy in locally advanced head and neck cancer. Head Neck. 2012;34:974-80.

55. Hamdan AL, Geara F, Rameh C, Husseini ST, Eid T, Fuleihan N. Vocal changes following radiotherapy to the head and neck for non-laryngeal tumors. Eur Arch Otorhinolaryngol. 2009;266:1435-9.

56. van der Molen L, van Rossum MA, Jacobi I, van Son RJ, Smeele LE, Rasch CR, et al. Pre- and posttreatment voice and speech outcomes in patients with advanced head and neck cancer treated with chemoradiotherapy: expert listeners' and patient's perception. J Voice. 2012;26:664.e25-33.

CHAPTER 6

Hyoid bone displacement as parameter for swallowing impairment in patients treated for advanced head and neck cancer



S.A.C. Kraaijenga
L. van der Molen
W.D. Heemsbergen
G.B. Remmerswaal
F.J.M. Hilgers
M.W.M. van den Brekel

Eur Arch Otorhinolaryngol. Online 2016 Apr 16.

ABSTRACT

Introduction: Reduced hyoid displacement is thought to contribute to aspiration and pharyngeal residues in head and neck cancer (HNC) patients with dysphagia. To further study hyoid elevation and anterior excursion in HNC patients, this study reports on temporal/kinematic measures of hyoid displacement, with the additional goal to investigate correlations with clinical swallowing impairment.

Methods: A single-blind analysis of data collected as part of a larger prospective study was performed at three time points before and after chemoradiotherapy. Twenty-five patients had undergone clinical swallowing assessments at baseline, 10-weeks, and 1-year post-treatment. Analysis of videofluoroscopic studies was done on different swallowing consistencies of varying amounts. The studies were independently reviewed frame-by frame by two clinicians to assess temporal (onset and duration) and kinematic (anterior/superior movement) measures of hyoid displacement (ImageJ), laryngeal penetration/aspiration, and presence of vallecula/pyriform sinus residues. Patient-reported oral intake and swallowing function were also evaluated.

Results: Mean maximum hyoid displacement ranged from 9.4 mm (23% of C2-4 distance) to 12.6 mm (27%) anteriorly, and from 18.9 mm (41%) to 24.9 mm (54%) superiorly, depending on bolus volume and consistency. Patients with reduced superior hyoid displacement perceived significantly more swallowing impairment. No correlation between delayed or reduced hyoid excursion and aspiration or residue scores could be demonstrated.

Conclusion: Hyoid displacement is subject to variability from a number of sources. Based on the results, this parameter seems not very valuable for clinical use in HNC patients with dysphagia.

KEY WORDS

Head and Neck neoplasms – Dysphagia – Hyoid Bone – Kinematics – Elevation – Displacement – Aspiration – Chemoradiotherapy

INTRODUCTION

Dysphagia, aspiration, or even the inability to swallow, is one of the most disabling adverse effects of treatment with concurrent chemoradiotherapy (CRT) for advanced head and neck cancer (HNC). Inefficient or unsafe swallowing may lead to severe consequences that may alter patients' nutritional status and quality of life. Although multiple swallowing abnormalities are likely present in patients with dysphagia, reduced hyolaryngeal elevation (hyoid bone displacement) is thought to be one of the prime contributors of impaired swallowing[1-4]. During the pharyngeal phase of swallowing, the hyoid bone usually elevates and moves anteriorly under the tongue base by contraction of the suprahyoid muscles, to initiate superior laryngeal movement and cricopharyngeal sphincter opening[5]. Unfortunately, in HNC patients, hyoid displacement is often considerably reduced, as a result of radiation-induced damage to anatomical structures involved in swallowing[3,6,7]. Consequently, reduced vertical excursion of the hyolaryngeal complex may lead to incomplete airway closure with an associated risk of aspiration, while reduced hyoid displacement in the anterior direction will lead to reduced opening of the upper esophageal sphincter, resulting in pyriform sinus residues, thus also increasing the risk of laryngeal penetration and/or aspiration[4].

Videofluoroscopy (VFS) has become the gold standard for objective evaluation of swallowing function, with the hyoid bone as anatomical point of interest. Several authors have reported on hyoid excursion by biomechanical analysis with VFS[8-10]. According to the literature, hyoid movement can be influenced by various factors such as body height[4], age and gender[11-14], aetiology of dysphagia[15], and bolus characteristics[16,17]. Unfortunately, the measurements are not always easy and reproducible, and are prone to measurement errors[18,19]. It is therefore not surprising that conflicting results of association between hyoid movement and aspiration are published[9,10]. Given the fact that hyoid excursion is widely variable in healthy adults[20], it is currently recommended to measure hyoid displacement in anatomically normalized units, i.e. in percentage of the distance between vertebra C2 and C4. In this way, magnification artefacts or sex-based differences attributable to variations in measurement technique are reduced[10].

In HNC patients with dysphagia, Wang and colleagues[3] recently assessed hyoid displacement in irradiated nasopharyngeal cancer patients. Hyoid excursion, especially in the anterior direction, was found to be significantly reduced compared to the control group. Correlation patterns between kinematic measures and swallowing impairment, however, were not investigated. Similarly, two other case studies reported on reduced hyoid displacement in HNC patients[7,21]. Percentages of restricted or reduced hyoid movement ranged from 42% to 97%, depending on primary tumor site. Correlations were again not investigated. The present study reports on hyoid displacement parameters in an advanced HNC patient cohort treated with CRT. The primary aim was to report on temporal and kinematic measures related to

hyoid displacement in this patient cohort. The secondary aim was to investigate correlations with persisting (clinical) swallowing impairment, and to assess the possible value of these parameters for clinical care.

MATERIAL AND METHODS

Patient population

Patients were diagnosed with advanced (stage III and IV) squamous cell carcinoma of the head and neck region and treated with concurrent chemoradiotherapy (CRT) at The Netherlands Cancer Institute from 2006 to 2008. Each patient received 100 mg/m^2 Cisplatin as a 40 min IV infusion on days 1, 22, and 43. Intensity-modulated radiotherapy (IMRT) of 70 Gy in 35 fractions was administered over seven weeks starting concurrently with chemotherapy[22]. In an attempt to prevent swallowing sequels following treatment, all patients had participated in a clinical trial on preventive and continued post-treatment swallowing rehabilitation[23]. Informed consent was obtained from all individual participants included in the study.

Twenty-five patients had undergone objective and subjective swallowing assessments until 1-year post-treatment and were included in the present study. Patients were analysed at baseline (approximately 2 weeks before treatment onset), at 10-weeks post-treatment, and at 1-year post-treatment. An overview of the analysed patients is demonstrated in Figure 1. Regarding temporal analysis, some VFS studies were excluded due to poor quality or missing data, resulting in a dataset of 22, 25, and 24 swallow studies, for analysis at baseline, at 10-weeks post-treatment, and at 1-year post-treatment, respectively. Regarding kinematic analysis, in eight patients poor VFS image quality or obstructed view of target structures precluded precise evaluation of hyoid displacement. At 1-year post-treatment, three more swallow studies had to be excluded due to poor image quality (n=1), obstructed view of vertebra C2-C4 (n=1), or missing data (n=1). This resulted in 17 patients for analysis at baseline and at 10-weeks post-treatment, and 14 patients for analysis at 1-year post-treatment.

Objective swallowing assessment

Patients had undergone a standardized, lateral VFS protocol, imaging the lips, oral cavity, cervical spine, and proximal cervical esophagus. An experienced speech language pathologist, clinical investigator, and a laboratory assistant performed all studies. Patients were seated upright and were asked to swallow different consistencies of varying amounts (3 cc and 5 cc thin liquid; 3 cc paste; and solid Omnipaque coated cake), delivered orally by a spoon or cup. Patients were instructed to sip and wait for a verbal cue from the clinical investigator before swallowing. A coin of ten eurocents was fixed on the chin as reference distance to correct for magnification.

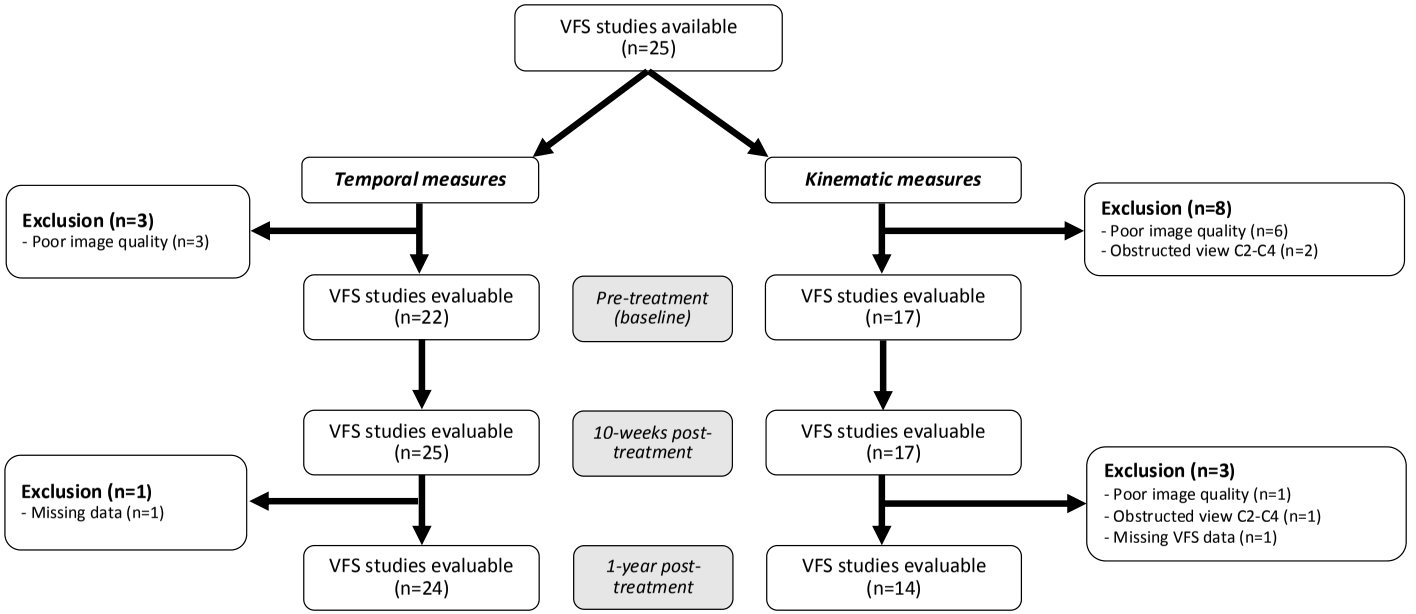


Figure 1. Consort flowchart of the available patient data

All VFS studies were recorded at 25 frames per second and matched (together with an external microphone) with an external computer via a framegrabber (Terratec). Subsequently, the studies were saved for movie editing by Magix (free download at http://magix-movie-edit-pro.en.softonic.com), and digitally captured with VirtualDub. Each VFS study was then reviewed in real-time, slow motion, and frame-by-frame, and rated on clinical, temporal, and kinematic measures independently by the two experienced researchers.

Clinical measures

According to the protocol, Penetration Aspiration Scale (PAS) scores and more than normal post-swallow residue scores (located at the tongue base, vallecula, or pyriform sinuses) were independently assessed. The PAS is a validated 8-point scale (score 1: material does not enter the airway, to score 8: material enters the airway, passes below the vocal folds, and no effort is made to eject) with the lowest score referring to normal swallowing functioning, whereas higher scores refer to more severe swallowing disability[24]. Aspiration status was determined using a binary reduction of the PAS, with any single swallow with a score of ≥3 resulting in classification of the patient as an aspirator[9]. The overall 'presence of residue' score was also assessed, ranging from 0 (no residue) to 3 (residue above and below the hyoid bone, with minimal residue in only the piriform sinus judged as normal)[25,26].

Temporal measures

Hyoid elevation onset and duration was reported in seconds, comparable to the methods described by Kendall et al.[27]. In short, B1 represents the first movement of the head of the food bolus from a stable or 'hold' position that passes the posterior nasal spine and results in all or part of the bolus entering the oropharynx. H1 represents the first superior-anterior movement of the hyoid bone that results in a swallow. H2 symbolizes the point at which the hyoid bone reaches its maximum displacement during the swallow. The onset of hyoid elevation relative to the onset of pharyngeal transit ('hyoid elevation start time') was calculated as H1 minus B1. The time required for the hyoid bone to reach maximal elevation ('maximum hyoid elevation time') was calculated as H2 minus H1.

Kinematic measures

Two picture frames (stills) of each VFS swallow study were generated in order to assess spatial measures of hyoid movement; one showing the resting position of the hyoid bone, and the other showing maximum displacement. The resting position was marked as the moment just before the bolus was propelled from the oral cavity towards the pharynx. The point of maximum displacement was defined as the point just before the hyoid bone began its descent to a resting position[28,29].

Both stills were individually opened with the program ImageJ 1.32 for structural movement tracing (http://imagej.nih.gov/ij/). The following structures were traced in each frame: the anterior-inferior corner of vertebra C4 (for the remainder of this article: 'C4'), the anterior-inferior corner of vertebra C2 ('C2'), the anterior-superior corner of the hyoid bone, and the length of the scaling reference coin (known length 19,75 mm), as used for calibration. A coordinate system was defined with the vertical y-axis running from C2 through C4, and the horizontal x-axis running perpendicular to this line through C4. All picture frames were rotated to a true vertical/90° angle. The angle of the line between C2 and C4 was used to rotate the image to the 90° angle. ImageJ provided calculated values of each point (x,y), and the following formulas were used to measure anterior and superior hyoid displacement: Anterior displacement: (x2 – x1) – (C4x2 – C4x1), and superior displacement: (y2 – y1) – (C4y2 – C4y1), where x1 and y1 are the starting (rest frame) coordinates of the hyoid bone, x2 and y2 are the compared image coordinates (maximum excursion coordinates), C4x1 and C4y1 are the coordinates of the anchor point in the rest frame, and C4x2 and C4y2 are the coordinates of the anchor point at maximum excursion[28,29]. Subsequently, hyoid displacement was transformed into anatomically normalized units, i.e. in percentage of the distance between vertebra C2 and C4[10]. This process was subsequently completed for each different consistency and amount of each single VFS swallow study on all three different time points. As an example, two lateral VFS images with the marked points are shown in Figure 2.

Subjective swallowing assessment

Patients' perceived swallowing function was assessed at the various assessment points with questions from a larger study-specific questionnaire, addressing specific HNC issues such as pain, oral dysfunction, speech problems, swallowing dysfunction, and interrupted social interaction. The 17 study-specific questions regarding diet, swallowing, and chewing are shown in Appendix I [30]. Especially the questions regarding swallowing function (questions 11–14) were taken into consideration. Each item was scored on a 3-point scale, and total subjective impairment scores were calculated using the sum score of these questions (maximum score: 11).

Reliability analysis

All VFS clinical and temporal assessments were done in consensus by the first author and an experienced speech language pathologist (SLP). The VFS kinematic measures were calculated by another trained researcher, with 15% of all measurements randomly repeated, to measure intrarater reliability, and 15% within one month randomly reviewed by the first author, as a measure of interrater reliability. Test-retest reliability was measured with two-way random intraclass coefficients (ICC(2,1)) for consistency. For intrarater reliability, anterior and superior displacement showed an ICC(2,1) 0.76 and 0.80, respectively. For interrater reliability, these

coefficients were 0.79 and 0.83 for anterior and superior displacement, respectively, showing acceptable agreement.

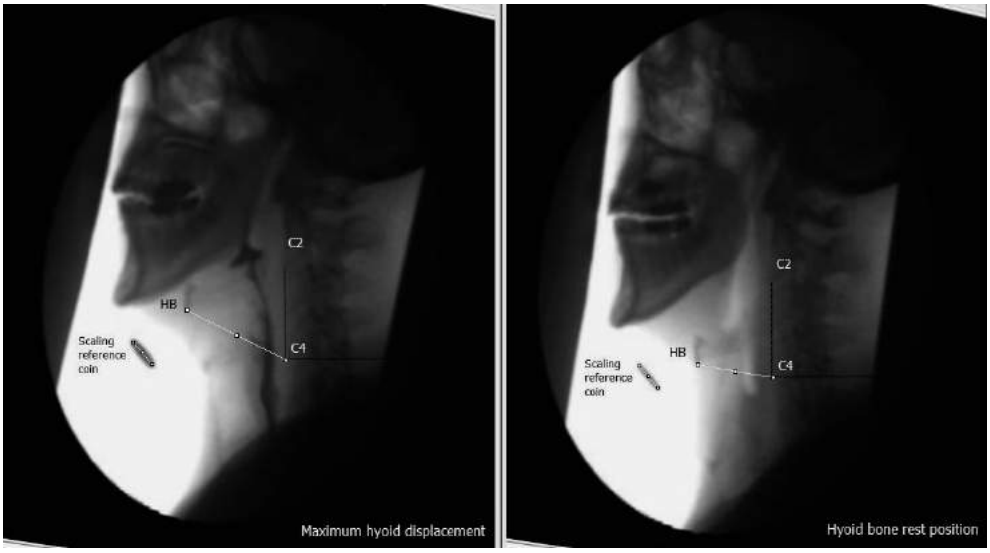


Figure 2. Two lateral VFS images showing (1) the resting position of the hyoid bone (right), and (2) the hyoid bone during maximum displacement (left). The relevant points are marked during frame-by-frame tracing. With the known length (19,75 mm) of the scaling reference coin, as used for calibration, the C2-C4 distance was measured as 51.76 mm. Hyoid displacement was then calculated absolute (in mm) and in anatomically normalized units (% of C2–C4 distance). Anterior displacement was measured here as (x2 – x1) – (C4x2 – C4x1) = (182,06 – 155,76) – (230,99 – 213,85) = 9,16 mm (17,7% of C2-C4 distance). Similarly, superior displacement was measured as (206,14 – 195,15) – (176,88 – 186,62) = 20,77 (40,1% of C2-C4 distance).

Statistical analysis

All measured temporal and kinematic data per assessment point were averaged across patients according to bolus size and direction of displacement. Data were described as means with standard deviations. Wilcoxon signed rank test was used to test statistical differences for various hyoid displacement parameters between baseline and 10-weeks post-treatment, and between baseline and 1-year post-treatment. Secondly, correlations with subjective swallowing impairment (study-specific questions) were calculated with the Spearman's rank test. All data were collected and analyzed in SPSS (Chicago, Illinois; version 23.0), and a significance level of $p < 0.05$ was used.

Table 1. Clinical patient and tumor characteristics of the initially included patients (n=25), the patients analysed at baseline and 10-weeks post-treatment (n=17), and the patients analysed at 1-year post-treatment (n=14).

	25 patients n (%)	17 patients n (%)	14 patients n (%)
Gender			
Male	19 (76)	14 (82)	12 (86)
Female	6 (24)	3 (18)	2 (14)
Mean age, y (range)	59 (39–77)	58 (39–77)	58 (39–77)
Tumor site			
Nasopharynx	3 (40)	3 (18)	2 (14)
Oral/ Oropharynx	12 (48)	8 (47)	7 (50)
Hypopharynx	10 (40)	6 (35)	5 (36)
Tumor stage			
Stage III	8 (32)	7 (41)	6 (43)
Stage IV	17 (68)	10 (59)	8 (57)
T stage			
T1	4 (16)	4 (24)	2 (14)
T2	7 (28)	4 (24)	4 (29)
T3	10 (40)	6 (35)	5 (36)
T4	4 (16)	3 (18)	3 (21)
N stage			
N0	3 (12)	2 (12)	2 (14)
N1	7 (28)	6 (35)	5 (36)
N2	11 (41)	7 (41)	5 (36)
N3	4 (16)	2 (12)	2 (14)

RESULTS

Details on the clinical characteristics of the study population are presented in Table 1. Pretreatment, 2/17 patients (12%) were diagnosed with dysphagia according to the binary classification from the PAS scores obtained from VFS assessment. At 10-weeks and 1-year post-treatment these numbers were 3/17 (18%) and 2/14 (14%), respectively. More than normal residue above and below the hyoid bone was present in 16/17 (94%) patients at baseline, in 8/17 (47%) patients at 10-weeks post-treatment, and in 13/14 (93%) patients at 1-year post-treatment. Regarding patients' perceived swallowing impairment, at baseline 6/17 patients (35%) reported swallowing issues, based ≥2 positive answers on the study-specific questions regarding swallowing function. At 10-weeks and at 1-year post-treatment these numbers were 53% and 29%, respectively.

Temporal measures

Both hyoid elevation start time (the onset of hyoid elevation relative to the onset of pharyngeal transit; H1−B1) and maximum hyoid elevation time (H2–B1) were calculated, separated per consistency and assessment point. At baseline, 10-weeks, and at 1-year post-treatment, 22, 25, and 24 patients, respectively, were evaluated. As can be seen in Table 2, hyoid elevation start time ranged from -.14 ± .28 seconds for a 5 cc thin liquid swallow to .16 ± .43 seconds for a solid swallow. Maximum hyoid elevation time varied from .47 ± .21 seconds to .96 ± .94 seconds for these consistencies. The onset of hyoid elevation relative to the onset of the swallow, and the time required for the hyoid bone to reach maximal elevation, seemed to increase with increases in bolus size or consistency, although these changes were statistically not significant (Wilcoxon signed rank test; p >.05 for the various assessment points). There were also no significant changes over time for hyoid elevation start time and maximum hyoid elevation time (p >.05 for all consistencies).

Table 2. Hyoid bone elevation onset and duration in seconds ± SD

	Bolus Size				
	Thin Liquid		Thick liquid	Solid	
	3cc	5cc	3 cc	cake	Valid N
Baseline					
H1–B1	.02 ± .37	-.09 ± .18	.03 ± .50	.16 ± .43	22
H2–H1	.67 ± .40	.51 ± .14	.69 ± .52	.96 ± .94	22
10-weeks					
H1–B1	-.08 ± .21	-.14 ± .28	.13 ± .58	.10 ± .33	25
H2–H1	.58 ± .25	.47 ± .21	.81 ± .60	.92 ± .92	25
1-year					
H1–B1	-.07 ± .20	-.09 ± .24	-.03 ± .35	.08 ± .34	24
H2–H1	.64 ± .17	.74 ± .40	.79 ± .39	.87 ± .62	24

Abbreviations: B1: the first movement of the head of the food bolus from a stable or 'hold' position that passes the posterior nasal spine and results in all or part of the bolus entering the oropharynx; H1: the first superior-anterior movement of the hyoid bone that results in a swallow; H2: the point at which the hyoid bone reaches its maximum displacement during the swallow; H1–B1: hyoid elevation onset relative to the onset of pharyngeal transit (= hyoid elevation start time); H2–B1: hyoid elevation duration (= maximum hyoid elevation time); SD = standard deviation.

Kinematic measures

Table 3A and 3B show the descriptive statistics for hyoid displacement (absolute in mm [A] and in 'anatomically normalized units'[4], i.e. percentage of C2-C4 distance [B]). As can be seen, mean maximum anterior and superior displacement ranged from 9.4 mm (23% of C2-4 distance) to 12.6 mm (27%), and from 18.9 mm (41%) to 24.9 mm (54%), respectively, depending on bolus volume and consistency. No significant changes over time were noted for all parameters, except for a swallow of 5 cc thin liquid, in which displacement was

significantly increased in the superior direction at 10-weeks post-treatment compared to baseline (Wilcoxon signed rank test; as % C2–C4: p =.039). This effect was predominantly seen in patients with a tumor in the oropharynx (change 5.9 mm; 12.3%) and hypopharynx (change 5.7 mm; 13.3%) and was absent in patients with a tumor in the nasopharynx (change -1.2 mm;-2.7%).

Table 3A. Hyoid bone displacement (absolute in mm)

	Bolus Size Thin Liquid		Thick liquid	Solid	
	3cc	5cc	3 cc	cake	Valid N
Baseline					
Anterior mean ± SD	10.7 ± 3.4	12.0 ± 4.3	12.2 ± 4.3	11.6 ± 3.8	17
Superior mean ± SD	18.9 ± 8.0	20.3 ± 5.9	20.5 ± 8.4	19.3 ± 8.6	17
Follow-up 10-weeks					
Anterior mean ± SD	10.5 ± 4.3	11.4 ± 5.3	11.2 ± 5.0	12.6 ± 4.7	17
Superior mean ± SD	22.6 ± 8.3	24.9 ± 9.2	24.7 ± 9.1	23.0 ± 7.5	17
Follow-up 1-year					
Anterior mean ± SD	9.4 ± 4.3	9.9 ± 4.1	10.7 ± 4.4	12.5 ± 5.0	14
Superior mean ± SD	19.9 ± 7.6	23.3 ± 7.4	19.9 ± 7.7	21.9 ± 6.9	14

Abbreviations: SD = standard deviation; mm = millimetres; cc = cubic centimetres

Table 3B. Hyoid bone displacement (% of C2-C4 distance)

	Bolus Size Thin Liquid		Thick liquid	Solid	
	3cc	5cc	3cc	cake	Valid N
Baseline					
Anterior mean ± SD	23 ± 7	26 ± 9	26 ± 8	25 ± 8	17
Superior mean ± SD	41 ± 17	44 ± 12	45 ± 17	42 ± 18	17
Follow-up 10-weeks					
Anterior mean ± SD	23 ± 9	25 ± 11	25 ± 10	27 ± 10	17
Superior mean ± SD	49 ± 18	54 ± 19	53 ± 21	50 ± 16	17
Follow-up 1-year					
Anterior mean ± SD	20 ± 9	22 ± 9	23 ± 10	27 ± 10	14
Superior mean ± SD	43 ± 17	51 ± 16	43 ± 17	48 ± 15	14

Abbreviations: SD = standard deviation; mm = millimetres; cc = cubic centimetres

Correlation with swallowing impairment

The number of patients showing penetration-aspiration on VFS assessments was low in the current study cohort (maximum 3 patients per assessment point), limiting the statistical power to investigate correlations between penetration-aspiration and hyoid displacement.

The patients showing penetration or aspiration did not show reduced hyoid displacement compared to the group mean. No correlations between delayed or reduced hyoid excursion and residue scores could be demonstrated. Regarding investigation of correlations with patient-reported outcomes based on (sub) total scores of the study-specific questions regarding swallowing function (questions 11–14; Appendix I), superior hyoid displacement significantly correlated with subjective swallowing impairment for various consistencies and assessment points. Especially superior displacement at baseline correlated well with swallowing function at 1-year post-treatment (see Table 4 for the *p*-values for a 5 cc thin and 3 cc thick liquid swallow). In Figure 3 this relationship for a 5 cc thin liquid swallow is illustrated in a scatter plot.

Table 4. Overview of Spearman's rank correlations between superior hyoid displacement at baseline and subjective swallowing impairment at 1-year post-treatment for a thin (5 cc) and thick (3 cc) liquid swallow

Superior displacement	Problems swallowing liquids	Problems swallowing soft foods	Problems swallowing solid foods	Swallowing more often	Total subjective score
Thin liquid swallow	.41	.41	.73**	.59*	.72**
Thick liquid swallow	.41	.41	.68**	.55*	.67**

Note: * means p <.05; ** means p <.01

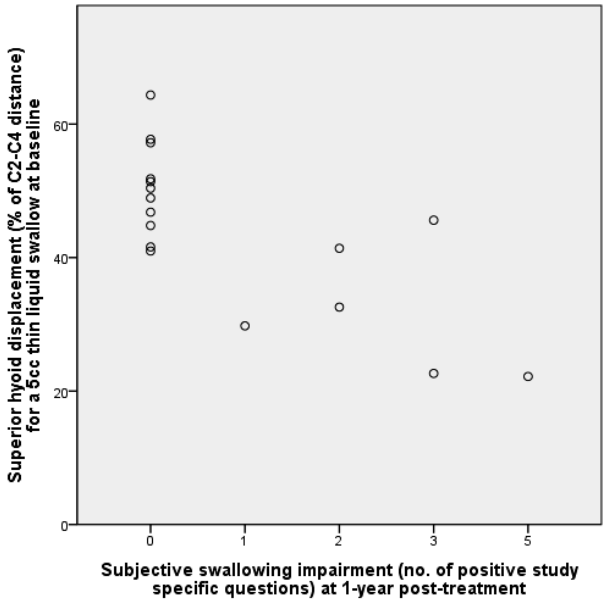


Figure 3. Scatter plot of the relationship between superior hyoid bone displacement for a 5 cc thin liquid swallow at baseline (measured as % of the C2-C4 distance) and subjective swallowing impairment based on the study-specific questionnaire at 1-year post-treatment.

DISCUSSION

The primary aim of the present study was to report on temporal and kinematic hyoid displacement parameters in HNC patients treated with chemoradiotherapy, with the secondary aim to investigate correlations with objective and subjective swallowing impairment. Regarding the first aim, the onset of hyoid elevation relative to the onset of the swallow did not change significantly over time or with increases in bolus size or consistency, nor did the time required for the hyoid bone to reach maximal elevation. Maximum hyoid displacement – scaled in cervical/anatomical units (% C2–C4 distance) – ranged from 23% to 27% in the anterior direction, and from 41% to 54% in the superior direction. These results are somewhat lower in comparison with 'normative' data from the literature concerning patients referred for dysphagia assessment, with results ranging from 36% to 38% anteriorly, and from 51% to 57% superiorly[4,9]. Although the predominant aetiology of dysphagia in those studies was neurogenic, whereby patients with a history of HNC were excluded, this possibly implicates that hyoid displacement in the current patient cohort was already limited at baseline, and might explain the lack of significant changes over time. Obviously, it is also quite difficult to demonstrated statistical differences in this small HNC sample. Regarding the second aim, we have not seen strong correlations between hyoid displacement en swallowing impairment, except for a significant association between reduced superior hyoid movement and subjective swallowing impairment based on four study-specific questions regarding swallowing function, which, however, was quite small.

Interestingly, in the current study cohort hyoid displacement in patients with a tumor at the oropharynx and hypopharynx had slightly increased in the superior direction for a 5 cc thin liquid swallow at 10-weeks post-treatment compared to baseline. Though these differences were significant only for the 5cc thin bolus, the higher values may reflect extra effort being exerted during these swallows. And if so, this could indicate that other issues, e.g. poor sensation, non-hyoid mechanical impairment, are present and responsible for the extra effort. For future studies it might be of interest to also look at overall transit times during swallowing, which can be prolonged with increased effort. Since we did not see this effect in the patients with a tumor located at the nasopharynx, it is also possible that the primary tumor, or pain due to the tumor, impaired the mobility of the hyoid bone at baseline in these patients, and that hyoid movement was 'restored' again after complete remission at 10-weeks post-treatment. However, there are much more parameters such as tumor volume, radiation dose effects and/or exercise therapy which might have played a role in this. In 2011 van der Kruis and colleagues revealed in their review significant improved hyoid excursion in several studies following treatment with swallowing manoeuvres and/or bolus modification[31]. A similar effect might be present in the current patient population: the participation in a preventive and continued post-treatment swallowing rehabilitation program might explain

these favourable 10-weeks hyoid elevation outcomes[32]. This could maybe also explain the limited number of patients who had aspiration, and the lower rate of more than normal residue scores at 10-weeks post-treatment. Finally, patients who are cautious or fearful about swallowing safety, that is, who perceive greater difficulty, may elevate the hyoid early, as in the 'rest' or 'hold' position. If so, their hyoid displacement may be reduced, as compared to healthy subjects, or as compared to less-fearful patients. Consequently, 'possible' hyoid displacement, or potential for hyoid displacement, may be difficult to determine in these cases.

Unfortunately, due to methodological issues (only 4 patients showing aspiration on VFS assessments), the hypothesis that patients with penetration or aspiration would show slower durations of hyoid movement and/or reductions in kinematic measures could not be statistically analysed. The significant association found between reduced superior hyoid movement and subjective swallowing impairment based on four study-specific questions regarding swallowing function was quite small. Possibly, other mechanical variables may have been impaired and accounted for patients' reported dysphagia. It is not exactly clear if hyoid elevation or anterior excursion is more important. Steele and colleagues (2011) reported significantly higher occurrence of penetration-aspiration in swallows where anterior movement was restricted[4]. However, Molfenter and colleagues (2014) found a trend towards lower maximum superior hyoid position and swallowing impairment[9]. In the current patient cohort correlations between residue ratings and hyoid displacement were also lacking. Residue, however, might be explained by other, non-hyoid, mechanical variables. Further research with larger sample sizes is necessary to confirm these correlation.

Although the raters in the current study used well-defined guidelines[28,29] and – following several training sessions – maximum consensus was reached about the definitions of the measured spatial variables[19], intra- and interrater reliability (with an ICC(2,1) ranging from 0.76 to 0.83) was acceptable, and did not reach the level of 'excellent' reliability. Besides, all measurements and analyses were very time consuming; not only because of the pre-experimental training sessions, but also due to inefficiency/lack of computerization in the current methods used. Software for automatic measurement and analysis extend of hyoid movement in the x-y coordinate system over time was unfortunately not available in our Institute. Consequently, all swallow studies were individually analysed, and the provided x and y coordinates by ImageJ were manually entered to Excel/SPSS to calculate the maximum anterior and superior displacement values. For future perspectives it is therefore recommended to use automatic systems for analysis of hyoid displacement.

CONCLUSION

In this study temporal and kinematic measures related to hyoid displacement in advanced HNC patients are reported up to 1 year after treatment with concurrent chemoradiotherapy. Compared to normative data, hyoid elevation and anterior excursion was already limited at baseline. Since hyoid displacement is subject to variability from a number of sources, this parameter seems not very valuable for clinical use in HNC patients.

ACKNOWLEDGEMENTS

The department of Head and Neck Oncology and Surgery receives an unrestricted research grant of Atos Medical AB, Sweden.

Appendix I. Selection of the translated Dutch study specific questionnaire.

A. Diet, swallowing and chewing complaints over the last week (17 questions)

1. Do you still have your own teeth?
   1 = yes 2 = yes, partially
   3 = no, I have a prosthesis 4 = no, and I don't wear a prosthesis
2. How often do you clean your teeth?
   1 = a couple of times a day 2 = once a day
   3 = less than once a day 4 = not at all
3. How do you experience your mouth opening?
   1 = normal 2 = a little bit limited
   3 = very limited 4 = I cannot open my mouth
4. What is your diet like?
   1 = I eat solid food 2 = I only eat soft (minced) food
   3 = I only eat liquid food 4 = I only have tube feeding
   5 = combination soft diet and tube feeding
5. Do you experience problems with eating, because of a limited mouth opening?
   1 = not at all 2 = a little
   3 = rather 4 = quite a lot
6. Do you experience problems with speech, because of a limited mouth opening?
   1 = not at all 2 = a little
   3 = rather 4 = quite a lot
7. Do you have problems with chewing your food?
   1 = not at all 2 = a little
   3 = rather 4 = quite a lot
8. Do you have problems with moving solid food around in your mouth?
   1 = not at all 2 = a little
   3 = rather 4 = quite bad
9. Do you have problems with moving soft/minced food around in your mouth?
   1 = not at all 2 = a little
   3 = rather 4 = quite a lot
10. Do you have problems with moving liquid food around in your mouth?
    1 = not at all 2 = a little
    3 = rather 4 = quite a lot
11. **Do you have problems with swallowing solid food?**
    1 = not at all 2 = a little
    3 = rather 4 = quite a lot

12. Do you have problems with swallowing soft/minced food?

1 = not at all **2 = a little**

3 = rather **4 = quite a lot**

13. Do you have problems with swallowing liquid food?

1 = not at all **2 = a little**

3 = rather **4 = quite a lot**

14. Do you have to swallow repeatedly to get rid of food?

1 = yes **2 = no**

3 = sometimes

15. Do you have to drink during a meal to ease food down?

1 = yes 2 = no

3 = sometimes

16. Do you have a normal amount of saliva (spit)?

1 = much less 2 = a bit less

3 = the same 4 = a bit more

5 = much more

17. Can you keep your saliva in the mouth without leakage?

1 = not at all 2 = a bit

3 = fairly well 4 = quite easily

REFERENCES

1. Perlman AL, VanDaele DJ, Otterbacher MS. Quantitative assessment of hyoid bone displacement from video images during swallowing. J Speech Hear Res. 1995;38:579-85.
2. Bingjie L, Tong Z, Xinting S, Jianmin X, Guijun J. Quantitative videofluoroscopic analysis of penetration-aspiration in post-stroke patients. Neurol India. 2010;58:42-7.
3. Wang TG, Chang YC, Chen WS, Lin PH, Hsiao TY. Reduction in hyoid bone forward movement in irradiated nasopharyngeal carcinoma patients with dysphagia. Arch Phys Med Rehabil. 2010;91:926-31.
4. Steele CM, Bailey GL, Chau T, Molfenter SM, Oshalla M, Waito AA, et al. The relationship between hyoid and laryngeal displacement and swallowing impairment. Clin Otolaryngol. 2011;36:30-6.
5. Pearson WG, Jr., Hindson DF, Langmore SE, Zumwalt AC. Evaluating swallowing muscles essential for hyolaryngeal elevation by using muscle functional magnetic resonance imaging. Int J Radiat Oncol Biol Phys. 2013;85:735-40.
6. Zu Y, Yang Z, Perlman AL. Hyoid displacement in post-treatment cancer patients: preliminary findings. J Speech Lang Hear Res. 2011;54:813-20.
7. Hutcheson KA, Lewin JS, Barringer DA, Lisec A, Gunn GB, Moore MW, et al. Late dysphagia after radiotherapy-based treatment of head and neck cancer. Cancer. 2012;118:5793-9.
8. Kim Y, McCullough GH. Maximal hyoid excursion in poststroke patients. Dysphagia. 2010;25:20-5.
9. Molfenter SM, Steele CM. Kinematic and temporal factors associated with penetration-aspiration in swallowing liquids. Dysphagia. 2014;29:269-76.
10. Steele CM, Cichero JA. Physiological factors related to aspiration risk: a systematic review. Dysphagia. 2014;29:295-304.
11. Logemann JA, Pauloski BR, Rademaker AW, Colangelo LA, Kahrilas PJ, Smith CH. Temporal and biomechanical characteristics of oropharyngeal swallow in younger and older men. J Speech Lang Hear Res. 2000;43:1264-74.
12. Kendall KA, Leonard RJ. Hyoid movement during swallowing in older patients with dysphagia. Arch Otolaryngol Head Neck Surg. 2001;127:1224-9.
13. Logemann JA, Pauloski BR, Rademaker AW, Kahrilas PJ. Oropharyngeal swallow in younger and older women: videofluoroscopic analysis. J Speech Lang Hear Res. 2002;45:434-45.
14. Kim Y, McCullough GH. Maximum hyoid displacement in normal swallowing. Dysphagia. 2008;23:274-9.
15. Paik NJ, Kim SJ, Lee HJ, Jeon JY, Lim JY, Han TR. Movement of the hyoid bone and the epiglottis during swallowing in patients with dysphagia from different etiologies. J Electromyogr Kinesiol. 2008;18:329-35.
16. Dodds WJ, Man KM, Cook IJ, Kahrilas PJ, Stewart ET, Kern MK. Influence of bolus volume on swallow-induced hyoid movement in normal subjects. AJR Am J Roentgenol. 1988;150:1307-9.
17. Nagy A, Molfenter SM, Peladeau-Pigeon M, Stokely S, Steele CM. The effect of bolus volume on hyoid kinematics in healthy swallowing. Biomed Res Int. 2014;2014:738971.
18. Sia I, Carvajal P, Carnaby-Mann GD, Crary MA. Measurement of hyoid and laryngeal displacement in video fluoroscopic swallowing studies: variability, reliability, and measurement error. Dysphagia. 2012;27:192-7.
19. Baijens L, Barikroo A, Pilz W. Intrarater and interrater reliability for measurements in videofluoroscopy of swallowing. Eur J Radiol. 2013;82:1683-95.
20. Molfenter SM, Steele CM. Physiological variability in the deglutition literature: hyoid and laryngeal kinematics. Dysphagia. 2011;26:67-74.
21. Lal PT, A; Verma, A; Maria Das, KP; Baijal, SS; Bajpai, R; Kumar, P; Srivastava, A; Kumar, S. Role

of videofluorography in assessing functional abnormalities in patients of head and neck cancer treated with chemoradiotherapy APJ of Clinical Oncology. 2009;5:264-9.

22. van der Molen L, Heemsbergen WD, de Jong R, van Rossum MA, Smeele LE, Rasch CR, et al. Dysphagia and trismus after concomitant chemo-Intensity-Modulated Radiation Therapy (chemo-IMRT) in advanced head and neck cancer; dose-effect relationships for swallowing and mastication structures. Radiother Oncol. 2013;106:364-9.

23. van der Molen L, van Rossum MA, Burkhead LM, Smeele LE, Rasch CR, Hilgers FJ. A randomized preventive rehabilitation trial in advanced head and neck cancer patients treated with chemoradiotherapy: feasibility, compliance, and short-term effects. Dysphagia. 2011;26:155-70.

24. Rosenbek JC, Robbins JA, Roecker EB, Coyle JL, Wood JL. A penetration-aspiration scale. Dysphagia. 1996;11:93-8.

25. Logemann JA. Evaluation and treatment of swallowing disorders: Pro-ed (2nd edition). Texas, Austin; 1998.

26. Pauloski BR, Rademaker AW, Logemann JA, Stein D, Beery Q, Newman L, et al. Pretreatment swallowing function in patients with head and neck cancer. Head Neck. 2000;22:474-82.

27. Kendall KA, McKenzie S, Leonard RJ, Goncalves MI, Walker A. Timing of events in normal swallowing: a videofluoroscopic study. Dysphagia. 2000;15:74-83.

28. Leonard RJ, Kendall KA, McKenzie S, Goncalves MI, Walker A. Structural displacements in normal swallowing: a videofluoroscopic study. Dysphagia. 2000;15:146-52.

29. Leonard RJ KK. Dysphagia assessment and treatment planning: a team approach. In: Group SDSP, editor.1997.

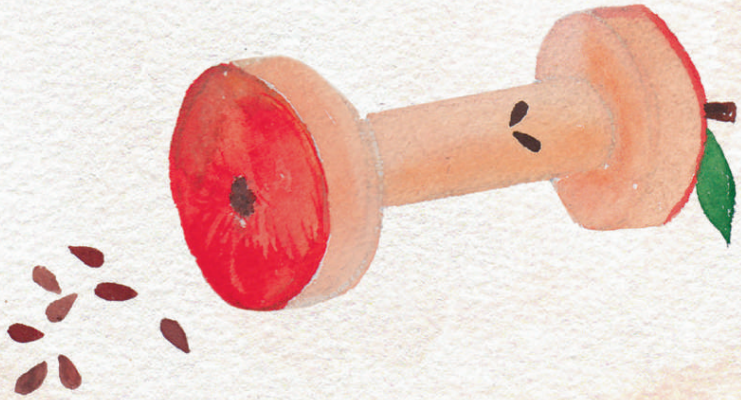
30. van der Molen L, van Rossum MA, Ackerstaff AH, Smeele LE, Rasch CR, Hilgers FJ. Pretreatment organ function in patients with advanced head and neck cancer: clinical outcome measures and patients' views. BMC Ear Nose Throat Disord. 2009;9:10.

31. van der Kruis JG, Baijens LW, Speyer R, Zwijnenberg I. Biomechanical analysis of hyoid bone displacement in videofluoroscopy: a systematic review of intervention effects. Dysphagia. 2011;26:171-82.

32. Kraaijenga SA, van der Molen L, Jacobi I, Hamming-Vrieze O, Hilgers FJ, van den Brekel MW. Prospective clinical study on long-term swallowing function and voice quality in advanced head and neck cancer patients treated with concurrent chemoradiotherapy and preventive swallowing exercises. Eur Arch Otorhinolaryngol. 2015;272:3521-31

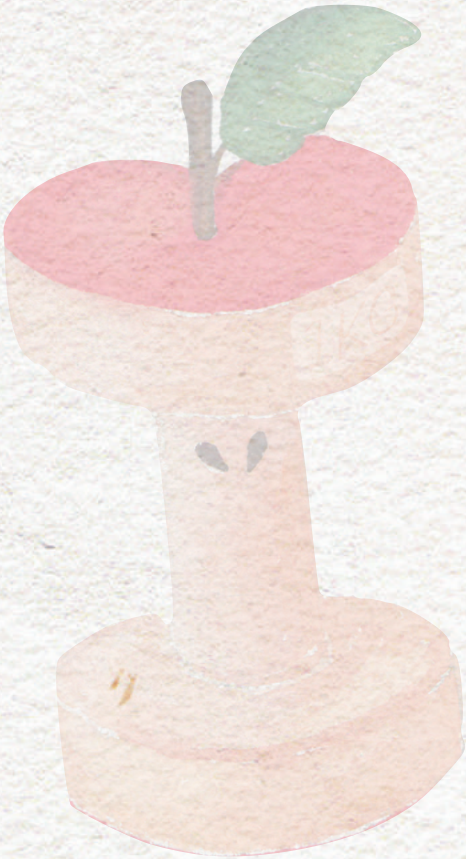
PART 2

PROSPECTIVE STUDIES



CHAPTER 7

Effects of strengthening exercises on swallowing musculature and function in senior healthy subjects: a prospective effectiveness and feasibility study



S.A.C. Kraaijenga
L. van der Molen
M.M. Stuiver
H.J. Teertstra
F.J.M. Hilgers
M.W.M. van den Brekel

Dysphagia. 2015; 30: 392-403.

ABSTRACT

Introduction: Head and neck cancer (HNC) patients may develop dysphagia due to muscle atrophy and fibrosis following chemoradiotherapy. Strengthening of the swallowing muscles through therapeutic exercise is potentially effective for improving swallowing function. We hypothesize that a customized Swallow Exercise Aid (SEA), developed for isometric and isokinetic strengthening exercises (against resistance), can help to functionally strengthen the suprahyoid musculature, which in turn can improve swallowing function.

Methods: An effectiveness/feasibility study was carried out with 10 senior healthy volunteers, who performed exercises 3 times per day for 6 weeks. Exercises included chin tuck against resistance (CTAR), jaw opening against resistance (JOAR), and effortful swallow exercises with the SEA. Multidimensional assessment consisted of measurements of maximum chin tuck and jaw opening strength, maximum tongue strength/endurance, suprahyoid muscle volume, hyoid bone displacement, swallowing transport times, occurrence of laryngeal penetration/aspiration and/or contrast residue, maximum mouth opening, feasibility/compliance (questionnaires), and subjective swallowing complaints (SWAL-QOL).

Results: After 6-weeks exercise, mean chin tuck strength, jaw opening strength, anterior tongue strength, suprahyoid muscle volume, and maximum mouth opening significantly increased (p <.05). Feasibility and compliance (median 86%, range 48–100%) of the SEA exercises were good.

Conclusion: This prospective effectiveness/feasibility study on the effects of CTAR/JOAR isometric and isokinetic strengthening exercises on swallowing musculature and function shows that senior healthy subjects are able to significantly increase swallowing muscle strength and volume after a 6-week training period. These positive results warrant further investigation of effectiveness and feasibility of these SEA exercises in HNC patients with dysphagia.

KEY WORDS

Head and Neck Cancer – Deglutition – Deglutition Disorders – Dysphagia – Strength Exercises – Isometric – Isokinetic – Chin Tuck – Jaw Opening

INTRODUCTION

Swallowing in general, and the various phases of this process (oral, pharyngeal, and esophageal), requires a complex interaction between the muscles in the tongue, floor of mouth, pharynx, and larynx[1-3]. This intricate physiologic course of muscle events and interactions is at risk in patients treated for head and neck cancer (HNC), and swallowing impairment/dysphagia is not uncommon in these patients. It can be caused by the tumor extension itself, but maybe even more so, by tissue reactions resulting from surgical resections or (organ preserving) chemoradiotherapy (CRT), e.g. radiation fibrosis or changes in innervation of the swallowing musculature. Additionally the occurrence of acute mucositis, fibrosis, xerostomia, pain and trismus often cause severe swallowing problems, which, in turn, limit oral intake and may require nasogastric tube feeding[4-7].

Tongue strength also plays a role in the swallowing physiology, particularly in the oral phase of the swallow[8-10]. In patients treated with primary CRT, lingual strength is reduced, which further limits oral and pharyngeal structural movement during the swallow[11]. As a result, the swallowing muscles are no longer actively used and might eventually atrophy[12], affecting both oral and pharyngeal phase swallowing function, especially in the long-term.

Recently, more attention has been drawn to prevention of non-use atrophy in patients with advanced HNC undergoing CRT. In compliant patients, implementation of preventive (swallowing) exercises has demonstrated to improve post-treatment swallowing function and quality of life[13-17]. These exercises include range of motion or resistance exercises (with or without medical devices such as the TheraBite® device), the (super-) supraglottic swallow[1, 18, 19], the effortful swallow[1, 20, 21], the Mendelsohn maneuver[19, 22], the Masako (tongue-holding) maneuver[21], and the Shaker (head-raising) exercise[23]. Especially the latter has proven to be effective in strengthening the suprahyoid musculature and reducing swallowing problems[24, 25], but with the major drawback that the exercise should be carried out in a supine position. This appears to be quite strenuous, and the compliance with this exercise is less due to sternocleidomastoid muscle discomfort, especially in elderly, frail patients[26, 27].

As an alternative therapeutic intervention for patients who find the Shaker exercise in the supine position physically challenging, Yoon et al. investigated another exercise to activate the suprahyoid musculature: the chin tuck against resistance (CTAR)[27]. This exercise involves tucking the chin as hard as possible on a rubber ball, which is placed between the chin and chest. The authors state that it can be carried out for both isometric and isokinetic tasks, and it would allow elderly/frail patients to perform the exercises based on their current strength level, without having to be strong enough to perform a head lift from the supine position. As such, it could qualify as an alternative to the Shaker exercise and potentially improve exercise compliance[27].

The TheraBite® device, originally developed for passive range of motion exercises in irradiated patients with trismus and/or patients with mandibular hypomobility[28, 29], can also be used in HNC patients to aid swallowing exercises during CRT treatment. With this device it appears to be possible to improve hyo-laryngeal elevation and swallowing muscle maintenance, and thus functional swallowing ability[15, 16].

Based on the positive experience with the TheraBite as an exercise tool with good compliance[15, 16], and the idea to combine proven isometric and isokinetic strength exercises in a single useful handheld device that is applicable in a seated position, we developed a new Swallow Exercise Aid (SEA). The device consists of commercially available and customized components, to enable exercises against variable/increasing resistance, allowing adaptation to individual performance improvement, and to provide adequate tactile feedback. In this way, a variation of exercises can be performed, which have the potential to functionally strengthen the suprahyoid and pharyngeal muscles relevant for swallowing. The effectiveness and feasibility/compliance of an exercise protocol using this device was studied in healthy subjects with a multidimensional assessment protocol.

MATERIAL AND METHODS

The present study was designed as an uncontrolled prospective effectiveness and feasibility study with a 6-week follow-up period, and was undertaken at the Department of Head and Neck Oncology and Surgery of the Netherlands Cancer Institute – Antoni van Leeuwenhoek in Amsterdam, the Netherlands.

Participants/volunteers

The study population consisted of 10 healthy, male subjects without history of swallowing impairment or other dysphagia symptoms (median total SWAL-QOL score at baseline 4.5, which is below the defined cut-off score of 14 by Rinkel et al. for swallowing problems[30]). Median age at baseline was 60 years (range 52–73 years); median weight was 88 kg (range 70–92 kg). This age and gender group was chosen to mimic the age distribution of the HNC patient population[31, 32], and because HNC occurs more frequently in males than in females, with a ratio ranging from 3:1 to 4:1[31, 32]. Moreover, in this way gender was not an effect modifier in this small-scale effectiveness and feasibility study. See Table 1 for volunteers' characteristics at baseline.

The Swallow Exercise Aid

The SEA was constructed with commercially available parts, i.e. the TheraBite Jaw Mobilization device complemented with one or two TheraBite ActiveBands made out of silicone rubber

(Atos Medical, Hörby, Sweden), and subsequently remodeled by our Institute's technician by adding a chest bar to one of the mouthpieces of the TheraBite (see Figure 1). The ActiveBand can be placed at various, marked positions around the handle. The force required to compress the chin bar onto the chest bar with one ActiveBand in the maximum position, according to the manufacturer's specifications, is 50 Newton (N). If a subject had enough strength with one ActiveBand at its maximum position to complete the set of exercises, a second ActiveBand was added at any one of the marked positions. This configuration allows progressive overload, which is a prerequisite for effective strength training[33].

Table 1. Volunteers' characteristics (n=10)

Subject	Gender	Age *(years)*	Weight *(kg)*	FOIS *(score)*	Follow-up	Assessments
1	M	52	70	7	6 wks, 2 days	All
2	M	66	88	7	6 wks, 2 days	No MRI
3	M	67	91	7	6 wks, 2 days	All
4	M	61	80	7	6 wks, 2 days	All
5	M	54	88	7	6 wks, 2 days	All
6	M	73	92	7	6 wks, 2 days	All
7	M	56	87	7	6 wks, 2 days	All
8	M	61	88	7	6 wks, 2 days	All
9	M	57	82	7	4 wks, 4 days	All
10	M	58	88	7	6 wks, 2 days	All

Abbreviations: FOIS = Functional Oral Intake Scale. Age and weight are assessed at baseline.

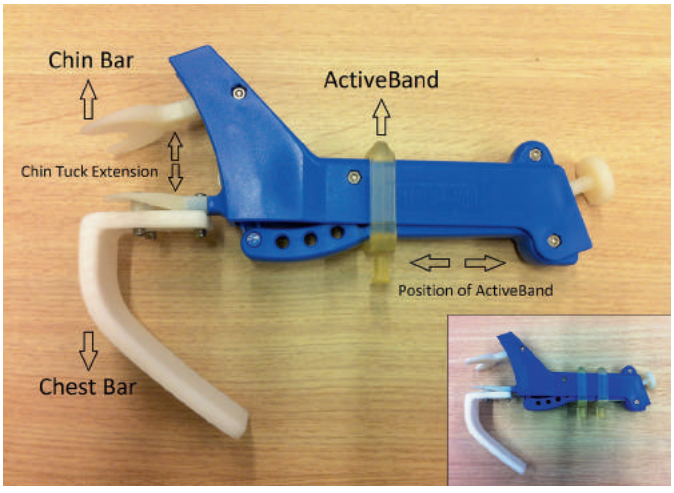


Figure 1. Swallow Exercise Aid (SEA) with ActiveBand, chin tuck and jaw opening extension, chin bar, and chest bar; insert shows possible addition of a second ActiveBand to further increase resistance.

Intervention

The training program consisted of three exercises, visualized in Figure 2:

The first exercise, the chin tuck against resistance (CTAR) exercise, was performed by pressing the chin downwards against the chin bar, while keeping the mouth closed, until the chin bar reached the chest bar attachment (providing tactile feedback). In this way, the exercise – comparable to the Shaker[23] and the 'ball' CTAR exercise[27] – focused on training the suprahyoid muscles.

The second exercise, the jaw opening against resistance (JOAR) exercise, was performed by pressing the mandible down while opening the mouth, to again compress the chin bar onto the chest bar. Given that suprahyoid muscles participate in opening the jaw[34], this exercise focused not only on the suprahyoid muscles, but also on other jaw opening musculature.

The third exercise, the effortful swallow (ES) exercise, was performed with the chin placed on the chin bar (pressed downwards for approximately 50%), whereby the subjects were asked to swallow with the mandible down and mouth closed, comparable to the formerly described TheraBite swallowing exercise[15]. This exercise is hypothesized to not only stimulate the suprahyoid and jaw muscles involved in mouth opening, but also the pharyngeal musculature, comparable to an effortful swallow[1, 20, 21].

Figure 2. Swallowing Exercise Aid (SEA) exercises (printed with permission of subject). Top left: start position; top right: exercise 1; chin tuck against resistance (CTAR) exercise; bottom left: exercise 2; jaw opening against resistance (JOAR) exercise; bottom right: exercise 3; effortful swallow exercise with 50% of maximum closure.

Exercise protocol

All subjects were asked to perform the SEA exercises three times per day for six weeks. Prior to participation, subjects received a written instruction sheet. They were instructed to hold the SEA in their preferred hand, to place the chest bar onto the sternum without excessive pressure, and to place the chin onto the chin bar. The ActiveBand was placed on the (individual) indicated position of the device, to ensure a specified amount of resistance.

Comparable with the Shaker exercise[23], the CTAR and JOAR exercises consist of both isometric and isokinetic strength exercises. The isokinetic exercises were performed 30 times consecutively at a fixed pace of 1s per contraction. The isometric exercises were performed three times, maintained for 60s, with a 60s rest period between each of the three. These two exercises were carried out first, with 60s rest between each session. Subsequently, the effortful swallow exercise was performed 10 times consecutively, after another 60s rest period. The total duration of the three exercises was estimated to be 15 minutes per session.

For the exercise prescription, only start-intensity was specified for individual subjects based on baseline strength assessments (dynamometry and 30-repetition maximum). Progression of intensity was based on self-perceived exertion; all subjects were instructed that the exercises should be perceived as strenuous, inducing substantial local muscle fatigue, and to increase resistance whenever they felt able to (that is: if they could complete the exercise without substantial exertion).

Subjects received three daily SMS text messages as a reminder to practice and were asked to record their performances by using tally sheets in a special exercise log. All subjects were instructed to stop the exercises if they felt discomfort or pain on the chest/chin or in/around their temporomandibular joint during the exercises.

Multidimensional assessment

All outcome parameters were recorded prior to participation (at baseline) and two days after the 6-week practice period (post-training). The total duration of the multidimensional assessment protocol was estimated to be 60 minutes per session. Primary outcome parameters were maximum chin tuck/jaw opening strength, maximum tongue strength/endurance, suprahyoid (swallowing) muscle volume, and hyoid bone displacement (HBD).

Muscle strength

Muscle strengths were measured with a 'handheld' dynamometer (Microfet™, Biometrics, Almere, the Netherlands) mounted into an adapted ophthalmic examination frame (see Figure 3), to avoid variations in head and chin position and to ensure consistent compression. A superior fixed belt stabilized the subject's head, and the height of both the chin rest and the superior belt could be adjusted to the subject's dimensions. Subjects were instructed to sit straight, and to press their chin down on the dynamometer as powerful as possible, once

with their mouth and teeth closed (like the CTAR exercise), and once by opening their jaw/mouth (like the JOAR exercise). The dynamometer digitally measured the maximal isometric chin tuck/jaw opening strength in Newton. Both measurements were preceded by one familiarization session, in order to exclude learning curve effects and to improve reliability of the values obtained[35]. After the familiarization session, both measurements were repeated three times, with a 60-seconds rest period between the trials. The mean maximum pressure of the highest two of three values was calculated and used as the subjects' maximum chin tuck/jaw opening strength[35]. Test-retest reliability with Intraclass Correlation Coefficient (ICC(2,1)) of this set-up was assessed in 14 (different) volunteers. The maximal chin tuck strength showed an ICC(2,1) of 0.98 (95% CI 0.93–0.99) and the maximal jaw opening strength showed an ICC(2,1) of 0.97 (95% CI 0.92–0.99) (which means a maximal measurement error of 17 N for chin tuck strength and 18 N for jaw opening strength in this SEA sample).

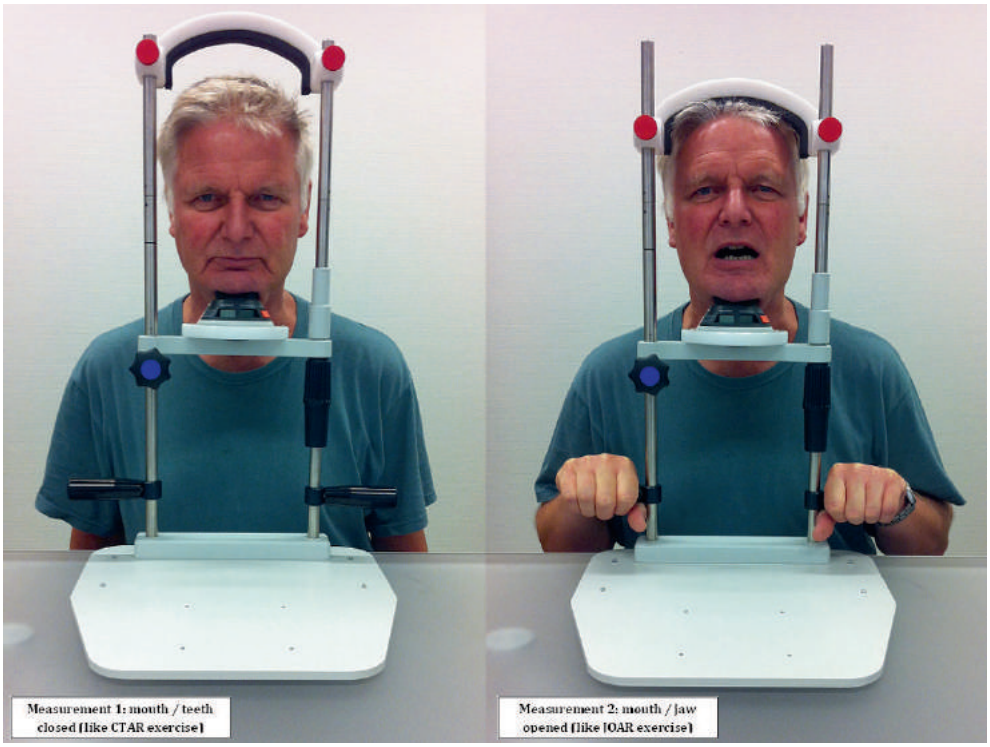


Figure 3. Muscle strength test set-up with an adapted ophthalmic examination frame and a dynamometer (Microfet™) fixed at the chin rest (printed with permission of subject). Left: measurement 1 (mouth closed, comparable to CTAR exercise); right: measurement 2 (mouth opened, comparable to JOAR exercise).

Tongue strength and endurance

The Iowa Oral Performance Instrument (IOPI) was used to measure maximum tongue pressures (at anterior and posterior locations) and endurance by means of a small air-filled bulb. There is ample evidence to support this tool for evaluating (isometric) tongue strength and endurance[33, 36]. Subjects had to press their tongue upwards on the air-filled bulb, in order to squeeze the bulb against the hard palate. Pressures were expressed in kPa and digitally displayed on the device. After one familiarization session, three trials of maximum (anterior and posterior) tongue pressure were obtained for each subject, with a 2-minute rest period between the trials. The mean maximum pressure of the highest two of three values was calculated and used as the subjects' maximal (anterior/posterior) tongue strength. Also endurance measures were analysed at anterior tongue location following the strength task, after a break of at least 5 minutes. Subjects were asked to maintain 50% of their maximal tongue strength as long as possible.

Muscle volume

Magnetic Resonance Imaging (MRI) at 3 Tesla (Philips Achieva release 3.2.1, Philips Medical Systems, Best, The Netherlands) was used to visualise the swallowing muscles in the oral cavity and pharynx[16]. A dedicated 16-channel SENSE neurovascular coil was used. Both T1 (Turbo Spin Echo (TSE), TRA:TR/TE:1761/10, ETL:6, recon voxel:0,5x0,5x1,5mm, FOV:100x100x91, 2 nex; SGT:TR/TE:1490/10 ms, ETL:7, recon voxel:0,5x-,5x1,5mm, FOV:100x200x91,2 nex; COR:TR/TE:877/10, ETL:7, recon voxel:0,28x0,28x1,5mm, FOV: 99x110x180,3 nex) and 3D T2 (Vista COR:TR/TE:1874/200 ETL:66, recon voxel:04x0,4x0,75, FOV:100x110x181, 3 nex) were acquired. Total duration of the MRI-investigation was 20 minutes. Subjects were instructed to lie down while keeping their tongue (relaxed) to the lower teeth during scanning. The acquired images were stored unto a PACS Workstation (Carestream Health Inc, Rochester, USA). Post-processing (volume measurements) was done using the Philips Intellispace Portal Tumor Tracking Application (Philips Medical Systems, Best, the Netherlands). With this application the contours of the muscle groups were delineated in three orthogonal planes (T1 coronal, transversal, and sagittal), and controlled with overlying T2 images. As an example, in Figure 4 a graphic representation of the delineated muscle contour with corresponding volume calculation in the coronal orthogonal plane is shown. Muscle volumes of the suprahyoid muscles (the combination of the geniohyoid, mylohyoid, and digastric (anterior belly) muscles) were determined. It appeared that the measurements of individual muscles was not practical, because of three reasons: the individual muscles are not easily distinguished from each other with MRI (especially the geniohyoideus and mylohyoideus), the individual muscles are small, therefore measuring will have a relatively large inherent variability and inaccuracy, and third: they can functionally be considered as one group, and we supposed an equal reaction to exercise.

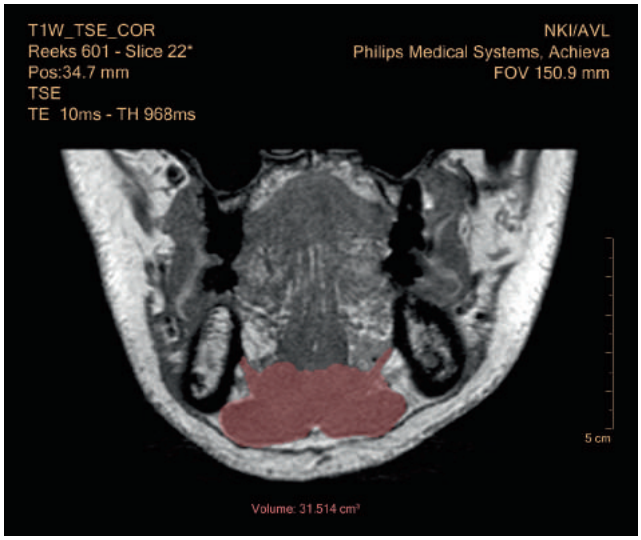


Figure 4. Graphic representation of delineated suprahyoid muscle contour with corresponding volume calculation in the coronal orthogonal plane assessed with MRI.

Videofluoroscopy swallowing parameters

Videofluoroscopy (VFS) is a validated method for objective assessment of all phases of the swallowing physiology[1]. The swallowing act was recorded in a lateral field of view encompassing the lips anteriorly, the cervical vertebrae posteriorly, the soft palate superiorly, and the lower end of the cervical esophagus inferiorly. The consistencies and amounts used were 1, 3, 5, and 10 cc thin liquid, 3 and 5 cc paste liquid, and a Omnipaque coated piece of gingerbread. Subjects were instructed to sip and wait for a verbal cue from the clinical investigator before swallowing, with clear instructions to sip as usual, without excessive force. The primary outcome measure was anterior/superior HBD, which is defined as the anterior/superior distance traveled by the hyoid bone to the point of maximal displacement during a swallow from its position during hold[37, 38]. Measures were done based on the methods of these authors, by 'subtracting' the still of hyoid elevation start time (HEST) from that of maximum hyoid elevation time (MHET). HEST is defined as the time between the first superior-anterior displacement of the hyoid bone that results in a swallow minus the time of the first movement of the head of the bolus past the posterior nasal spine (onset of pharyngeal transit). MHET is defined as the time between the frame in which the hyoid bone had reached its maximum superior-anterior excursion during the swallow, and again pharyngeal transit onset time[39]. Other VFS parameters assessed were presence of laryngeal penetration and/or aspiration[40], and occurrence of contrast residue.

Additional outcome parameters in the multidimensional assessment protocol were mouth opening, subjective swallowing complaints, and feasibility and compliance of/with the SEA exercises. Maximum mouth opening was measured in millimeters using disposable

TheraBite range of motion scales. Subjective swallowing complaints were recorded pre- and post-training with the 44-item Swallowing Quality of Life (SWAL-QOL) questionnaire[41], which assesses patients' swallowing impairment based on 10 QOL domains, each ranging from 0–100 with a higher score indicating more impairment. Feasibility of the SEA exercises (use of the exercise regimen, familiarity with the exercises, and occurrence of adverse events) was monitored with a study-specific questionnaire. Compliance with the SEA exercises was monitored with tally sheets in a daily exercise log.

Imaging assessment procedures

Both MRI and VFS assessments were done by two assessors independently: the first author and one dedicated head and neck radiologist (for MRI; JT), or the participating SLP (for VFS; LvdM). For MRI, both assessors were blinded to pre- or post-intervention status of the image. The delineated muscle volumes were reviewed in a consensus meeting, while maintained blinding, and the consensus volumes were used in the analysis. For VFS categorical measurements, a similar blinded consensus procedure was followed, in this respect with the participating SLP. For VFS anterior and superior HBD assessments, 10% of the measurements (stills of all consistencies in lateral view pre- and post-intervention) were repeated by the first author (as a measure of intrarater reliability) and 10% were reviewed by the SLP (as a measure of interrater reliability). Measurements were deemed in concordance if pairwise testing showed a greater than 95% chance of measuring statistically indistinguishable values in the two measurement sessions[25].

Statistical analyses

Descriptive statistics were generated for all outcome measures. Data from muscle strength tests, IOPI measurements, MRI, VFS, and questionnaires of the total study population were summarised as medians and median differences, whereby 95% confidence intervals for the median differences were obtained with bootstrapping. Wilcoxon signed rank tests were used to compare the repeated measurements. A two-sided p-value of 0.05 was considered to indicate statistical significance. Statistical analysis was performed using Statistical Package of Social Sciences (SPSS) software version 20.0.

RESULTS

For 9 subjects, the post-intervention multidimensional evaluation protocol was carried out two days after the 6-week exercise period. In one subject, this had to be done already after four and a half weeks since he had professional commitments abroad. All collected data are shown in Table 2. In the following paragraphs the most relevant/significant results are described in more detail.

Table 2. Data collection per subject before and after the 6-week exercise period.

	S01	S02	S03	S04	S05	S06	S07	S08	S09	S10	Median	Median difference	95% CI difference	*p* value
Chin tuck strength (N)														
Pre	198,5	81,0	51,0	63,0	228,5	83,0	78,0	132,0	126,5	100,0	82.0			
Post	242,4	99,2	93,4	118,1	238,9	142,4	112,5	152,3	132,0	189,5	132.0	38.5	20.3–59.4	**p=.005**
Jaw opening strength (N)														
Pre	128,5	70,5	36,5	55,0	232,0	69,0	94,0	96,5	54,0	100,0	82.3			
Post	229,8	117,0	87,8	107,9	283,4	145,0	102,1	125,4	120,0	189,5	122.7	52.1	28.9–89.5	**p=.005**
Ant. tongue strength (kPa)														
Pre	70,5	54,5	57,0	55,0	74,5	58,5	45,5	49,0	60,0	57,5	57.4			
Post	72,0	65,0	58,0	64,0	73,5	57,5	57,0	54,0	61,5	62,0	61.8	2.9	-1.0–9.0	**p=.016**
Post. tongue strength (kPa)														
Pre	75,0	75,5	57,5	64,0	63,5	47,0	49,5	47,5	56,0	53,5	56.8			
Post	76,5	76,5	57,5	64,0	70,0	46,0	56,5	45,5	60,0	63,5	61.8	1.3	-1.0–7.0	*p* =.080
Ant. tongue endurance (s)														
Pre	44	30	30	31	24	106	71	19	27	29	30.0			
Post	53	29	61	32	35	260	41	16	47	37	39.0	8.5	-3.0–20.0	*p* =.126
Suprahyoid muscle mass (cm^2)														
Pre	27,3	x	24,1	22,5	32,1	26,8	29,5	26,8	27,4	22,2	26.8			
Post	29,5	x	27,5	23,8	34,3	32,9	34,1	29,6	30,8	23,4	29.6	2.9	1.3–4.6	**p=.008**
Mouth opening (mm)														
Pre	42	67	56	61	52	49	60	48	51	46	51.5			
Post	42	70	56	64	52	53	64	50	52	52	52.5	2.5	0.0–4.0	**p=.018**
Ant. HBD 1cc thin liq. (mm)														
Pre	8,19	13,57	7,76	12,33	10,14	9,73	12,6	9,98	9,47	8,83	9.9			
Post	12,09	15,45	7,96	7,61	11,58	13,7	9,19	14,97	14,45	8,83	11.8	1.7	-3.4–2.9	*p* =.173
Sup. HBD 1cc thin liq. (mm)														
Pre	22,25	15,56	6,2	13,32	13,85	20,74	13,1	17,09	24,42	14,73	15.1			
Post	14,33	22,35	15,05	14,4	22,71	15,91	28,72	9,56	27,36	27,69	19.1	4.9	-1.9–13.0	*p* =.169
Ant. HBD 3cc thin liq. (mm)														
Pre	8,62	11,58	8,28	11,35	12,18	9,3	14,61	11,87	8,97	13,03	11.5			
Post	13,43	12,2	9,29	8,41	9,86	15,91	11,58	14,97	x	11,64	11.6	0.6	-2.9–3.8	*p* =.594
Sup. HBD 3cc thin liq. (mm)														
Pre	17,99	14,76	10,34	13,32	14,36	22,86	14,11	19,47	13,96	14,3	14.3			
Post	12,53	21,13	14,61	12,4	22,71	16,35	25,93	4,57	x	26,49	16.3	4.3	-3.7–11.8	*p* =.594

Ant. HBD 5cc thin liq. (mm)														
Pre	14,51	9,57	7,25	9,87	12,68	9,3	13,1	9,98	7,97	13,87	9.9			
Post	14,78	11,79	10,18	9,6	13,71	15,46	12,78	15,8	13,42	11,64	13.1	1.6	-0.3–2.6	*p* =.093
Sup. HBD 5cc thin liq. (mm)														
Pre	21,97	19,55	4,14	15,3	13,85	28,78	20,15	12,35	14,45	13,04	14.9			
Post	12,09	24,38	16,83	6,79	27,42	15,46	22,34	2,5	34,58	27,29	19.6	3.5	-9.9–13.5	*p* =.386
Ant. HBD 10cc thin liq. (mm)														
Pre	15,84	10,78	8,8	11,35	14,7	9,73	15,62	8,08	6,97	13,03	11.1			
Post	15,67	10,98	9,73	11,2	14,57	15,46	13,57	14,97	5,68	11,24	12.4	-0.1	-1.8–0.6	*p* =.959
Sup. HBD 10cc thin liq. (mm)														
Pre	7,09	20,74	5,17	9,87	16,38	21,16	21,16	13,29	10,97	14,3	13.8			
Post	13,88	28,44	16,83	11,6	27,42	16,35	30,33	0	26,84	25,69	21.3	8.4	1.7–11.4	*p* = .093
Ant. HBD 5cc thick liq. (mm)														
Pre	13,76	10,38	9,31	15,3	20,79	9,3	15,12	9,5	9,47	15,98	12.1			
Post	17,02	12,6	11,51	10,8	15,85	15,46	10,78	14,14	18,58	15,65	14.8	2.2	-4.5–3.3	*p* =.445
Sup. HBD 5cc thick liq. (mm)														
Pre	12,19	21,54	2,06	3,94	9,28	30,89	10,59	11,39	9,96	15,98	11.0			
Post	6,27	24,38	13,72	8,8	23,99	18,56	21,55	0	25,29	19,67	19.1	4.3	-4.3–11.3	*p* =.333
Ant. HBD paste liq. (mm)														
Pre	14,38	11,18	8,28	13,82	19,27	11,85	11,59	12,35	11,97	17,66	12.2			
Post	15,67	15,45	14,17	12,8	16,72	19	12,38	x	x	18,06	15.6	1.0	-1.0–5.1	*p* =.161
Sup. HBD paste liq. (mm)														
Pre	8,66	20,07	-0,49	11,71	15,55	19,69	12,92	7,21	8,04	8,79	10.8			
Post	9,78	16,59	11,77	11,01	26,44	11,74	23,86	x	x	19,44	14.9	6.2	-2.2–11.5	*p* =.161
Hyoid elevation start time (s)														
Pre	0,42	-0,36	-0,09	-0,03	-0,2	0,15	0,24	0,05	-0,13	0,17	0.04			
Post	0,42	0,12	-0,07	0,34	0,31	0,33	0,23	0,42	0,07	0,13	0.22	0.1	-0.0–0.4	*p* =.093
Max. hyoid elevation time (s)														
Pre	1,16	0,57	0,55	1,03	0,71	0,76	0,68	0,84	0,43	0,85	0.77			
Post	0,94	0,59	0,49	0,81	0,82	0,88	0,74	0,98	0,4	0,72	0.74	-0.1	-0.2–0.0	*p* =.241
Total SWAL-QoL score														
Pre	22,9	8,9	0	1,8	47,1	7,1	0	16,7	0	0	4.5			
Post	22,9	29,5	0	1,8	56,0	7,1	0	66,6	0	0	4.5	0.0	0.0–10.3	*p* =.109

Abbreviations: S01 to S10 = subject 1 to subject 10; CI = confidence interval; N = Newton; kPa = kilopascal; s = seconds; cm2 = cc = cubic centimeters; mm = millimeters; HBD = hyoid bone displacement; ant. = anterior; sup. = superior; liq. = liquid; max. = maximum; SWAL-QOL score = Swallowing Quality of Life score (a higher score means worse quality of life based on swallowing function); x = not available.

Muscle strength

After 6-weeks of swallowing training, median chin tuck strength significantly increased with 38.5 N (95% CI 20.3 to 59.4 N; p =.005), from a median of 82.0 N to a median of 132.0 N. The median jaw opening strength significantly increased with 52.1 N (95% CI 28.9 to 89.5 N; p =.005), from a median of 82.3 N to 122.7 N. The individual improvements are visualized in Figures 5 and 6.

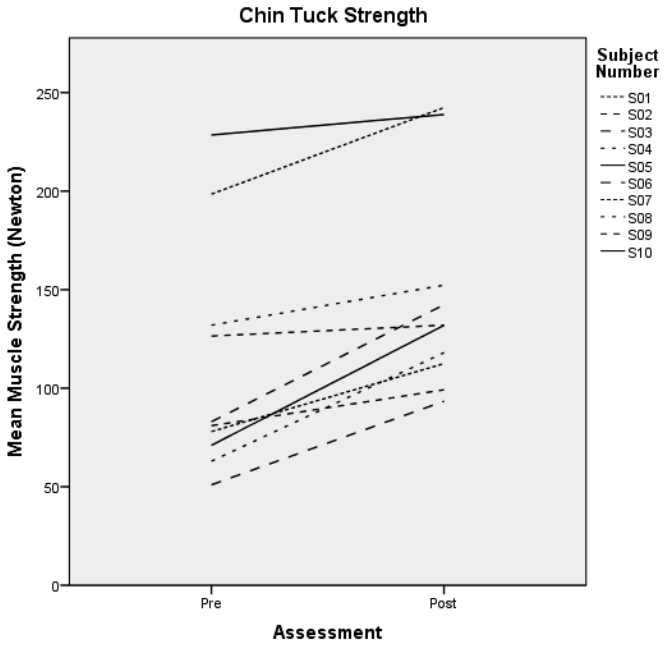


Figure 5. Change in individual maximum chin tuck strength after the 6-week exercise period.

Tongue strength and endurance

Median anterior tongue strength (IOPI) significantly increased with 2.9 kPa (95% CI -1.0 to 9.0 kPa; p =.016), from a median of 57.4 kPa to a median of 61.8 kPa. There was a trend for posterior tongue strength increase with a median increase of 1.3 kPa (95% CI-1.0 to 7.0 kPa; p =.080). The increase in anterior tongue endurance with a median of 8.5 seconds was not statistically significant (p =.126).

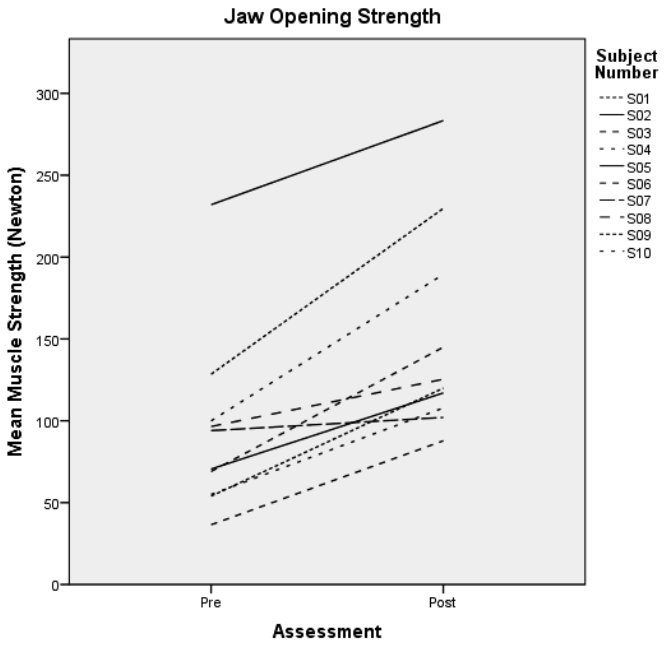


Figure 6. Change in individual maximum jaw opening strength after the 6-week exercise period.

Muscle volume

After 6-weeks of swallowing training, median suprahyoid muscle volume (the mylohyoid, geniohyoid and anterior belly of digastric muscles combined) significantly increased with 2.9 cm^3 (95% CI 1.3 to 4.6 cm^3; p =.008), from a median of 26.8 cm^3 to a median of 29.6 cm^3. The individual improvements are visualized in Figure 7.

VFS swallowing parameters

As can be seen in Table 1, HBD outcomes were quite variable over the various consistencies and subjects, and did not differ significantly over time. After the 6-week exercise period, HBD had increased in particular in the superior direction compared to the anterior direction. As an example, the lowest increase was seen for a 5 cc thin liquid swallow (superior HBD increased with a median of 3.5 mm) and the highest increase was seen for a 10 cc thin liquid swallow (superior HBD increased with a median of 8.4 mm). At both assessment points, subjects showed normal swallowing function on the VFS. There was no laryngeal penetration/aspiration or more than normal contrast residue seen after the swallow (this applied to all consistencies). Mean hyoid bone elevation start time and hyoid bone maximum elevation time did not differ significantly between the two assessment points (median difference 0.1 s and-0.1 s respectively).

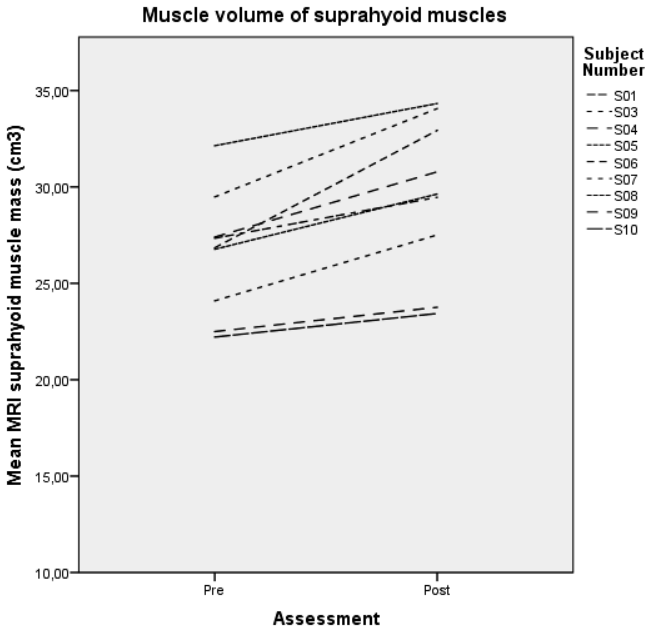


Figure 7. Change in individual muscle volume of suprahyoid muscles after the 6-week exercise period.

Additional outcome parameters

Although none of the tested subjects had any swallowing complaints, trismus, or dietary limitations, still we found an increase in mouth opening after the training program. Median maximal inter-incisor opening significantly increased with 2.5 mm (95% CI 0.0 to 4.0 mm; p =.018), from a median of 51.5 mm to a median of 52.5 mm. There were no subjective swallowing complaints or adverse events. Total duration of the exercises was reported to be 15 to 20 minutes. Feasibility of the SEA exercises was considered acceptable, i.e. "time consuming, but doable". Out of 129 exercise sessions (3 times a day during 6 weeks with one additional day at the end of the exercise period), median compliance was 86% (range 48–100%). Except for one subject, all participants had at least practiced 1 session a day, and none of the participants had missed more than 2 sessions consecutively. Half of the participants added a second ActiveBand during the 6 weeks exercise period, because of increased ease of closing the chin bar onto the chest bar. None of the subjects reported unacceptable discomfort or pain on the chest/chin or in/around their temporomandibular joint during the exercises.

DISCUSSION

This prospective effectiveness and feasibility study on the effects of this newly assembled Swallow Exercise Aid (SEA), enabling chin tuck against resistance (CTAR) and jaw opening against resistance (JOAR) exercises, shows that senior healthy subjects are able to improve and increase swallowing muscle strength and volume after a 6-week training period, even at the absence of swallowing problems. The increases in muscle strength are highly significant and potentially clinically relevant. Moreover, with a median increase of 38.5 N and 52.1 N, they exceed the possible measurement error associated with the measurement setup, which was 17 N for chin tuck strength and 18 N for jaw opening strength in this sample, based on the established reliability. Therefore, the observed increase in swallowing muscle strength can be attributed to the 6-week exercise regimen with confidence. On top of that, subjects' anterior tongue strength and mouth opening significantly increased as well. The positive results found in this study warrant a trial for this SEA in head and neck cancer (HNC) patients with dysphagia.

The results found in this study are more or less in concordance with some earlier studies on strengthening the suprahyoid musculature by JOAR and/or CTAR exercises, applied to improve swallowing function. Wada et al. investigated the effects of the JOAR exercise on decreased upper esophageal sphincter (UES) opening on videofluoroscopy in eight patients with dysphagia while swallowing, and these authors found significant improvements in the extent of upward hyoid bone movement, amount of UES opening and time for pharynx passage after four weeks of training[34]. Although that study population consisted of only eight patients and no objective assessment of suprahyoid muscle strength was performed, the significant increase in upward movement of the hyoid bone following four weeks of practice suggests that the suprahyoid musculature (especially the mylohyoid muscle and anterior belly of the digastric muscles) were strengthened. This would be in line with the significant improved suprahyoid muscle strength (and volume) found in the present study after six weeks of comparable JOAR and CTAR exercises, although we did not find a significant increase in hyoid bone displacement (HBD), which is not surprising in this group of healthy subjects without swallowing issues.

As already briefly mentioned in the introduction, Yoon et al. recently investigated the CTAR exercise for both isometric and isokinetic tasks in comparison with the Shaker exercise, by measuring maximum and mean surface electromyography (sEMG) activity of the suprahyoid muscles during the exercise regimen[27]. The CTAR exercise was performed by tucking the chin as hard as possible on a rubber ball, placed between the chin and chest. Both exercises resulted in elevated maximum and mean sEMG values, reflecting suprahyoid muscle activity. Given the fact that suprahyoid muscle activity/strength is strongly correlated with hyoid bone displacement[42] and thus an important indicator of swallowing function[34], and given the fact

that suprahyoid muscle strength significantly improved in our study, it can be assumed that the CTAR and JOAR exercises with the SEA positively affect swallowing function too. The observed increased suprahyoid muscle volume contributes to this hypothesis. Compared to the Shaker exercise, interestingly, Yoon et al. found that the CTAR exercise with a rubber ball resulted in significantly greater maximum and mean activation levels during the isometric and isokinetic tasks, even though it was reported as less strenuous. This latter fact might further increase compliance with the ball exercise, aside from the advantage that no inconvenient and uncomfortable supine position is needed, which also allows elderly/frail patients to perform the exercises based on their current strength level[27]. The same holds true for the SEA, which has the additional advantage of using one or two elastic silicone ActiveBands to specify and increase the amount of resistance during the exercises. The closure of the chin bar onto the chest bar and the option to add a second elastic band to further increase resistance also give biofeedback for patient's performance. This latter fact was also supported by anecdotal feedback from our volunteers, and might further improve subjects' compliance with the exercises. However, the lack of a structured protocol for exercise progression may have resulted in a sub-optimal training effect. This underscores the potential of the exercise regimen, given the large effect sizes that we observed in this study. In future clinical studies, a structured prescription for exercise progression may result in even greater gains in muscle strength.

Despite the physiological range of motion during mouth opening, and the fact that all subjects already showed a normal maximum mouth opening (>35 mm) at baseline without swallowing complaints or dietary limitations, there was a small but statistically significant increase in maximum mouth opening after the 6-week exercise period. A following trial in HNC patients (with damaged swallowing muscles) will evaluate if maximum mouth opening can also increase in these patients, following six weeks of swallowing training.

Although submental sEMG recordings are commonly used in the field of dysphagia research and measured sEMG activity is thought to reflect actions of the suprahyoid musculature, we chose not to record sEMG activity. The main reason is that it is not possible to delineate which individual muscle (i.e. mylohyoid, anterior belly of the digastric, geniohyoid, and genioglossus) contributes most to the derived sEMG recordings[43]. Instead, we used muscle volume measurements with MRI, which provides information on possible hypertrophy of the muscles of interest. In addition, MRI might be more useful in a clinical research setting, because in most patients with advanced head and neck cancer MRIs are readily available for diagnosis and treatment response evaluation.

A limitation of the current study is that assessment of muscle function was limited to maximal muscle strength for the performed exercises. As a result, we cannot be sure how well the increase in swallowing muscle strength results in overall better functional swallowing ability (due to potential specificity effects). Regarding the literature, maximal chin-tuck and

jaw-opening strength are associated with better swallowing function[27, 34]. However, to better understand how these exercises influence swallowing function, future studies could include measurements of lingua-palatal pressures produced during effortful and non-effortful swallows. Furthermore, the sample size of this preliminary study was limited to 10 highly motivated subjects, therefore, the results should be interpreted with some caution.

CONCLUSION

This prospective effectiveness and feasibility trial on the effects of chin tuck against resistance (CTAR) and jaw opening against resistance (JOAR) isometric and isokinetic strength exercises on swallowing musculature and function, shows that senior healthy subjects are able to improve and increase swallowing muscle strength and volume after a 6-week period of extensive swallowing training. The positive results found in this study warrant a trial with this SEA in HNC patients with dysphagia.

ACKNOWLEDGEMENTS

This study was made possible by grants provided by “Stichting de Hoop” and the “Verwelius Foundation”. Atos Medical (Hörby, Sweden) is acknowledged for providing the TheraBites and ActiveBands, used for the customized SEAs.

REFERENCES

1. Logemann JA. Evaluation and treatment of swallowing disorders. Texas, Austin: Pro-ed (2nd ed); 1998.
2. Perlman AL, Schulze-Delrieu, K.S. Deglutition and its disorders. San Diego: Singular Publishing; 1997.
3. Pearson WG, Jr., Hindson DF, Langmore SE, Zumwalt AC. Evaluating swallowing muscles essential for hyolaryngeal elevation by using muscle functional magnetic resonance imaging. Int J Radiat Oncol Biol Phys. 2013;85:735-40.
4. Lazarus CL, Logemann JA, Pauloski BR, Colangelo LA, Kahrilas PJ, Mittal BB, et al. Swallowing disorders in head and neck cancer patients treated with radiotherapy and adjuvant chemotherapy. Laryngoscope. 1996;106:1157-66.
5. Smith RV, Kotz T, Beitler JJ, Wadler S. Long-term swallowing problems after organ preservation therapy with concomitant radiation therapy and intravenous hydroxyurea: initial results. Arch Otolaryngol Head Neck Surg. 2000;126:384-9.
6. Nguyen NP, Moltz CC, Frank C, Vos P, Smith HJ, Karlsson U, et al. Dysphagia following chemoradiation for locally advanced head and neck cancer. Ann Oncol. 2004;15:383-8.
7. Agarwal J, Palwe V, Dutta D, Gupta T, Laskar SG, Budrukkar A, et al. Objective assessment of swallowing function after definitive concurrent (chemo)radiotherapy in patients with head and neck cancer. Dysphagia. 2011;26:399-406.
8. Lazarus CL, Logemann JA, Pauloski BR, Rademaker AW, Larson CR, Mittal BB, et al. Swallowing and tongue function following treatment for oral and oropharyngeal cancer. J Speech Lang Hear Res. 2000;43:1011-23.
9. Robbins J, Kays SA, Gangnon RE, Hind JA, Hewitt AL, Gentry LR, et al. The effects of lingual exercise in stroke patients with dysphagia. Arch Phys Med Rehabil. 2007;88:150-8.
10. Clark HM, Henson PA, Barber WD, Stierwalt JA, Sherrill M. Relationships among subjective and objective measures of tongue strength and oral phase swallowing impairments. Am J Speech Lang Pathol. 2003;12:40-50.
11. Lazarus C. Tongue strength and exercise in healthy individuals and in head and neck cancer patients. Semin Speech Lang. 2006;27:260-7.
12. Chen AM, Li BQ, Lau DH, Farwell DG, Luu Q, Stuart K, et al. Evaluating the role of prophylactic gastrostomy tube placement prior to definitive chemoradiotherapy for head and neck cancer. Int J Radiat Oncol Biol Phys. 2010;78:1026-32.
13. Kulbersh BD, Rosenthal EL, McGrew BM, Duncan RD, McColloch NL, Carroll WR, et al. Pretreatment, preoperative swallowing exercises may improve dysphagia quality of life. Laryngoscope. 2006;116:883-6.
14. Carroll WR, Locher JL, Canon CL, Bohannon IA, McColloch NL, Magnuson JS. Pretreatment swallowing exercises improve swallow function after chemoradiation. Laryngoscope. 2008;118:39-43.
15. van der Molen L, van Rossum MA, Burkhead LM, Smeele LE, Rasch CR, Hilgers FJ. A randomized preventive rehabilitation trial in advanced head and neck cancer patients treated with chemoradiotherapy: feasibility, compliance, and short-term effects. Dysphagia. 2011;26:155-70.
16. Carnaby-Mann G, Crary MA, Schmalfuss I, Amdur R. "Pharyngocise": randomized controlled trial of preventative exercises to maintain muscle structure and swallowing function during head-and-neck chemoradiotherapy. Int J Radiat Oncol Biol Phys. 2012;83:210-9.
17. van der Molen L, van Rossum MA, Rasch CR, Smeele LE, Hilgers FJ. Two-year results of a prospective preventive swallowing rehabilitation trial in patients treated with chemoradiation for advanced head and neck cancer. Eur Arch Otorhinolaryngol. 2014;271:1257-70.
18. Logemann JA, Pauloski BR, Rademaker AW, Colangelo LA. Super-supraglottic swallow in irradiated head and neck cancer patients. Head Neck. 1997;19:535-40.

19. Lazarus C, Logemann JA, Gibbons P. Effects of maneuvers on swallowing function in a dysphagic oral cancer patient. Head Neck. 1993;15:419-24.

20. Hind JA, Nicosia MA, Roecker EB, Carnes ML, Robbins J. Comparison of effortful and noneffortful swallows in healthy middle-aged and older adults. Arch Phys Med Rehabil. 2001;82:1661-5.

21. Lazarus C, Logemann JA, Song CW, Rademaker AW, Kahrilas PJ. Effects of voluntary maneuvers on tongue base function for swallowing. Folia Phoniatr Logop. 2002;54:171-6.

22. Kahrilas PJ, Logemann JA, Krugler C, Flanagan E. Volitional augmentation of upper esophageal sphincter opening during swallowing. Am J Physiol. 1991;260:G450-6.

23. Shaker R, Kern M, Bardan E, Taylor A, Stewart ET, Hoffmann RG, et al. Augmentation of deglutitive upper esophageal sphincter opening in the elderly by exercise. Am J Physiol. 1997;272:G1518-22.

24. Shaker R, Easterling C, Kern M, Nitschke T, Massey B, Daniels S, et al. Rehabilitation of swallowing by exercise in tube-fed patients with pharyngeal dysphagia secondary to abnormal UES opening. Gastroenterology. 2002;122:1314-21.

25. Logemann JA, Rademaker A, Pauloski BR, Kelly A, Stangl-McBreen C, Antinoja J, et al. A randomized study comparing the Shaker exercise with traditional therapy: a preliminary study. Dysphagia. 2009;24:403-11.

26. Easterling C, Grande B, Kern M, Sears K, Shaker R. Attaining and maintaining isometric and isokinetic goals of the Shaker exercise. Dysphagia. 2005;20:133-8.

27. Yoon WL, Khoo JK, Rickard Liow SJ. Chin tuck against resistance (CTAR): new method for enhancing suprahyoid muscle activity using a Shaker-type exercise. Dysphagia. 2014;29:243-8.

28. Buchbinder D, Currivan RB, Kaplan AJ, Urken ML. Mobilization regimens for the prevention of jaw hypomobility in the radiated patient: a comparison of three techniques. J Oral Maxillofac Surg. 1993;51:863-7.

29. Kraaijenga S, van der Molen L, van Tinteren H, Hilgers F, Smeele L. Treatment of myogenic temporomandibular disorder: a prospective randomized clinical trial, comparing a mechanical stretching device (TheraBite(R)) with standard physical therapy exercise. Cranio. 2014;32:208-16.

30. Rinkel RN, Verdonck-de Leeuw IM, Langendijk JA, van Reij EJ, Aaronson NK, Leemans CR. The psychometric and clinical validity of the SWAL-QOL questionnaire in evaluating swallowing problems experienced by patients with oral and oropharyngeal cancer. Oral Oncol. 2009;45:e67-71.

31. Mehanna H, Paleri V, West CM, Nutting C. Head and neck cancer--Part 1: Epidemiology, presentation, and prevention. BMJ. 2010;341:c4684.

32. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. 2011;61:69-90.

33. Burkhead LM, Sapienza CM, Rosenbek JC. Strength-training exercise in dysphagia rehabilitation: principles, procedures, and directions for future research. Dysphagia. 2007;22:251-65.

34. Wada S, Tohara H, Iida T, Inoue M, Sato M, Ueda K. Jaw-opening exercise for insufficient opening of upper esophageal sphincter. Arch Phys Med Rehabil. 2012;93:1995-9.

35. Adams V, Mathisen B, Baines S, Lazarus C, Callister R. A systematic review and meta-analysis of measurements of tongue and hand strength and endurance using the Iowa Oral Performance Instrument (IOPI). Dysphagia. 2013;28:350-69.

36. Hewitt A, Hind J, Kays S, Nicosia M, Doyle J, Tompkins W, et al. Standardized instrument for lingual pressure measurement. Dysphagia. 2008;23:16-25.

37. Leonard RJ, Kendall KA. Dysphagia assessment and treatment planning: a team approach. San Diego: Singular Pub. Group.; 1997.

38. Leonard RJ, Kendall KA, McKenzie S, Goncalves MI, Walker A. Structural displacements in normal swallowing: a videofluoroscopic study. Dysphagia. 2000;15:146-52.

39. Kendall KA, McKenzie S, Leonard RJ, Goncalves MI, Walker A. Timing of events in normal swallowing: a videofluoroscopic study. Dysphagia. 2000;15:74-83.

40. Rosenbek JC, Robbins JA, Roecker EB, Coyle JL, Wood JL. A penetration-aspiration scale. Dysphagia. 1996;11:93-8.

41. Lemmens J, Bours GJ, Limburg M, Beurskens AJ. The feasibility and test-retest reliability of the Dutch SWAL-QOL adapted interview version for dysphagic patients with communicative and/or cognitive problems. Qual Life Res. 2013;22:891-5.

42. Crary MA, Carnaby Mann GD, Groher ME. Biomechanical correlates of surface electromyography signals obtained during swallowing by healthy adults. J Speech Lang Hear Res. 2006;49:186-93.

43. Palmer PM, Luschei ES, Jaffe D, McCulloch TM. Contributions of individual muscles to the submental surface electromyogram during swallowing. J Speech Lang Hear Res. 1999;42:1378-91.

Appendix I. SEA instructieformulier

Oefeningen

Er kunnen 3 verschillende oefeningen worden uitgevoerd met de Swallow Exercise Aid (SEA):

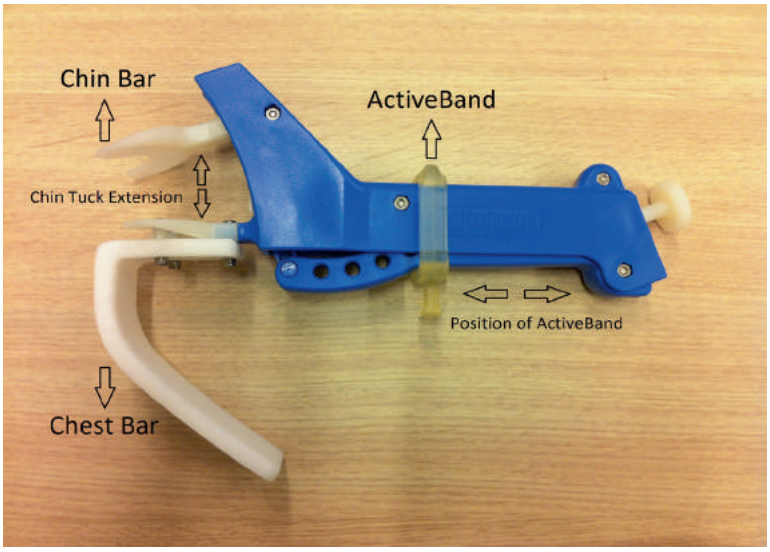
* *Oefening 1 en 2* bestaan uit bewegende (isokinetische) en statische (isometrische) krachtoefeningen
    - De bewegende oefening wordt 30 keer achter elkaar uitgevoerd (1 keer per seconde)
    - De statische oefening wordt 3 keer (gedurende 1 minuut vasthouden) achter elkaar uitgevoerd met 1 minuut rust tussen de oefeningen

* *Oefening 3* bestaat uit een slikoefening die 10 keer wordt uitgevoerd

Alle oefeningen worden 3 keer per dag worden uitgevoerd: 's ochtends, 's middags en 's avonds.
Alles wordt gedocumenteerd worden op het daarvoor bestemde 'Patiënten Logboek'

Algemene instructies

- Houdt de SEA in de hand van voorkeur
- Schuif de ActiveBand naar de (vooraf bepaalde) positie, om een specifieke hoeveelheid weerstand te verkrijgen
- Plaats de borststeun ('chest bar') op het borstbeen, zonder veel druk uit te oefenen
- Plaats de kin op de bovenste kinsteun ('chin bar')



Figuur 1. De Swallow Exercise Aid met ActiveBand, 'chin bar' (kinsteun) en 'chest bar' (borststeun).

Oefening 1 **(7 min.)**

- Plaats de borststeun op de borst zonder veel druk uit te oefenen
- Plaats de kin op de kinsteun
- Houdt de mond gesloten en duw met de kin de kinsteun naar beneden, zodat deze contact maakt met de borststeun

Duur en hoeveelheid:

- Herhaal de oefening 30 keer, met een ritme van 1 herhaling per seconde (= isokinetische oefening)
- Houdt nu minimaal 1 minuut rust
- Herhaal de oefening en zorg ervoor dat de kinsteun gedurende 60 seconden contact maakt met de borststeun (= isometrische oefening)
- Houdt weer minimaal 1 minuut rust
- Herhaal deze laatste oefening nog twee keer met daartussen steeds 1 minuut rust

Oefening 1

Oefening 2 **(7 min.)**

- Plaats de borststeun op de borst zonder veel druk uit te oefenen
- Plaats de kin op de kinsteun
- Duw met de onderkaak de kinsteun naar beneden, door de mond te openen, zodat deze contact maakt met de borststeun

Duur en hoeveelheid:

- Herhaal de oefening 30 keer, met een ritme van 1 herhaling per seconde (= isokinetische oefening)
- Houdt nu minimaal 1 minuut rust
- Herhaal de oefening en zorg ervoor dat de kinsteun gedurende 60 seconden contact maakt met de borststeun (= isometrische oefening)
- Houdt weer minimaal 1 minuut rust
- Herhaal deze laatste oefening nog twee keer met daartussen steeds 1 minuut rust

Oefening 2

Oefening 3 **(<1 min.)**

- Plaats de borststeun op de borst zonder veel druk uit te oefenen
- Plaats de kin/onderkaak op de bovenste kinsteun
- Houdt de mond open (tanden niet op elkaar) maar de lippen gesloten
- Slik met de lippen gesloten, tegen de weerstand van de SEA

Duur en hoeveelheid:

- Herhaal deze oefening 10 keer, met ongeveer een ritme van 1 herhaling per 2 seconden

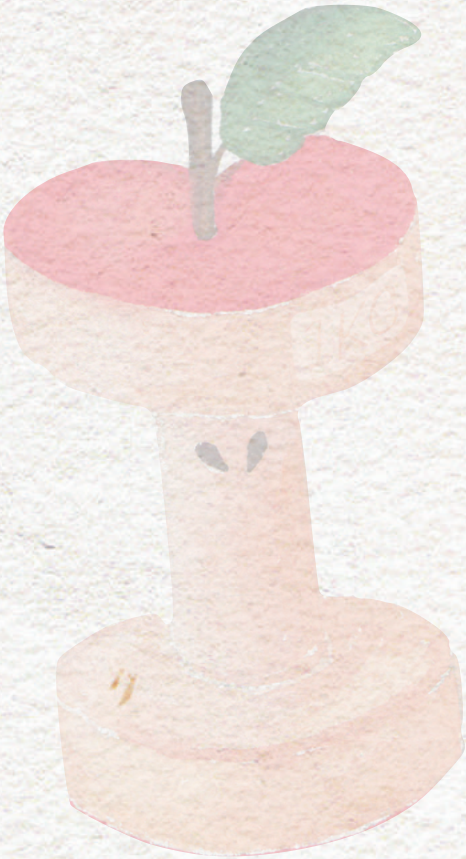
Oefening 3

CHAPTER 8

Efficacy of a novel swallowing exercise program for chronic dysphagia in long-term head and neck cancer survivors

S.A.C. Kraaijenga
L. van der Molen
M.M. Stuiver
R.P. Takes
A. Al-Mamgani
M.W.M. van den Brekel
F.J.M. Hilgers

Submitted.



ABSTRACT

Background: The efficacy of rehabilitative exercises for chronic dysphagia treatment in head and neck cancer (HNC) survivors has not been studied extensively and is ambiguous.

Methods: A prospective clinical phase 2 study using an intensive strength training program was carried out in 18 HNC survivors with chronic dysphagia. Both swallow and non-swallow exercises were performed for 6-8 weeks with a newly developed tool allowing for progressive muscle overload, including chin tuck, jaw opening, and effortful swallow exercises. Outcome parameters were feasibility, compliance, and parameters for effect.

Results: Overall and specific compliance with the 3 daily exercise sessions were 89% and 97%, respectively. After the training period, chin tuck, jaw opening, and anterior tongue strength had substantially improved. All but one patients reported to benefit from the exercises.

Conclusions: Feasibility and compliance were high. Some objective and subjective effects of progressive load on muscle strength and swallowing function could be demonstrated.

KEY WORDS

Head and Neck Cancer – Deglutition – Deglutition Disorders – Dysphagia – Rehabilitation – Strength Training – Swallow Exercise Aid – Chin Tuck – Jaw Opening

INTRODUCTION

Dysphagia is a significant complication in patients treated with radiotherapy (RT) or concurrent chemoradiotherapy (CRT) for advanced head and neck cancer (HNC). It may increase in severity over time, even years after treatment, as a result of progressive fibrosis and/or non-use atrophy following radiation to the swallowing musculature and structures[1-8]. Given its associated morbidity and devastating impact on physical and emotional wellbeing, there is a great demand for accurate, evidence-based dysphagia management[9, 10]. Growing evidence supports the benefit of preventive swallowing therapy to reduce the incidence and severity of dysphagia after CRT, although not all studies demonstrate an effect depending on the chosen endpoints[11-17]. Moreover, also post-treatment swallowing rehabilitation is potentially effective for reducing laryngeal penetration and/or aspiration in patients with chronic dysphagia[18-24].

Several swallowing interventions are applied for dysphagia, varying from compensatory techniques (e.g. postural changes, diet/bolus modifications) to rehabilitative techniques that aim to strengthen the swallowing musculature. Rehabilitative techniques include swallowing maneuvers such as the effortful swallow[25-27], and non-swallow exercises such as tongue strengthening exercises and the Shaker (head-lift) exercise[18, 28]. Swallow exercises are used during the swallow with the aim to increase the success of the swallow itself by training the involved muscles[25, 29]. Non-swallow exercises aim to improve range of motion and strength of the swallowing and neck musculature (i.e. the tongue or suprahyoid musculature), while allowing patients to progress through a training protocol safely, without limitations that may be imposed during actual swallowing[29].

Typically, repetitive exercises are used based on methods applied in sports medicine[30-33]. The exercises should be built on all principles (i.e. specificity, individuality, and overload) that adhere to strength or endurance training[29, 30, 32-35]. Swallowing is considered a submaximal muscular activity. This means that the muscular strength generated to successfully complete the swallowing act is less than the so-called 1-repetition maximum (1RM), i.e. the maximal force that can be generated by the swallowing muscles in a single repetition[30, 32]. Consequently, most strength training regimens start with an initial resistance of 60–75% of 1RM[19, 31, 36]. To maximize improvements over time, the application of the progressive muscle overload principle during the exercise period has to be an essential part of such a training regimen[29, 32, 35]. Recently, Langmore and Pisegna (2015) reported that increasing or decreasing the resistive load of swallowing is still an elusive challenge[35].

Based on the positive experiences with a jaw mobilization device (TheraBite®, Atos Medical, Sweden) that showed good compliance and cost-effectiveness[13, 37], recently an adapted device was developed, that enables both swallow and non-swallow exercises. The device allows adaptation to individual patient's capacity, and thus for applying progressive overload during

the training program. Moreover, it provides adequate tactile feedback during the exercises, and visual feedback on the resistance level[38]. The effectiveness and feasibility of this Swallow Exercise Aid (SEA)-based exercise regimen has been demonstrated in a prospective study in senior healthy subjects[38]. Compliance appeared to be high (86%), and there was a significant increase of swallowing muscle strength and volume, anterior tongue strength, and increased mouth opening after six weeks of intensive swallowing training. Although these results are promising, it remains to be demonstrated whether in patients with chronic dysphagia the targeted, often atrophied and/or fibrosed muscle groups are trainable with such a tool, and whether increased strength indeed has an impact on swallowing function. Many studies have tested the effects of training on normal, healthy individuals[39-42], but not in patients with dysphagia[35]. Therefore, as a next step, a prospective clinical study was conducted in a HNC patient cohort with chronic, therapy-resistant dysphagia, with the primary aim to assess the feasibility and compliance, and the secondary aim to establish the short-term efficacy of this SEA-based strength training protocol.

MATERIAL AND METHODS

The present study was designed as a multicenter, uncontrolled, prospective clinical phase 2 study. The study was undertaken at the Departments of Head and Neck Oncology and Surgery of the Netherlands Cancer Institute – Antoni van Leeuwenhoek (Amsterdam) and the Radboud University Medical Center (Nijmegen), both in the Netherlands. The study was approved by the local ethical committees of both institutes, and informed consent was obtained from each participant prior to inclusion. The study followed the guidelines of the Helsinki Declaration.

Patients

During the enrolment period (November 2014–December 2015), patients with chronic, therapy-resistant dysphagia, and in complete remission after treatment with RT or concurrent CRT for advanced HNC, were recruited at the outpatient clinic of both institutes. The dysphagia had to be persistent for at least 1 year, despite previous targeted swallowing exercise programs. The diagnosis dysphagia was based on the presence of penetration and/or aspiration (PAS ≥4) on at least 1 bolus on recent (<3 months) videofluoroscopy, and/or on a seriously limited intake of a normal diet (FOIS ≤4), i.e. feeding tube dependency. At the end of the enrolment period, 18 patients were included and signed informed consent. Median age at baseline was 65 years (range 42–74 years); median weight was 69 kg (range 45–98 kg); median BMI was 22 (range 16-31).

Treatment

All patients had completed a full dose of 60-70 Gray (Gy) as target volume to the primary tumor, except for one patient, who had received treatment with a total dose of 39 Gy as planned target volume. Elective nodal areas were given a total dose of 44 Gy. One patient was re-irradiated and had received an additional dose of 46 Gy with a boost to 56 Gy one year after initial treatment due to local recurrence. The prescribed dose was delivered in 30-35 fractions, as either three-dimensional (3D) conventional radiotherapy (3D-RT) in 8 patients (44%), or as intensity-modulated radiation therapy (IMRT) in 10 patients (56%). Concurrent chemotherapy was given in 8 patients (44%). Patients treated surgically for HNC, except for any kind of neck dissection, were excluded. With a median of 119 months (10 years) post-treatment, patients were well past the stages of recovery of acute toxicity. In Table 1 the patient and treatment characteristics at baseline are shown.

The Swallow Exercise Aid

The technical and functional features of the SEA have been described extensively before[38]. In short, the SEA is constructed on the basis of the TheraBite Jaw Mobilization device, modified with an added chest bar to the lower mouthpiece (see Figure 1). It is complemented with an ActiveBand that can be placed at various, marked positions around the handle. To increase resistance, the ActiveBand can be moved per position towards the final position 6. The force required for compressing the chin bar onto the chest bar with one ActiveBand around the handle ranges from 4 Newton in position 1 (minimal resistive load) to 50 Newton in position 6 (maximal resistive load; see Table 2). If required, a second ActiveBand can be added to further increase resistance. This configuration enables the progressive overload needed for effective strength training[32].

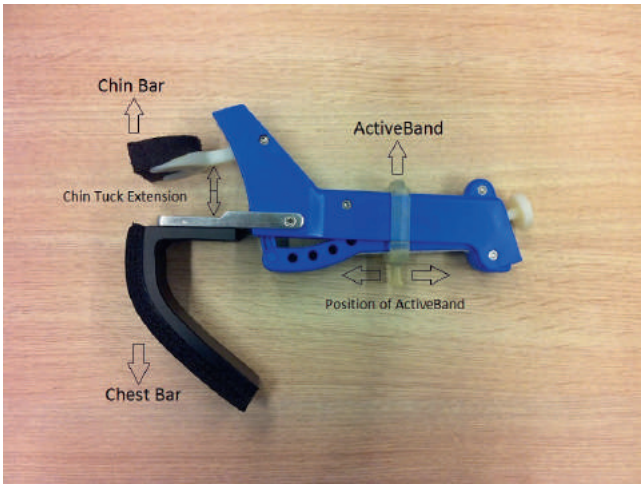


Figure 1. Swallow Exercise Aid (SEA) with ActiveBand, chin tuck and jaw opening extension, chin bar, and chest bar.

Table 1. Patients' and treatment characteristics at baseline (n=18).

Patient			Tumor		Treatment				Nutritional status				Pneumonia
No.	Gender	Age	Location	TNM	Year	RT	Dose	Chemo	FOIS	PRG	Weight	BMI	≥2 last yr
1	M	42	Oropharynx	T4N2c	2007	IMRT	68 Gy	yes	1	yes	85	22,8	no
2	M	71	Oropharynx	T2N1	1987	3-D	60 Gy	no	6	no	72	24,9	no
3	M	71	Parotic gland	TxN3	2013	IMRT	70 Gy	yes	1	yes	76	24,3	no
4	M	58	Oropharynx	T3N2a	2008	IMRT	70 Gy	yes	2	yes	45	16,1	yes
5	M	71	Hypopharynx	T1N1	1984	3-D	68 Gy	no	1	yes	70	21,8	yes
6	M	71	Oral cavity	T2N1	1984	3-D	60 Gy	no	4	no	98	30,9	no
7	M	62	Oropharynx	T2N0	2014	IMRT	66 Gy	no	2	no	72	21,7	no
8	V	60	Oropharynx	T3N2c	2004	IMRT	70 Gy	yes	6	yes	67	23,3	yes
9	V	61	Hypopharynx	T2N1	2004	IMRT	70 Gy	yes	7	no	48	17,2	yes
10*	M	65	Oropharynx	T4N3	2014	IMRT	68 Gy	yes	5	no	58	19,6	no
11	M	69	Neck metastasis	TxN1	2012	IMRT	39 Gy	no	6	no	65	20,5	no
12*	M	65	Hypopharynx	T2N1	2007	3-D	68 Gy	no	7	no	62	21,6	yes
13*	M	74	Oropharynx	T2N0	2003	3-D	68 Gy	no	6	no	62	18,1	yes
14*	V	67	Oropharynx	T3N2c	2000	3-D	68 Gy	no	6	no	76	29,7	no
15*	M	65	Larynx	T3N2c	2002	3-D	68 Gy	no	3	yes	76	24,0	yes
16	M	46	Oropharynx	T4N2	2011	IMRT	70 Gy	yes	4	no	82	24,0	no
17	V	72	Oral cavity	T2N0	1999	3-D	60 Gy	no	6	no	59	21,2	yes
18	V	65	Nasopharynx	T2N1	2011	IMRT	70 Gy	yes	6	no	68	23,0	no

Note: patients indicated by a dot (*) were included at the Radboud University; all other patients were included at the Netherlands Cancer Institute. Abbreviations: TNM = Tumor Node Metastasis; RT = Radiotherapy; IMRT = Intensity-Modulated Radiotherapy; 3-D = Three-Dimensional Radiotherapy; FOIS = Functional Oral Intake Scale; PRG = Percutaneous Radiologic Gastrostomy; BMI = Body Mass Index; yr = year.

Table 2. Estimated resistance in Newton at various positions of the ActiveBand.

Baseline chin tuck strength (1RM)	Position of ActiveBand	Estimated resistance (60–70% of 1RM)
0 – 12 N	1	1 – 8 N
13 – 24 N	2	9 – 16 N
25 – 36 N	3	17 – 25 N
37 – 50 N	4	26 – 34 N
51 – 65 N	5	35 – 44 N
66 – 80 N	6	45 – 54 N

Abbreviations: 1RM = one repetition maximum; N = Newton.

Intervention

The training program consists of three (non-swallow and swallow) exercises, visualized in Figure 2:

Figure 2. Swallowing Exercise Aid (SEA) exercises (printed with permission of patient). Top left: start position; top right: exercise 1; chin tuck against resistance (CTAR) exercise; bottom left: exercise 2; jaw opening against resistance (JOAR) exercise; bottom right: exercise 3; effortful swallow exercise with 50% of maximum closure.

The first exercise, the chin tuck against resistance (CTAR) exercise, is performed by pressing the chin downwards against the chin bar, while keeping the mouth closed, until the chin bar reaches the chest bar attachment (providing tactile feedback). This exercise – comparable to the Shaker[18, 25, 28] and another CTAR exercise[43] – is directed at the suprahyoid muscles, and aims at improvement of hyolaryngeal elevation and upper oesophageal sphincter (UES) opening.

The second exercise, the jaw opening against resistance (JOAR) exercise, is performed by pressing the mandible down while opening the mouth, again compressing the chin bar against the chest bar. This exercise targets the jaw opening musculature, including the suprahyoid muscles, and aims at improvement of hyoid elevation, amount of UES opening, and time for pharynx passage[23].

The third exercise, the effortful swallow exercise, is performed with the chin placed on the chin bar (pressed downwards for 50%), whereby the subjects swallow with the mandible down and mouth closed, comparable to the formerly described TheraBite swallowing exercise[13]. This exercise is hypothesized to also stimulate the pharyngeal musculature, to increase tongue base retraction and decrease the amount of pharyngeal residue, comparable to an effortful swallow[25-27].

Exercise protocol

Prior to participation, the patients visited the clinical investigator and received a written instruction sheet. To allow for the calculation of test-retest reliability of the chin tuck and jaw opening strength measurements, muscle strength testing was performed during that first visit. After a 3-week interval, the patients again visited the investigator for the actual instruction visit, and they received the necessary instruments. They were instructed to hold the SEA in their preferred hand, to place the chest bar onto the sternum without excessive pressure, and to place the chin onto the chin bar. Subsequently, all baseline measurements were performed, including the muscle strength tests. The ActiveBand was then placed on the appropriate position of the device, to ensure a specified amount of resistance, based on the most recent chin tuck strength (see Table 2). The individual starting position of the ActiveBand was determined following the principle of 1-repetition maximum (1RM), i.e. for this study the maximum chin tuck strength assessed at baseline (see below). A force of approximately 60–70% of the 1RM was used as initial resistance[32]. Subsequently, progression of intensity was based upon interim strength measurements and self-perceived exertion.

Comparable with the Shaker exercise[28], the CTAR and JOAR exercises were performed both as isometric and isokinetic exercises. The isokinetic exercises were performed 30 times consecutively at a fixed pace of 1s per contraction, with the aim to improve maximal muscle strength[32]. The isometric exercises were performed three times, maintained for 60s, with a 60s rest period between each of the three, with the aim to improve endurance of sustained

muscle activity[32]. These two exercises were carried out first, with 60s rest between each session. Subsequently, the effortful swallow exercise was performed 10 times consecutively as an isokinetic flexion, after another 60s rest period. The total duration of the three exercises is 25 minutes per session[38].

All patients were asked to perform the SEA exercises three times daily for at least 6 and maximum 8 weeks, which is based on Burkhead et al. (2007), who suggested that at least 5 weeks of strength training are needed before a meaningful gain in strength in skeletal muscles can be achieved[32]. During the exercise period, the patients visited the clinical investigator for mid-term evaluations (including muscle strength tests) after the first week, and subsequently every 2 weeks. Patients were asked to record their performances by using tally sheets in a special exercise log (see Appendix I). When patients felt the exercises became too easy, they were allowed to advance the ActiveBand to the next position in consultation with the clinical investigator. Patients were instructed to cease the exercises if they felt discomfort or pain on the chest/chin or in/around their temporomandibular joint during the exercises.

Multidimensional assessment

The outcome parameters were recorded prior to participation (at baseline) and two days after the practice period (post-training). Primary outcome parameters were feasibility and compliance of this SEA-based strength training protocol in this HNC patient cohort with chronic dysphagia. Secondary outcome measures were parameters to obtain an estimate of effect: maximum chin tuck and maximum jaw opening strength, maximum tongue strength/endurance, maximum mouth opening, presence of laryngeal penetration or aspiration, oral intake, hyoid bone displacement, subjective swallowing complaints, and general health status.

Feasibility and compliance

Feasibility of the SEA exercises (e.g. ease of handling of the device, practicality of the exercise regimen, familiarity with the exercises, occurrence of adverse events) was monitored with a study-specific questionnaire (see Appendix II for a translation in English). Compliance with the SEA exercises was monitored interim by the clinical investigator and at the post-treatment assessment point with tally sheets from the daily exercise log (Appendix I).

Swallowing muscle strength

Muscle strengths for chin tuck and jaw opening were measured in Newton (N), using a 'handheld' dynamometer (MicrofetTM, Biometrics, Almere, the Netherlands) mounted into an adapted ophthalmic examination frame (see Figure 3), to avoid variations in head and chin position and to ensure consistent compression[38]. A superior fixed belt stabilized the patient's head, and the height of both the chin rest and the superior belt could be adjusted

to the patient's dimensions. Patients were instructed to sit straight, and to press their chin down on the dynamometer as powerful as possible, once with their mouth and teeth closed (like the CTAR exercise), and once by opening their jaw/mouth (like the JOAR exercise). Both measurements were preceded by one familiarization session, in order to exclude learning curve effects and to improve reliability of the values obtained[44]. After the familiarization session, both measurements were repeated three times, with a 60-seconds rest period between the trials. The mean maximum pressure of the highest two of three values was used as the patients' maximum chin tuck/jaw opening strength[44].

Test-retest reliability coefficients (ICC(3,2)) for this set-up were 0.89 (95% CI 0.70–0.93) for maximal chin tuck strength, and 0.97 (95% CI 0.90–0.99) for maximal jaw opening strength, in these 18 patients. This implies a smallest detectable change (SDC) of 15 N for chin tuck strength and 7.5 N for jaw opening strength in this sample.

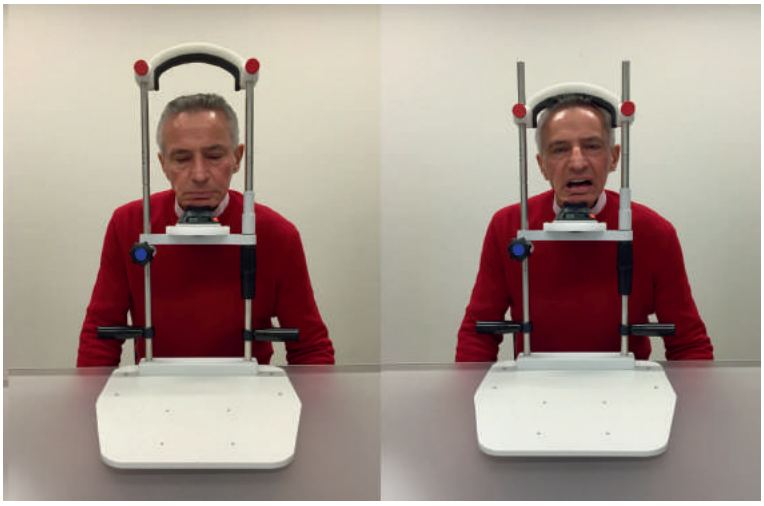


Figure 3. Muscle strength test set-up with an adapted ophthalmic examination frame and a dynamometer (Microfet™) fixed at the chin rest (printed with permission of patient). Left: measurement 1 (mouth closed, comparable to CTAR exercise); right: measurement 2 (mouth opened, comparable to JOAR exercise). Note: if patients feel more comfortable, during the JOAR exercise they may also hold the handle bars.

Tongue strength and endurance

The Iowa Oral Performance Instrument (IOPI) was used to measure maximum tongue pressures (at anterior and posterior locations) and endurance by means of a small air-filled bulb[32, 45]. Patients had to press their tongue upwards on the air-filled bulb, in order to squeeze the bulb against the hard palate. Pressures were expressed in kPa and digitally displayed on the device. After one familiarization session, three trials of maximum (anterior and posterior)

tongue pressure were obtained for each patient, with a 2-minute rest period between the trials. The mean maximum pressure of the highest two of three values was used as the patients' maximal (anterior/posterior) tongue strength. Also endurance measures were analysed at anterior tongue location following the strength task, after a break of at least 5 minutes. Patients were asked to maintain 50% of their maximal tongue strength as long as possible.

Videofluoroscopy

Videofluoroscopy (VFS) was used for objective assessment of all phases of the swallowing physiology according to the protocol of Logemann et al. (1998)[46]. In brief, the swallowing act was recorded in upright position in a lateral field of view. The consistencies and amounts used were 3 and 10 cc thin liquid, 5 cc thickened liquid, and an Omnipaque coated piece of gingerbread. Each bolus was repeated twice, resulting in a total of 8 swallows per patient per assessment.

Swallowing function was evaluated with the validated Penetration Aspiration Scale (PAS) score[47], ranging from 1–8 (score 1: material does not enter the airway, to score 8: material enters the airway, passes below the vocal folds, and no effort is made to eject). If a patient aspirated on 2 consecutive boluses of thin liquid of the same volume, larger volumes of thin liquid were not administered anymore. Similarly, if boluses of more solid food were deemed not to be safe (i.e. high likelihood of severe aspiration), these boluses were avoided. All boluses deemed to be unsafe were given a PAS score of 8[24]. Overall median PAS scores and median PAS scores per consistency were calculated[24]. Other VFS parameters such as presence of contrast residue and anterior/superior hyoid bone displacement were also assessed[48, 49]. The overall 'presence of residue' score ranges from 0–3 (score 0: no residue, to score 3: residue above and below the vallecula, with minimal residue judged as normal)[46, 50].

PAS and amount of residue scores were scored by two evaluators independently: the first author and the participating SLP. Both evaluators were blinded to pre- or post-intervention status of the swallow study. Subsequently, the scores were reviewed in a consensus meeting, under maintained blinding, and the consensus scores were used for analysis. For hyoid bone displacement, 10% of the measurements (stills of all consistencies in lateral view pre- and post-intervention) were repeated by the first author (to assess intrarater reliability), and 10 % were reviewed by the SLP (to assess interrater reliability). Measurements were deemed in concordance if pairwise testing showed a greater than 95% chance of measuring clinically indistinguishable values in the two measurement sessions[22, 38].

Oral intake and nutritional status

Oral intake was assessed with the Functional Oral Intake Scale (FOIS) and nutritional status with BMI and weight change. The FOIS ranges from 1–7 with score 1: nothing by mouth, to score 7: total oral diet without restrictions.

Mouth opening

Maximum mouth opening was measured in millimeters with the disposable TheraBite range of motion scale. Two measurements were performed at both assessment points, with the highest value recorded as the maximum mouth opening. Trismus was defined as a MIO of ≤35 mm[51].

Patient-reported outcomes

Subjective swallowing complaints were recorded pre- and post-training with the validated Dutch version of the 44-item Swallowing Quality of Life (SWAL-QOL) questionnaire[52]. The SWAL-QOL assesses patients' swallowing impairment based on 10 quality of life domains, each ranging from 0–100 with a higher score indicating more impairment. Feasibility and compliance were assessed with a structured study-specific questionnaire (see Appendix II for the English translation of this questionnaire). The study-specific questionnaire also contained a rating of global perceived benefit, and an open question to specify what the experienced benefit was. Additionally, health status was assessed with the EQ-5D questionnaire to provide a simple, generic measure of health for clinical and economic appraisal[53]. The EQ-5D consists of a descriptive system comprising five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) with three levels (no problems, some problems, severe problems) for each dimension, and a visual analogue scale (VAS) recording the respondent's self-rated health on a vertical VAS ranging from 0 to 100[53].

Statistical analyses

The aimed sample size was 20 HNC patients, based on the previous improvements (cohen's d >0.6) demonstrated in the healthy volunteer sample[38]. In this way, the study would have 80% power to detect an effect size (cohen's d) of 0.70 with a power of 80% and an alpha of 0.05, while allowing for a 10% attrition rate, using a paired t-test. For all outcome measures descriptive statistics were generated. Data from muscle strength tests, IOPI measurements, VFS, mouth opening, and questionnaires of the total study population were summarised as medians and median differences, with 95% confidence intervals for the median differences obtained with bootstrapping. Statistical analysis was performed using Statistical Package of Social Sciences (SPSS) software version 23.0.

RESULTS

Although the aim was to include 20 patients, due to the strict inclusion criteria only 18 patients could be included during the planned study period of 1 year. Of these 18 patients, two patients withdrew from the study. One patient decided to withdraw from the study after

the second baseline assessment point, before starting the exercise program. The second patient decided to resign from the study after 3 weeks of exercise due to substantial pain around the temporomandibular joint during the exercises. There was no obvious substrate for that discomfort, but the patient still opted out. At the final check at the second baseline assessment point, a third patient appeared to not meet the inclusion criteria, because she only had slightly affected oral intake (FOIS score: 6) and no penetration/aspiration demonstrated during VFS assessment. She still opted to complete the program, but was excluded for further effect analysis. Hence, 16 patients completed the exercise program, resulting in an overall compliance of 89%, but only 15 patients were included for further effect analysis. All collected data are shown in Table 3 and 4. In the following paragraphs the most relevant results (n=15) are described in more detail.

Feasibility and compliance

Patients executed, as intended, the exercises minimally 6 and maximally 8 weeks (mean: 47 days, median: 45 days, range: 40–56 days). All but one patient had practiced at least 1 session daily during the exercise period. The total duration of the exercises was reported to be 20–30 minutes per session. The patients were familiar with the exercises after a median of 1 week. One patient reported the exercises as 'very unpleasant', 4 patients as 'a bit unpleasant', 8 patients as 'neither pleasant nor unpleasant', and 2 patients as 'a bit pleasant'. The median compliance in terms of the 3 daily exercise sessions was 97% (range 86–100%). At the start of treatment, 6 patients reported (some) muscle pain around their temporomandibular joints during the exercises, which disappeared within 1 hour after completing the exercises in all of them. There was one patient with an episode of aspiration pneumonia during the first week of the trial period.

Muscle strength

All patients started at position 2–4 of the ActiveBand and all but three (#4, #8 and #9) had ultimately reached position 6. Two patients (#2 and #7) were able to go past position 6 by adding a second ActiveBand to further increase resistive load. At the end of treatment, an increase in median chin tuck strength of 13.5 N (95% CI 2.0–29.5 N) was observed, from a median of 31.5 N (95% CI 6.8–45.4 N) at baseline to a median of 49.5N (95% CI 11.8–71.5 N) post-treatment (effect size with cohen's d = 0.7). The median jaw opening strength increased with 22 N (95% CI 11.0–35.3 N), from a median of 21.5N (95% CI 10.5–28.0 N) at baseline to a median of 43.5 N (95% CI 27.3–57.5 N) at the end of treatment (cohen's d = 1.8). The individual improvements are visualized in Figures 4 and 5.

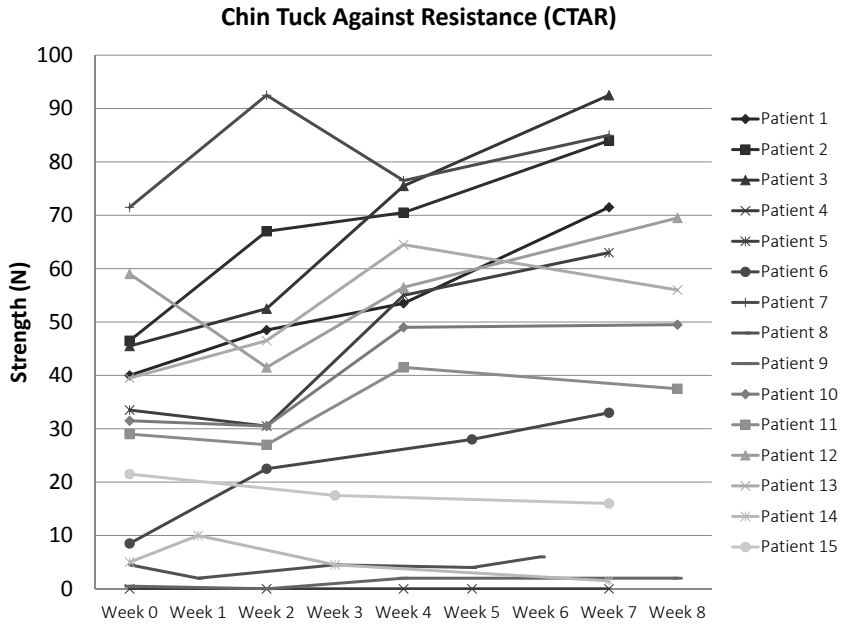


Figure 4. Change in individual maximum chin tuck strength after the 6 to 8-weeks exercise period.

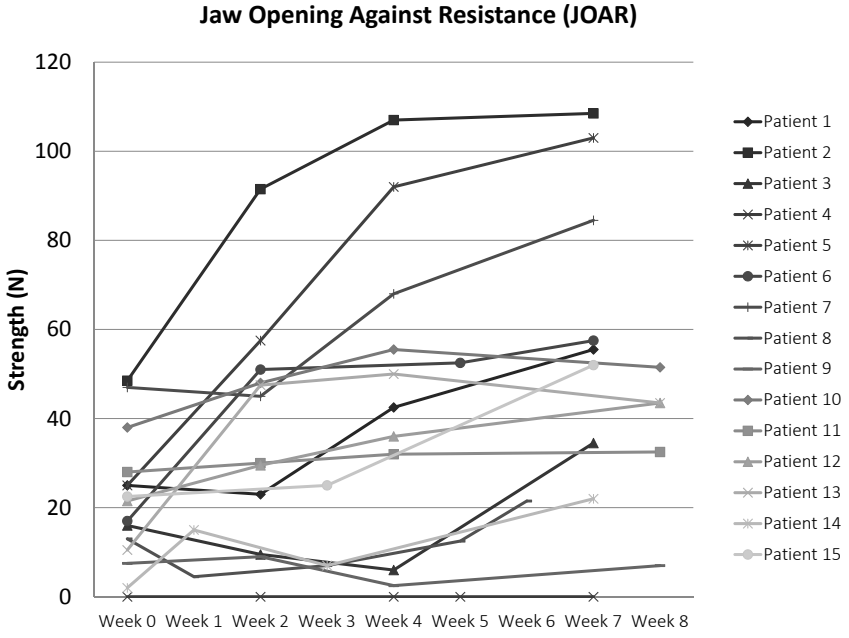


Figure 5. Change in individual maximum jaw opening strength after the 6 to 8-weeks exercise period.

Tongue strength and endurance

Median anterior tongue strength (IOPI) increased with 3.0 kPa (95% CI 0–6.5 kPa), from a median of 34.5 kPa (95% CI 30.5–42.3 kPa) at baseline to a median of 40.0 kPa (95% CI 32.5–49.3 kPa) at the end of treatment. There were no meaningful improvements observed for posterior tongue strength, or anterior tongue endurance.

Swallowing and mouth opening

For thickened liquid swallows, the PAS score had clinically improved in 5 patients (33%): from aspiration to penetration in 3 patients (#5, #10, and #12), and from aspiration/penetration to normal swallowing in 2 patients (#9 and #15; Table 4). The PAS scores had clinically deteriorated in 3 patients (#6, #7, and #11; 20%). The mean PAS score for thickened liquid swallows showed a small to moderate effect size (cohen's d = 0.3). No clinically relevant improvements in other consistencies were observed. There were also no improvements in anterior or superior hyoid bone displacement for the various consistencies used. Based on the FOIS scores, oral intake had improved in 4 patients (#2, #6, #10, #13), and had stayed the same in the remaining 11 patients. There were also 4 patients who had gained some weight following the exercise period (#2, #8, #12, and #15; Table 4), whereas 2 patients had lost some weight (#4 and #14). Mouth opening had slightly increased with a median of 1.0 mm after the training program (95% CI 0–1.0 mm).

Patient-reported outcomes

Results of the SWAL-QOL questionnaire, divided per sub domain are shown in Table 4. Overall, no major improvements at the post-treatment assessment point were observed. After a median of 3 weeks, 14 out of 15 patients reported to benefit from the exercises, varying from 'a little bit' (n=6), to 'quite a bit' (n=7), and to 'a lot' (n=1). Patients mainly reported more confidence and ease during swallowing (some patients had actually tried to eat meat or bread again), and less coughing/choking during a meal.

Patients' overall self-rated health, as assessed with the EQ-5D questionnaire, showed a small improvement from a median of 70 to a median of 75 after treatment. There were no improvements on one of the five dimensions of this questionnaire.

Table 3. Strength training data per patient before and after the training period. Note: patient #2 and #7 were able to add a second ActiveBand on (position 2 of) the SEA at the end of the exercise period. The position of the ActiveBand was specified for exercise 1 and 2. For exercise 3 the same resistance as used for exercise 2 was applied.

Patient	ActiveBand	Swallowing muscle strength		Tongue strength & endurance			Mouth opening
	Position	CTAR (N)	JOAR (N)	Anterior (kPa)	Posterior (kPa)	Endurance (s)	MIO (mm)
1 Pre	4- 3	40.0	25.0	34.5	37.0	22	21
Post	6- 5	71.5	55.5	47.0	48.0	29	21
2 Pre	4- 4	46.5	48.5	32.5	29.5	48	40
Post	6*- 6*	84.0	108.5	34.0	29.0	43	41
3 Pre	4- 2	45.5	16,0	33.5	28.5	44	15
Post	6- 6	92.5	34.5	40.0	37.5	28	15
4 Pre	2- 2	0	0	39.5	35.0	55	20
Post	4- 4	0	0	65.0	32.0	51	21
5 Pre	3- 3	33.5	25.0	39.0	35.0	20	38
Post	6- 6	63.0	103.0	42.0	36.5	25	37
6 Pre	2- 2	8.5	17.0	48.5	30.5	12	37
Post	5- 6	33.0	57.5	43.0	41.5	42	38
7 Pre	6- 4	71.5	47.0	66.0	52.5	36	54
Post	6*- 6*	85.0	84.5	69.0	38.5	38	55
8 Pre	1- 2	4.5	13.0	15.5	14.0	40	37
Post	5- 5.5	6.0	21.5	17.0	15.5	41	35
9 Pre	1- 2	0.5	7.5	45.0	42.0	37	48
Post	5- 5	2.0	7.0	51.5	47.5	51	51
10 Pre	3- 4	31.5	38.0	18.0	10.5	22	29
Post	6- 6	49.5	51.5	15.5	12.5	34	30
11 Pre	3- 3	29.0	28.0	35.5	12.5	5	51
Post	6- 5	37.5	32.5	35.5	10.0	3	54
12 Pre	4- 3	59.0	21.5	30.5	31.0	11	33
Post	6- 5	69.5	43.5	32.5	29.0	11	33
13 Pre	4- 2	39.5	10.5	63.0	47.0	14	31
Post	6- 5	56.0	43.5	70.0	53.5	12	40
14 Pre	3- 2	5.0	2.0	27.5	25.5	12	20
Post	6- 6	7.5	22.0	22.5	28.5	37	21
15 Pre	3- 2	21.5	22.5	31.0	33.0	31	42
Post	6- 5.5	16.0	52.0	36.5	40.5	30	43
Median (95% CI) pre		31.5 (7–45)	21.5 (11–28)	34.5 (31–42)	31 (27–36)	22 (12–39)	37 (25–41)
Median (95% CI) post		49.5 (12–72)	43.5 (27–58)	40.0 (33–49)	36.5 (29–42)	34 (27–42)	37 (26–42)
Median (95% CI) change		13.5 (2–30)	22.0 (11–35)	3.0 (0–7)	2.0 (-1–8)	1.0 (-2.0–9.5)	1.0 (0–1.0)

Abbreviations: CTAR = Chin Tuck Against Resistance; JOAR = Jaw Opening Against Resistance; ANT = anterior; POST = posterior; END = endurance; MIO = Maximal Interincisor Opening; N = Newton; kPa = kilopascal; s = seconds; mm = millimetres; CI = Confidence Interval.

Table 4. VFS, nutrition, and patient-reported data on swallowing function per patient before and after the training period. Note: patient #3, #4, and #5 were still (completely) feeding tube dependent at the post-treatment assessment point. Hence, the post-treatment SWAL-QOL results were identical to their previous results.

				PAS				SSQ	SWAL-QOL										EQ-5D
Patient		Weight	FOIS	Thin 3cc	10cc	Thick 5cc	Solid cake	Did you benefit?	General Burden	Food selection	Eating duration	Eating desire	Fear of eating	Sleep	Fatigue	Commu-nication	Mental Health	Social Function	Symptom scale	Self-rated health
1	Pre	85	1	8	8	4	8		88	NA	NA	75	100	13	50	63	75	65	NA	75
	Post	85	1	6	8	3	8	+	88	NA	NA	75	100	50	25	63	75	65	NA	75
2	Pre	72	6	1	4	1	3		38	25	50	58	44	13	17	50	55	25	63	90
	Post	73	7	1	4	1	1	–	38	38	63	17	38	0	0	50	30	25	50	90
3	Pre	76	1	8	8	8	8		100	NA	NA	100	NA	0	0	75	75	65	NA	70
	Post	76	1	8	8	8	8	+	100	NA	NA	100	NA	0	0	75	75	65	NA	60
4	Pre	45	2	8	8	8	3		100	50	75	42	75	75	83	25	40	60	71	15
	Post	42	2	8	8	8	3	++	100	50	75	42	75	75	83	25	40	60	70	25
5	Pre	70	1	8	8	8	8		50	NA	NA	75	NA	0	25	50	56	55	NA	75
	Post	70	1	8	8	2	8	++	50	NA	NA	75	NA	0	25	50	56	55	NA	75
6	Pre	98	4	1	2	1	1		50	63	25	42	63	63	75	25	45	60	54	60
	Post	98	5	4	4	3	1	+	50	38	38	50	69	63	50	75	50	55	52	70
7	Pre	72	2	8	5	3	1		100	NA	NA	50	100	0	17	0	55	70	54	60
	Post	72	2	5	6	5	3	++	88	NA	NA	50	100	25	0	0	45	70	52	50
8	Pre	67	5	7	8	6	4		0	0	0	17	0	38	83	0	0	20	11	75
	Post	69	5	7	8	7	4	++	25	0	0	17	19	63	42	38	0	0	30	60
9	Pre	48	7	4	8	5	1		0	25	38	33	44	25	33	25	0	0	30	90
	Post	48	7	8	8	1	1	+	0	0	63	33	44	25	25	25	0	0	23	90
10	Pre	58	5	7	7	8	5		75	88	63	67	6	50	42	100	90	65	46	80
	Post	58	6	7	7	4	5	++	63	75	88	42	25	50	33	75	75	65	52	90
11	Pre	65	5	8	8	3	3		100	75	100	75	69	50	50	75	80	70	66	60
	Post	65	5	8	2	8	1	+	88	50	88	75	50	50	50	50	95	70	55	70
12	Pre	62	6	8	8	6	2		38	25	63	33	56	63	67	50	35	25	57	70
	Post	65	6	7	8	4	2	+++	50	38	63	8	44	63	33	50	25	25	43	85
13	Pre	62	6	1	8	1	1		50	38	100	83	25	25	33	38	5	25	39	50
	Post	62	7	5	8	1	1	++	50	0	75	17	44	38	75	25	0	60	21	75
14	Pre	76	5	1	8	1	8		75	50	100	50	56	63	58	75	75	35	68	70
	Post	75	5	1	6	1	8	++	63	63	100	42	38	75	50	50	35	20	57	78
15	Pre	76	3	4	8	8	8		75	50	63	50	63	38	50	50	50	65	27	70
	Post	77	3	1	8	1	8	+	63	25	63	33	63	63	50	38	50	50	36	63

Abbreviations: FOIS = Functional Oral Intake Scale; PAS = Penetration Aspiration Scale; SSQ = Study-Specific Questionnaire:- means no benefit, + means a little benefit, ++ means quite some benefit, +++ means a lot of benefit; SWAL-QOL = Swallowing Quality of Life questionnaire; NA = not applicable.

DISCUSSION

This study prospectively investigated the feasibility, compliance, and short-term efficacy of an intensive strength training protocol with a dedicated Swallow Exercise Aid (SEA) in HNC patients with chronic dysphagia after treatment with (chemo-)radiotherapy, who had been refractory for usual care. Regarding the first aim of the study, the results showed that the exercises were indeed feasible in the current patient cohort with often atrophied and/or fibrosed swallowing muscles, with almost all patients executing the exercises according to the protocol. The patients were also compliant with the prescribed exercises. Despite their long-lasting dysphagia, they were eager to participate, resulting in high overall compliance (89%), and high compliance with regards to the set daily exercise sessions (97%). The 15 evaluated patients had missed only 0 to 14% (median 3%) of the targeted number of exercise sessions. The majority of patients even continued practicing after the study period, because they experienced clinical benefits (i.e. more confidence and ease during swallowing/eating) since they had started their exercises. The closure of the chin bar onto the chest bar and the option to increase resistance with this band gave biofeedback for patient's performance. This was supported by anecdotal feedback from our patients, and is a strong point of the device, since it improves patients' compliance with the exercises[38].

Secondly, with respect to the short-term efficacy of this SEA-based exercise regimen, it can be concluded that the swallowing muscles are still trainable. Results of the strength tests showed substantial improvements in strength of the trained muscles in almost all patients, with a median increase of 13.5 N for chin tuck strength, 21.5 N for jaw opening strength, and 3.0 kPa for anterior tongue strength. This coincides well with the observation that all but three patients had been able to ultimately reach position 6 of the ActiveBand, with two of them being able to add a second band.

It should be noted, though, that the posterior tongue strength did not increase much, and that the median increase in chin tuck strength of 13.5 N is just below the smallest detectable change (SDC) of 15 N, based on the established reliability, implicating that the observed increase in chin tuck strength cannot be attributed to the exercise regimen with complete confidence. Three patients (#4, #8, and #9) showed no major improvements in muscle strength. Their scores remained below 10 N, and they were considered 'non-responders'. However, half of the patients achieved an increase in chin tuck strength that well exceeded the SDC, and the median increase in jaw opening strength of 22 N is well above the SDC of 7.5 N for this test, which indicates that this increase is confidently attributable to the SEA exercises. As compared to the formerly ICC values obtained from healthy subjects[38], the test-retest reliability of the muscle strength assessment setup in the current patient population was good. Hence, the current ICC values indicate that the muscle strength measurement procedure is highly reliable and suitable for future use in individual patients.

Interestingly, the median strengths of 31.5 and 49.5 N for chin tuck and jaw opening, respectively, at the post-treatment assessment point were still considerably lower than the >80 N achieved by 10 healthy subjects at the pre-treatment assessment point in our previous study[38]. This was also demonstrated for maximum anterior and posterior tongue strength, with maximum values of 36.5 to 40 kPa in our HNC patient cohort, as compared to values of >60 kPa in healthy subjects[38]. This clearly underlines that damaged, atrophied and/or fibrosed muscles due to radiation loose (part of) their function. One could question whether 6 to 8 weeks of strength training is enough to achieve sufficient increase in muscle strength for clinical improvements in these (often feeding tube dependent) patients more than 10-years post-treatment. On the other hand, most increase in muscle strength in the individual patients was observed in the first weeks of treatment. In particular in this stage, central and neuromuscular adaptations (and not yet hypertrophy) do occur. The question is therefore whether ongoing training will lead to a further increase in muscle strength, or whether a plateau will be reached after optimization of the remaining muscle function. At least, the present study shows that these damaged muscles are, up to a certain point, still trainable.

To date, there are no large clinical trials that have studied and proven efficacy for rehabilitative (swallow and/or non-swallow) exercises for their long-term effect in patients with HNC and chronic dysphagia[24, 35], except for the Shaker exercise[18, 25, 28]. As swallow exercises are applied to make a swallow stronger or faster[29], the advantage of non-swallow exercises is that they allow patients to improve through a training protocol safely without limitations that may be imposed during swallowing, or during nothing per oral status. Especially the combination of swallow and non-swallow exercises, leading to different activation patterns encountered during various swallowing circumstances, may be more effective[32]. Obviously, the effortful swallow exercise of the current SEA-based exercise protocol is in concordance with the specificity principle of neural plasticity[29, 34, 35]. And also the muscle overload principle is applicable to the SEA exercises. By contrast, the amount of load in the Shaker exercise is not easily quantifiable, and cannot be manipulated progressively over the course of treatment[32]. Moreover, the sternocleidomastoid muscles are probably significantly more activated and fatigued during the Shaker exercise than during the SEA exercises[42]. As swallowing is a submaximal activity[32], whereby increase in muscle volume is not the focal point, for the current study a resistive load of approximately 60–70% of the estimated 1RM was maintained as the resistance level. Besides, in this HNC patient population with chronic, severe dysphagia, hypertrophy is anyway not expected.

Unfortunately, the increase in muscle strengths did not result in overall better functional swallowing ability, since the clinical swallowing outcomes (i.e. FOIS and PAS scores), and hyoid elevation did not improve after the training period. Apparently, 6 to 8 weeks of strength training are probably not enough for achieving improvements in clinical endpoints in this

challenging patient population. Although results of the study-specific questionnaire revealed some improvements as perceived by the patients themselves (and certainly no harm), these results did not correspond with the improvements in muscle strength. As reported by Langmore et al. (2015), the suggestion is made that 'the simple act of practicing swallowing will improve the patients' skill, ease, and rate of eating, helping them to more safely and efficiently swallow more challenging foods'[24]. This is in line with a recent study of Hutcheson et al., who found in particular small improvements in functional status or quality of life after an individualized, high-intensity swallowing therapy program in more or less the same patient population, with few major improvements such as tube removal or improved PAS scores[54]. However, another explanation could be that other muscles involved in swallowing play an important role, or that fibrosis or nerve dysfunction at long-term prohibit functional improvement in spite of improved muscle strength.

In conclusion, this study investigated a SEA-based strength training protocol with swallow and non-swallow exercises for the rehabilitation of chronic, therapy-resistant dysphagia in HNC patients. Feasibility and compliance appeared to be high and some objective and subjective effects of progressive load on muscle strength and swallowing function were demonstrated, indicating that the swallowing muscles at long-term still are trainable. To further study the efficacy and effectiveness of rehabilitative exercises in patients with chronic dysphagia, larger, prospective studies of longer duration ensuring adequate numbers of patients, and structured treatment protocols are needed[16, 32].

Since significant benefits of preventive exercises during organ-preservation treatment already have been demonstrated[14, 16, 55, 56], and major clinical improvements at long-term seem difficult, starting rehabilitation before treatment onset, or at least as soon as possible in case of post-treatment rehabilitation, is preferable. Further, a minimum baseline muscle strength of 10 N or higher seems to be required, since the non-responders all showed baseline muscle strengths below 10 N, and the device appeared to work better with the resistance minimally on position 2 or higher. Therefore, as a next step in the validation process of the SEA-based exercise protocol, a following phase 3 randomized controlled trial in the preventive or early rehabilitation setting of HNC treatment is planned.

ACKNOWLEDGEMENTS

Wim Kraan, emeritus-technician at the Netherlands Cancer Institute, is greatly acknowledged for the technical construction of the Swallow Exercise Aid (SEA). Jan-Ove Persson (Atos Medical, Hörby, Sweden) and Corina J van As-Brooks (PhD, SLP, MBA; Atos Medical and Netherlands Cancer Institute) are acknowledged for their input in the development of the SEA. Merel Latenstein (SLP; the Netherlands Cancer Institute), Hanneke Kalf (SLP, PhD; Radboud University) and Simone Knuijt (SLP; Radboud University) are acknowledged for their support with the patient selection. Prof. dr. J.H.A.M. Kaanders is greatly acknowledged for sorting out the relevant data on previous radiotherapy treatment in the Radboud University, Nijmegen.

Appendix I. Patient exercise log

M14SEA

Phase-1/2 clinical trial on the treatment of chronic dysphagia in head and neck cancer patients with dedicated strengthening exercises using the Swallow Exercise Aid

Patient Exercise Log

Name: .....

Date of birth: .....

Instructions:

Please note if you have performed your exercises three times a day during the total exercise period

* If you have performed your exercises less than 3 times a day, please note the number of practice sessions during that day

* If you haven't performed your exercises one day, please leave that day empty

Week 1 / 2 / 3 / 4 5 / 6 / 7 / 8		**Exercise 1** Chin Tuck Against Resistance		**Exercise 2** Jaw Opening Against Resistance		**Exercise 3** Effortful Swallow	**Remarks**
		30 x	*3 x 60s*	*30 x*	*3 x 60s*	*10 x*	
Monday	*Morning*						
	Afternoon						
	Evening						
Tuesday	*Morning*						
	Afternoon						
	Evening						
Wednesday	*Morning*						
	Afternoon						
	Evening						
Thursday	*Morning*						
	Afternoon						
	Evening						
Friday	*Morning*						
	Afternoon						
	Evening						
Saturday	*Morning*						
	Afternoon						
	Evening						
Sunday	*Morning*						
	Afternoon						
	Evening						

Appendix II. Study-specific questionnaire

Please fill in this questionnaire at the follow-up visit at the end of the exercise period.

1) Have you performed your exercises three times a day?
   1= yes (continue to question 6)
   2= no, I have exercised approximately …… times a **day**
   3= no, I have exercised approximately …… times a **week**

2) After how many days did you stop with your exercises?
   After day #:

3) Why did you stop with your exercises?

4) Did you re-continue your exercises after you having stopped earlier?
   1= yes
   2= no (continue to question 6)

5) After how many days did you re-continue?
   After …… days

6) How many days did you perform the exercises in total?
   Number of days:

7) How did you experience the exercises?
   1= very unpleasant
   2= a bit unpleasant
   3= not unpleasant or pleasant
   4= quite pleasant
   5= very pleasant

8) Can you try to explain why?

9) How many days did it take you to get used to the exercises?
   Approximately …… days:

10) Did you have the feeling to benefit from the exercises?
    1= not at all
    2= a little bit
    3= quite a bit
    4= very much

11) If yes, can you try to explain what benefit?

12) After how many days, if any, did you notice this benefit?
    After …… days:

13) Did you have problems getting used to or performing the exercises?

14) What is your general impression of the exercises?

15) Would you keep practicing, if recommended by your therapist?
    1= yes, absolutely
    2= probably
    3= probably not
    4= no

16) General remarks:

REFERENCES

1. Nguyen NP, Moltz CC, Frank C, Vos P, Smith HJ, Karlsson U, et al. Dysphagia following chemoradiation for locally advanced head and neck cancer. Ann Oncol. 2004;15:383-8.
2. Eisbruch A, Schwartz M, Rasch C, Vineberg K, Damen E, Van As CJ, et al. Dysphagia and aspiration after chemoradiotherapy for head-and-neck cancer: which anatomic structures are affected and can they be spared by IMRT? Int J Radiat Oncol Biol Phys. 2004;60:1425-39.
3. Lewin JS. Dysphagia after chemoradiation: prevention and treatment. Int J Radiat Oncol Biol Phys. 2007;69:S86-7.
4. Caudell JJ, Schaner PE, Meredith RF, Locher JL, Nabell LM, Carroll WR, et al. Factors associated with long-term dysphagia after definitive radiotherapy for locally advanced head-and-neck cancer. Int J Radiat Oncol Biol Phys. 2009;73:410-5.
5. Chen AM, Li BQ, Lau DH, Farwell DG, Luu Q, Stuart K, et al. Evaluating the role of prophylactic gastrostomy tube placement prior to definitive chemoradiotherapy for head and neck cancer. Int J Radiat Oncol Biol Phys. 2010;78:1026-32.
6. Agarwal J, Palwe V, Dutta D, Gupta T, Laskar SG, Budrukkar A, et al. Objective assessment of swallowing function after definitive concurrent (chemo)radiotherapy in patients with head and neck cancer. Dysphagia. 2011;26:399-406.
7. Langmore S, Krisciunas GP, Miloro KV, Evans SR, Cheng DM. Does PEG use cause dysphagia in head and neck cancer patients? Dysphagia. 2012;27:251-9.
8. Hutcheson KA, Yuk MM, Holsinger FC, Gunn GB, Lewin JS. Late radiation-associated dysphagia with lower cranial neuropathy in long-term oropharyngeal cancer survivors: video case reports. Head Neck. 2015;37:E56-62.
9. Kraaijenga SA, van der Molen L, van den Brekel MW, Hilgers FJ. Current assessment and treatment strategies of dysphagia in head and neck cancer patients: a systematic review of the 2012/13 literature. Curr Opin Support Palliat Care. 2014;8:152-63.
10. Riffat F, Gunaratne DA, Palme CE. Swallowing assessment and management pre and post head and neck cancer treatment. Curr Opin Otolaryngol Head Neck Surg. 2015;23:440-7.
11. Kulbersh BD, Rosenthal EL, McGrew BM, Duncan RD, McColloch NL, Carroll WR, et al. Pretreatment, preoperative swallowing exercises may improve dysphagia quality of life. Laryngoscope. 2006;116:883-6.
12. Carroll WR, Locher JL, Canon CL, Bohannon IA, McColloch NL, Magnuson JS. Pretreatment swallowing exercises improve swallow function after chemoradiation. Laryngoscope. 2008;118:39-43.
13. van der Molen L, van Rossum MA, Burkhead LM, Smeele LE, Rasch CR, Hilgers FJ. A randomized preventive rehabilitation trial in advanced head and neck cancer patients treated with chemoradiotherapy: feasibility, compliance, and short-term effects. Dysphagia. 2011;26:155-70.
14. Carnaby-Mann G, Crary MA, Schmalfuss I, Amdur R. "Pharyngocise": randomized controlled trial of preventative exercises to maintain muscle structure and swallowing function during head-and-neck chemoradiotherapy. Int J Radiat Oncol Biol Phys. 2012;83:210-9.
15. van der Molen L, van Rossum MA, Rasch CR, Smeele LE, Hilgers FJ. Two-year results of a prospective preventive swallowing rehabilitation trial in patients treated with chemoradiation for advanced head and neck cancer. Eur Arch Otorhinolaryngol. 2013.
16. Virani A, Kunduk M, Fink DS, McWhorter AJ. Effects of 2 different swallowing exercise regimens during organ-preservation therapies for head and neck cancers on swallowing function. Head Neck. 2015;37:162-70.
17. van den Berg MG, Kalf JG, Hendriks JC, Takes RP, van Herpen CM, Wanten GJ, et al. Normalcy of food intake in patients with head and neck cancer supported by combined dietary counseling and swallowing therapy: A randomized clinical trial. Head Neck. 2014.
18. Shaker R, Easterling C, Kern M, Nitschke T, Massey B, Daniels S, et al. Rehabilitation of

swallowing by exercise in tube-fed patients with pharyngeal dysphagia secondary to abnormal UES opening. Gastroenterology. 2002;122:1314-21.

19. Robbins J, Gangnon RE, Theis SM, Kays SA, Hewitt AL, Hind JA. The effects of lingual exercise on swallowing in older adults. J Am Geriatr Soc. 2005;53:1483-9.

20. Robbins J, Kays SA, Gangnon RE, Hind JA, Hewitt AL, Gentry LR, et al. The effects of lingual exercise in stroke patients with dysphagia. Arch Phys Med Rehabil. 2007;88:150-8.

21. Yeates EM, Molfenter SM, Steele CM. Improvements in tongue strength and pressure-generation precision following a tongue-pressure training protocol in older individuals with dysphagia: three case reports. Clin Interv Aging. 2008;3:735-47.

22. Logemann JA, Rademaker A, Pauloski BR, Kelly A, Stangl-McBreen C, Antinoja J, et al. A randomized study comparing the Shaker exercise with traditional therapy: a preliminary study. Dysphagia. 2009;24:403-11.

23. Wada S, Tohara H, Iida T, Inoue M, Sato M, Ueda K. Jaw-opening exercise for insufficient opening of upper esophageal sphincter. Arch Phys Med Rehabil. 2012;93:1995-9.

24. Langmore SE, McCulloch TM, Krisciunas GP, Lazarus CL, Van Daele DJ, Pauloski BR, et al. Efficacy of electrical stimulation and exercise for dysphagia in patients with head and neck cancer: A randomized clinical trial. Head Neck. 2015.

25. Logemann JA. Evaluation and treatment of swallowing disorders. Texas, Austin: Pro-ed; 1998.

26. Hind JA, Nicosia MA, Roecker EB, Carnes ML, Robbins J. Comparison of effortful and noneffortful swallows in healthy middle-aged and older adults. Arch Phys Med Rehabil. 2001;82:1661-5.

27. Lazarus C, Logemann JA, Song CW, Rademaker AW, Kahrilas PJ. Effects of voluntary maneuvers on tongue base function for swallowing. Folia Phoniatr Logop. 2002;54:171-6.

28. Shaker R, Kern M, Bardan E, Taylor A, Stewart ET, Hoffmann RG, et al. Augmentation of deglutitive upper esophageal sphincter opening in the elderly by exercise. Am J Physiol. 1997;272:G1518-22.

29. Robbins J, Butler SG, Daniels SK, Diez Gross R, Langmore S, Lazarus CL, et al. Swallowing and dysphagia rehabilitation: translating principles of neural plasticity into clinically oriented evidence. J Speech Lang Hear Res. 2008;51:S276-300.

30. Powers SK, Howley ET. Exercise Physiology. New York: McGraw-Hill; 2001.

31. Rhea MR, Alvar BA, Burkett LN, Ball SD. A meta-analysis to determine the dose response for strength development. Med Sci Sports Exerc. 2003;35:456-64.

32. Burkhead LM, Sapienza CM, Rosenbek JC. Strength-training exercise in dysphagia rehabilitation: principles, procedures, and directions for future research. Dysphagia. 2007;22:251-65.

33. Steele CM. Exercise-based approaches to dysphagia rehabilitation. Nestle Nutr Inst Workshop Ser. 2012;72:109-17.

34. Kleim JA, Jones TA. Principles of experience-dependent neural plasticity: implications for rehabilitation after brain damage. J Speech Lang Hear Res. 2008;51:S225-39.

35. Langmore SE, Pisegna JM. Efficacy of exercises to rehabilitate dysphagia: A critique of the literature. Int J Speech Lang Pathol. 2015;17:222-9.

36. Sapienza CM, Wheeler K. Respiratory muscle strength training: functional outcomes versus plasticity. Semin Speech Lang. 2006;27:236-44.

37. Retel VP, van der Molen L, Steuten LM, van den Brekel MW, Hilgers FJ. A cost-effectiveness analysis of using TheraBite in a preventive exercise program for patients with advanced head and neck cancer treated with concomitant chemo-radiotherapy. Eur Arch Otorhinolaryngol. 2015.

38. Kraaijenga SA, van der Molen L, Stuiver MM, Teertstra HJ, Hilgers FJ, van den Brekel MW. Effects of Strengthening Exercises on Swallowing Musculature and Function in Senior Healthy Subjects: a Prospective Effectiveness and Feasibility Study. Dysphagia. 2015;30:392-403.

39. Watts CR. Measurement of hyolaryngeal muscle activation using surface electromyography for comparison of two rehabilitative dysphagia exercises. Arch Phys Med Rehabil. 2013;94:2542-8.

40. Hughes T, Watts CR. Effects of 2 Resistive Exercises on Electrophysiological Measures of Submandibular Muscle Activity. Arch Phys Med Rehabil. 2015.

41. Mishra A, Rajappa A, Tipton E, Malandraki GA. The Recline Exercise: Comparisons with the Head Lift Exercise in Healthy Adults. Dysphagia. 2015;30:730-7.

42. Sze WP, Yoon WL, Escoffier N, Rickard Liow SJ. Evaluating the Training Effects of Two Swallowing Rehabilitation Therapies Using Surface Electromyography-Chin Tuck Against Resistance (CTAR) Exercise and the Shaker Exercise. Dysphagia. 2016.

43. Yoon WL, Khoo JK, Rickard Liow SJ. Chin tuck against resistance (CTAR): new method for enhancing suprahyoid muscle activity using a Shaker-type exercise. Dysphagia. 2014;29:243-8.

44. Adams V, Mathisen B, Baines S, Lazarus C, Callister R. A Systematic Review and Meta-analysis of Measurements of Tongue and Hand Strength and Endurance Using the Iowa Oral Performance Instrument (IOPI). Dysphagia. 2013.

45. Hewitt A, Hind J, Kays S, Nicosia M, Doyle J, Tompkins W, et al. Standardized instrument for lingual pressure measurement. Dysphagia. 2008;23:16-25.

46. Logemann JA. Evaluation and treatment of swallowing disorders. Texas, Austin: Pro-ed (2nd ed); 1998.

47. Rosenbek JC, Robbins JA, Roecker EB, Coyle JL, Wood JL. A penetration-aspiration scale. Dysphagia. 1996;11:93-8.

48. Leonard RJ, Kendall KA. Dysphagia assessment and treatment planning: a team approach. San Diego: Singular Pub. Group.; 1997.

49. Leonard RJ, Kendall KA, McKenzie S, Goncalves MI, Walker A. Structural displacements in normal swallowing: a videofluoroscopic study. Dysphagia. 2000;15:146-52.

50. Pauloski BR, Rademaker AW, Logemann JA, Stein D, Beery Q, Newman L, et al. Pretreatment swallowing function in patients with head and neck cancer. Head Neck. 2000;22:474-82.

51. Dijkstra PU, Huisman PM, Roodenburg JL. Criteria for trismus in head and neck oncology. Int J Oral Maxillofac Surg. 2006;35:337-42.

52. Lemmens J, Bours GJ, Limburg M, Beurskens AJ. The feasibility and test-retest reliability of the Dutch SWAL-QOL adapted interview version for dysphagic patients with communicative and/or cognitive problems. Qual Life Res. 2013;22:891-5.

53. Dolan P. Modeling valuations for EuroQOL health states. Med Care. 1997;35:1095-108.

54. Hutcheson KA, Kelly S, Barrow MP, Barringer DA, Perez DP, Little LG, et al. Offering More for Persistent Dysphagia after Head & Neck Cancer: The Evolution of Boot Camp Swallowing Therapy. http://wwwresearchposterscom/Posters/COSM/COSM2015/C058pdf. 2015.

55. van der Molen L, van Rossum MA, Rasch CR, Smeele LE, Hilgers FJ. Two-year results of a prospective preventive swallowing rehabilitation trial in patients treated with chemoradiation for advanced head and neck cancer. Eur Arch Otorhinolaryngol. 2014;271:1257-70.

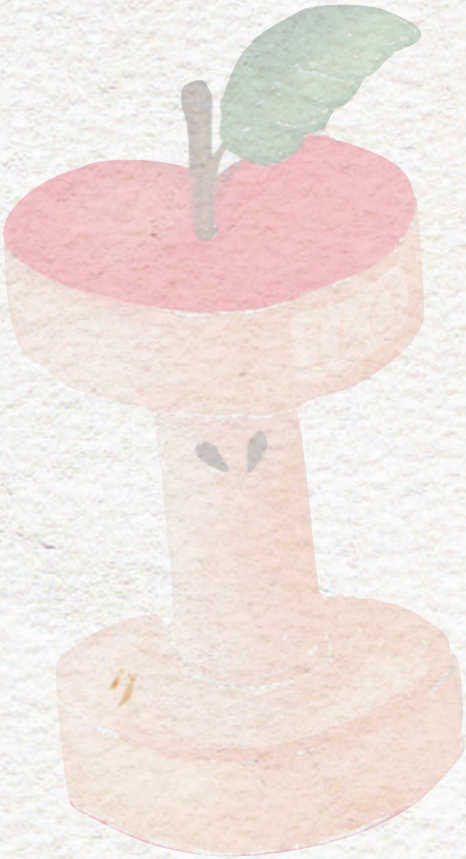
56. Kotz T, Federman AD, Kao J, Milman L, Packer S, Lopez-Prieto C, et al. Prophylactic swallowing exercises in patients with head and neck cancer undergoing chemoradiation: a randomized trial. Arch Otolaryngol Head Neck Surg. 2012;138:376-82.

CHAPTER 9

Feasibility and potential value of lipofilling in post-treatment oropharyngeal dysfunction

S.A.C. Kraaijenga
O. Lapid
L. van der Molen
F.J.M. Hilgers
L.E. Smeele
M.W.M. van den Brekel

The Laryngoscope. Online 2016 Apr 14.



ABSTRACT

Objective: Head and neck cancer (HNC) patients may develop oropharyngeal dysfunction as result of volume loss or muscle atrophy of the tongue or pharyngeal musculature following treatment with surgery and/or chemoradiotherapy. If intensive swallowing therapy offers no further improvement, and the functional problems persist, transplantation of autologous adipose tissue (lipofilling) might restore functional outcomes by compensating the existing tissue defects or tissue loss.

Study Design: Case series.

Methods: In this prospective pilot feasibility study, the application of lipofilling was studied in seven HNC patients with chronic dysphagia. The procedure was carried out under general anesthesia in several sessions using the Coleman technique. Swallowing outcomes were evaluated with standard videofluoroscopy (VFS) for obtaining objective Penetration Aspiration Scale (PAS) and residue scores. Subjective Functional Oral Intake Scale scores and SWAL-QOL questionnaires were also completed. MRI was used to evaluate the post-treatment injected fat.

Results: Five patients completed the intended three lipofilling sessions, while two completed two injections. One patient dropped out of the study after two injections because of progressive dysphagia requiring total laryngectomy. Four of the six remaining patients showed improved PAS scores on post-treatment VFS assessments, with two patients no longer showing aspiration for a specific consistency. Two patients were no longer feeding tube dependent. Patient-reported swallowing and oral intake improved in four out of six patients.

Conclusion: Based on the results, the lipofilling technique seems safe and – in selected cases – of potential value for improving swallowing function in this small therapy-refractory HNC patient cohort.

KEY WORDS

Head and Neck Neoplasms – Deglutition – Deglutition Disorders – Lipofilling – Fat Transfer – Autologous Fat Injection

INTRODUCTION

Patients with advanced head and neck cancer (HNC) are usually treated with (a combination of) surgery, radiotherapy, or chemotherapy. Despite increasing survival as a result of improved treatment modalities and combinations for most sites[1], damage to the anatomical structures by the primary tumor or its treatment may adversely impact patients' functional outcome and quality of life. Swallowing problems occur frequently in these patients, and may be a consequence of tissue loss, fibrosis, mucositis, xerostomia, pain and/or trismus[2,3]. The situation may even worsen when the swallowing musculature is no longer actively used, and so-called 'non-use' atrophy occurs, causing further deterioration of swallowing[4].

Many factors contribute to dysphagia, aspiration and even the inability to swallow. Often, due to insufficient contact between the base of tongue and posterior pharyngeal wall, the food bolus is swallowed less powerful, leading to stagnation of food ('residue'), with a high risk of aspiration of the residue. A combination of decreased tongue strength, deficient/reduced hyolaryngeal elevation, lack of pharyngeal constrictor activity, lack of oropharyngeal seal, or insufficient opening of the esophageal inlet may also play a role in aspiration[5,6]. Long term and even lifelong feeding tube dependency is sometimes unavoidable, and quality of life in these patients is often seriously impaired[7].

Current treatment strategies of dysphagia include continued use of swallowing musculature during treatment (the "use it or lose it" concept), by avoiding prolonged periods of nothing per oral and adherence to (prophylactic) targeted swallowing exercises[8]. Although promising results on pharyngeal swallowing function are reported[9,10], severe, therapy-refractory dysphagia may still exist in some patients.

Lipofilling, or fat grafting, is a technique for transplanting autologous, living fat cells within one individual. Due to the regenerative properties of adipose tissue –stem cells have been demonstrated at cellular level[11] – the technique can be used for both aesthetic and reconstructive purposes. Common indications are tissue loss, pain, and/or fibrosis due to surgery, irradiation, burns, or other (post-traumatic) causes[12,13]. To date, except for skin contouring indications[13], lipofilling is rarely used in HNC as there is, to the best of our knowledge, only one case history published about this technique being applied to treat oropharyngeal dysfunction following treatment for HNC[14]. In that study, lipofilling filled the existing defect in the vallecula that was the cause of significant stagnation of the food bolus, and the added volume elevated the epiglottis and thus improved airway protection. In the present study, the feasibility and potential value of lipofilling in seven HNC patients with chronic, therapy-refractory dysphagia was prospectively assessed.

PATIENTS AND METHODS

The present study was designed as a small-scale prospective pilot feasibility study, and was undertaken at the Department of Head and Neck Oncology and Surgery of the Netherlands Cancer Institute in collaboration with the Department of Plastic Surgery of the Academic Medical Center, in Amsterdam, the Netherlands. The study was performed according to guidelines of both institutes and those of the Helsinki Declaration.

Study cohort

All patients had chronic dysphagia (1-year plus) as a consequence of tissue loss and/or muscle atrophy after treatment with surgery or (chemo-) radiotherapy for advanced HNC. Patients were offered to participate after their persistent, seriously debilitating dysphagia appeared to be unresponsive to intensive swallowing training by the Speech Language Pathologist (SLP). None of the patients had been enrolled in a pretreatment prophylactic swallowing exercise program[15].

The initial study cohort consisted of seven patients treated between 1997 and 2012 for advanced HNC, and in complete remission. Six patients had a primary tumor located at the oropharynx (tonsillar arch, pharyngeal wall, base of tongue, and/or vallecula). The other patient had a primary tumor in the oral cavity. The patient and tumor characteristics of the initial patient cohort are summarized in Table 1.

Table 1. Patient- and tumor characteristics at baseline (n=7)

Patient	Gender	Age	Tumor		Treatment		Injection
			Location	TNM	CRT	Surgery	
1	F	71	Base of tongue	Benign	-	2007	Base of tongue
2	M	50	Tonsil	T2N2b	2011	2012	Base of tongue
3	M	63	Vallecula	T2N2b	-	1997	Base of tongue
4	M	40	Tonsil	T4N2c	2007	-	Pharyngeal wall
5	F	59	Base of tongue	T3N2c	2004	-	Base of tongue
6	M	66	Oral cavity	T3N2c	1997	1997	Base of tongue
7	F	70	Pharyngeal wall	T3N2	2000	-	Base of tongue

Abbreviations: F = female; M = male; TNM = Tumor Node Metastasis; CRT = chemoradiotherapy

Informed consent was obtained and the patients were told about the experimental design of the study. Patients were aware that - due to absorption (up to 30-50%) of adipose tissue[16] – multiple (probably at least three) treatment sessions would be necessary before a therapeutic effect could be expected. All patients were free to end their participation at any time during the study.

One patient (#7; Table 1) dropped out of the study due to progression to total laryngectomy. This patient was admitted at our Institute because of severe bowel obstruction not related to her second injection two weeks previously. During the unavoidable hospitalization patient's physical condition deteriorated and she developed twice aspiration pneumonia and respiratory insufficiency, which became so problematic that a permanent tracheotomy was unavoidable. She opted to have a total laryngectomy for controlling her severely disabling and potentially life-threatening aspiration problems. This patient thus went off study and was not further analyzed, but is mentioned here for completeness of the original study cohort.

Procedure and technique

The lipofilling procedure was carried out under general anesthesia using the Coleman technique[17]. This technique aims to prevent damage to the fragile adipose cells as much as possible during transplantation, and thus to promote tissue survival. The procedure starts with harvesting fat cells by aspiration from the upper abdominal wall or inner thigh, after infiltration of antibiotics and tumescence fluid (ringers lactate, lidocaine, and adrenaline). Adipose tissue from the infra-umbilical abdominal wall or inner thigh is very suitable as donor site because of the high number of local fat cells, and the fact that no position change on the operating table is needed[12]. The fat sample is then transferred in 10 ml tubes for centrifugation, which is done for 3 minutes at 3100 rounds per minute, producing 1228 x g centrifugal force. After the centrifugation process, the specimen, besides fat cells, also consists of a layer of oil, a layer of fluid (including blood and tumescent fluid), and a layer of cell pellets/residue. The top supernatant oil and bottom blood cells and debris are then removed with the decanter technique (see Figure 1). The remaining, purified fat cells are then injected using 1cc syringes with blunt tip cannulas (St'rim, Thiebaud SAS, Paris, France) at the predetermined spots, after the mucosa is first punctured using a 21G needle. During injection small aliquots of fat are transferred with multiple passes at different depths. Control of the depth of injection is performed with the non-dominant hand. This is done with multiple passes in order to assure even distribution within the tissue. In Figure 2 a lipofilling injection into the base of tongue is illustrated. For reasons of safety, all patients were hospitalized for observation for one night following the procedure.

Multidimensional assessment

Functional data were collected using multidimensional objective and subjective outcome measures. The protocol included standard videofluoroscopy (VFS) to determine the injection sites based on the degree of contact between the base of tongue and posterior pharyngeal wall during swallowing, and to objectively assess general swallowing function, Penetration and Aspiration Scale (PAS) scores, and overall 'presence of residue' scores. The PAS is a tool with an acceptable reliability and consists of an 8-point scale, ranging from 1–8 (score 1:

material does not enter the airway, to score 8: material enters the airway, passes below the vocal folds, and no effort is made to eject)[18].

Figure 1. After the centrifugation process, the specimen, besides fat cells, also consists of a layer of oil, a layer of fluid (including blood and tumescent fluid), and a layer of cell pellets/residue.

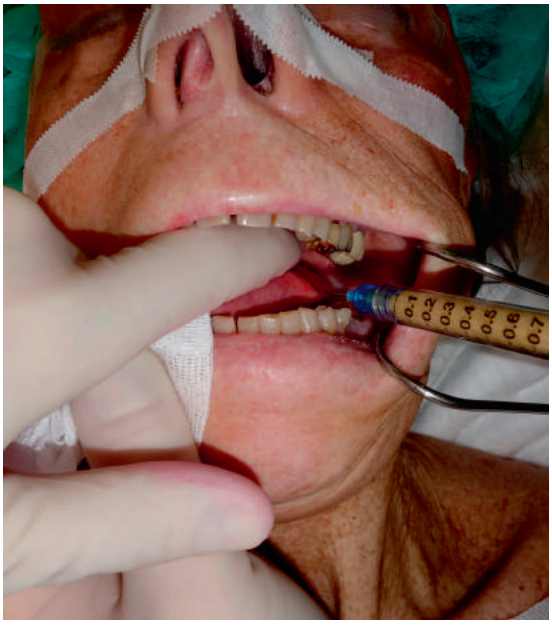


Figure 2. Lipofilling injection into the base of tongue (#7; table 1): intra-orally a long needle is arranged at the lateral tongue edge, and under palpation the tip of the needle is advanced into the base of tongue, where the fat depositions are placed.

The overall 'presence of residue' score ranges from 0–3 (score 0: no residue, to score 3: residue above and below the vallecula, with minimal residue judged as normal)[19,20]. Magnetic Resonance Imaging (MRI) was used to visualize the potential injection site in the oral cavity and pharynx (i.e. to estimate tongue and pharyngeal wall muscles and volumes) and the post-treatment volumes of the injected fat. Additionally, patients' perceived oral intake/nutritional status was assessed with the validated Functional Oral Intake Scale (FOIS; ranging from 1–7 with score 1: nothing by mouth, to score 7: total oral diet without restrictions). Patients' perception of swallowing function was assessed with the Swallowing Quality of Life (SWAL-QOL) questionnaire[21]. The Dutch SWAL-QOL has been translated and validated for use with oral, oropharyngeal, and laryngeal cancer patients. A cut-off score of 14 points (or higher) has been established for identifying HNC patients with clinically relevant swallowing problems swallowing problems. A score difference of 12 points or more is proposed to be used in study designs with multiple assessments[22,23].

All primary outcome parameters were recorded at baseline prior to participation and approximately one to three months after the final fat injection. After each intervention, patients consulted the principal clinician at the outpatient clinic and underwent interim VFS assessments if necessary.

RESULTS

Patient characteristics

All patients had chronic dysphagia, with four patients being (completely) dependent on permanent tube feeding (FOIS ≤3). The other two patients had a restricted diet of only one consistency (FOIS 4) or with specific food limitations (FOIS 6), and were included because of recurrent aspiration pneumonia. Furthermore, two patients with dysphagia were also diagnosed with some degree of dysphonia (articulation disorder).

At baseline, penetration and/or aspiration was demonstrated with VFS in all but one patient. Absent or reduced contact between the base of tongue and pharyngeal wall during swallowing was demonstrated in all six patients, resulting in more than normal contrast residue above and below the hyoid bone. Figure 3 shows a static pre-operative VFS image of one of the patients with a severe atrophied tongue. Furthermore, volume loss or atrophy of the tongue was confirmed with MRI in five patients. In the other patient there was reduced tonsillar tissue (asymmetry) in the right tonsillar arch.

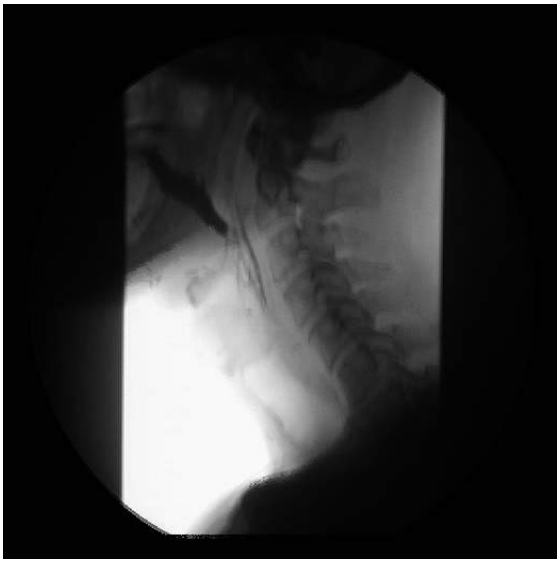


Figure 3. Pre-operative static VFS image of one of the patients (#6) with an atrophied tongue. As can be seen, during swallowing there is hardly any contact (due to volume loss) between the base of tongue and posterior pharyngeal wall.

Procedure and technique

In total 17 autologous fat transplantations were carried out from October 2013 to February 2015, ranging from 2 to 3 sessions per patient with three-month intervals. One patient (#4) noticed insufficient improvement following two lipofilling sessions and decided to discontinue the treatment. The other patients (n=5) had completed the planned (three) consecutive lipofilling sessions. In total 20–35 cc adipose tissue was transplanted in these patients (Table 2). Possible complications at the site of injection, such as necrosis, infection, or intravascular injection were not observed. There were also no complications such as swelling/edema with dyspnea, hematoma formation, scar formation, or damage to the underlying structures on the donor site. Postoperative pain was not reported.

Swallowing outcomes

The functional (applicable) objective and subjective swallowing outcomes per patient pre- and post-treatment are shown in Table 2. The patient (#4) who did not complete the protocol did not show any clinically relevant improvement on the outcome parameters. Of the remaining 5 patients, at 1-2 months follow-up 4 patients had improved on the PAS scores, with 2 patients no longer showing aspiration on follow-up VFS assessments for a specific (thin or thick liquid) consistency. Two of these 4 patients were no longer feeding tube dependent following the lipofilling injections. Patients' subjective perspective on their swallowing function based on

the SWAL-QOL sub scores had improved in these 4 patients, as well (see Table 3). All patients had distinguishable fat deposits spread out at the base of tongue in their post-treatment MRI (median follow-up 14 weeks).

Table 2. Functional objective and subjective swallowing outcomes pre- and post-treatment (n=6)

	Injected fat			Intake	PAS							Residue		
	No.	Amount		FOIS	Thin liquid			Thick liquid			Solid	Thin	Thick	Solid
					≤3cc	5cc	≥10cc	≤3cc	5cc	10cc	cake			
1	3	29,5 cc	Pre	4			3		1	1	3	3	1	3
			Post	6			3		1		1	3	3	1
			Change	+			=		=		+	=	–	+
2	3	30 cc	Pre	1	8			4	6			3	3	
			Post	3	3	3	6		4		2	3	3	3
			Change	+	+				+			=	=	
3	3	20 cc	Pre	6	8		7		6			3	3	
			Post*	5	6	6	6		4		4	3	3	3
			Change	–	+		+		+			=	=	
4	2	11 cc	Pre	1	4			6				3	3	
			Post	1	8			NA				3	1	
			Change	=	–			–				=	+	
5	3	34,5 cc	Pre	1	NA			NA					3	
			Post	6	7			6	6	6		3	3	
			Change	+	+			+					=	
6	3	32 cc	Pre	3			4		4		3	3	3	3
			Post	6	3		4		2		3	3	3	3
			Change	+			=		+		=	=	=	=

Abbreviations/Notes: No. = number; FOIS = Functional Oral Intake Scale: range 1–7; higher scores mean better oral intake; PAS = Penetration Aspiration Scale: range 1–8; lower scores mean better/safer swallowing function; Residue scores: range 0–3 with score 0: no residue, to score 3: residue above and below the vallecula; NA = not applicable (i.e. no transport possible); (+) means improvement, (–) deterioration, and (=) equality; * means minimal compensation maneuver (chin on chest) was applied without instruction.

Case histories

The first case concerns a 71-year old female who had undergone surgical resection of a large benign mucinous cyst adenoma of the tongue in 2007. Afterwards she developed functional swallowing and articulation problems, primarily based on volume loss. Following three consecutive lipofilling sessions into the base of tongue, the patient could swallow solid food much better, as also confirmed with VFS findings, and reported improved speech.

The second patient underwent radiotherapy in 2011 followed by surgical resection and reconstruction in 2012 for a recurrent left tonsillar carcinoma. Extensive treatment by the SLP

did not improve the persisting swallowing problems. However, following three fat injections into the base of tongue, the patient perceived improvement and was able to again resume consistent oral intake alongside his tube feeding.

The third patient participated because of progressive dysphagia after a supraglottic laryngectomy and bilateral cervical lymph node dissection followed by postoperative radiotherapy for a stage IV vallecula carcinoma in 1997. VFS evaluation following the three lipofilling sessions showed no more aspiration of thick liquids, and solids were swallowed more easily.

The fourth case concerns a 40-year old male treated with chemoradiotherapy in 2007 for a stage IV oropharyngeal carcinoma. Severe dysphagia was present directly after treatment. Previous treatments such as physical therapy, hyperbaric oxygen, esophageal dilatation, cricopharyngeal myotomy, and larynx suspension were carried out without success. After two fat injections the patient noticed insufficient improvements and decided to discontinue the treatment.

The fifth patient with a stage IV base of tongue tumor in 2004 was treated with concurrent chemoradiotherapy. She developed severe dysphagia and dysarthria due to oropharyngeal scarring and base of tongue atrophy. Despite intensive swallowing training, the patient remained completely dependent on tube feeding. Aspiration occurred even at 1 cc swallows. MRI showed an atrophic tongue, sagged posteriorly. After three lipofilling injections the patient was able to eat and drink again for the first time since 10 years. The patient was very satisfied, and MRI showed increased tongue volume at the right base of tongue (Figure 4), but VFS evaluation still showed aspiration. At 8 months post-lipofilling, she remains happy with the procedure, although safe oral intake cannot be guaranteed.

The last patient was treated with local resection, partial mandibulectomy and free fibula reconstruction, and post-operative RT in 1997 for a stage IV floor of mouth carcinoma. In 2013 he presented with progressive dysphagia requiring permanent tube feeding. Since exercise therapy for more than one year did not improve the persisting problems, he underwent three lipofilling procedures into the base of tongue. Already after the second injection the patient noticed improvement in swallowing. Following the third injection he resumed oral intake and his feeding tube was removed. VFS assessment confirmed improved PAS scores for thick liquids. The effects are still maintained at 6 months post treatment.

Table 3. Patients' perceived SWAL-QOL scores pre- and post-treatment (n=6)

		SWAL-QOL										
		General Burden	Food selection	Eating duration	Eating desire	Fear of eating	Sleep	Fatigue	Commu-nication	Mental Health	Social Function	Symptom scale
1	Pre											
	Post	75.0	50.0	88.0	17.0	63.0	38.0	8.0	50.0	5.0	20.0	61.0
	Change											
2	Pre	50.0	100.0	100.0	17.0	50.0	0	0	50.0	50.0	60.0	45.0
	Post	25.0	50.0	50.0	33.0	25.0	0	0	25.0	25.0	25.0	25.0
	Change	+	+	+	+	+	=	=	+	+	+	+
3	Pre	100.0	125.0	125.0	67.0	75.0	38.0	67.0	63.0	75.0	15.0	84.0
	Post	0	0	63.0	17.0	44.0	0	0	25.0	10.0	10.0	36.0
	Change	+	+	+	+	+	+	+	+	+	+	+
4	Pre	25.0	25.0	75.0	25.0	38.0	38.0	33.0	100.0	30.0	25.0	45.0
	Post	88.0			75.0	100.0	13.0	50.0	63.0	75.0	65.0	
	Change	–			–	–	+	–	+	–	–	
5	Pre	13.0	75.0	125.0	67.0	38.0	50.0	50.0	25.0	100.0	45.0	95.0
	Post	0	0	0	17.0	0	38.0	42.0	0	0	20.0	11.0
	Change	+	+	+	+	+	+	=	+	+	+	+
6	Pre	88.0	75.0	88.0	50.0	56.0	38.0	50.0	100.0	45.0	55.0	57.0
	Post	25.0	38.0	88.0	25.0	63.0	50.0	50.0	50.0	35.0	55.0	48.0
	Change	+	+	=	+	=	–	=	+	=	=	+

Abbreviations/Notes: SWAL-QOL = Swallowing Quality of Life Questionnaire: range 0–120; lower sores mean better subjective swallowing function; a difference score of 12 points or more was used to demonstrate improvement (+), deterioration (–), or equality (=).

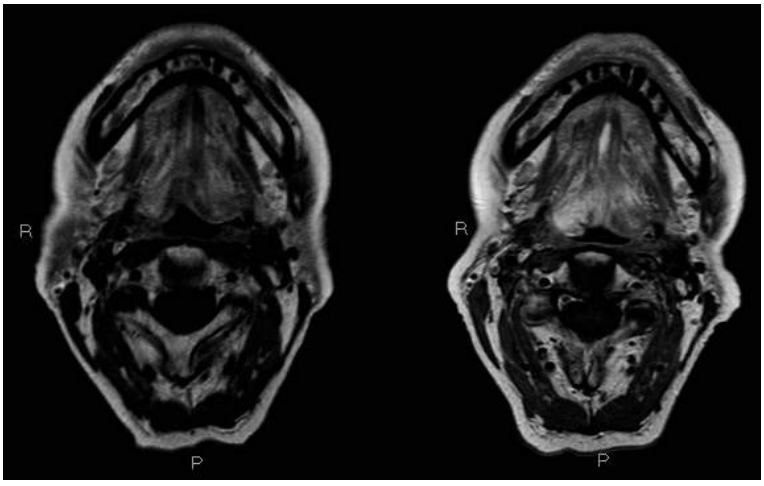


Figure 4. Pre and post-operative MRI showing increased tongue volume as a result of several fat depositions at the right base of tongue (patient #5).

DISCUSSION

In this prospective pilot feasibility study the potential value of autologous adipose tissue transplantation (lipofilling) for improvement of oropharyngeal swallowing was assessed in six HNC patients with chronic dysphagia following HNC treatment, with one additional patient taken off study because of intercurrent disease and subsequent total laryngectomy.

Regarding feasibility and safety of the procedure, in this small series there were no complications or adverse events at the injection or donor site. All patients were admitted for observation for only one postoperative night, and none of the patients developed post-operative problems such as airway obstruction due to edema or swelling by the injected adipose tissue. Also pain was not an issue. Based on this limited experience, we now assume that hospital admissions might not be necessary. For future perspectives this technique might even be performed without general anesthesia, especially in light of the need for multiple injections. It should be stressed, though, that the lipofilling injections were performed very carefully, starting with minimal (4 cc) amounts of adipose tissue, to avoid potential respiratory problems due to post-operative swelling or overfilling in the oropharyngeal area.

The effectiveness of the procedure varied per patient. Although there was one patient who noticed no clear benefit from the lipofilling injections and did not want to complete all three procedures (#4), there were four patients with severe dysphagia reporting significantly better swallowing function after the injections. At follow-up VFS assessments these patients actually showed improvements on some of the FOIS and PAS scores, and two of them were even able to discontinue their enteral feeding. However, swallowing function was still not entirely safe in all of these patients. One patient (#6) experienced improvement in oral intake based on the FOIS scores, while there was no 'true' improvement in function based on the PAS scores. After the lipofilling sessions she had one more episode of aspiration pneumonia treated conservatively, but this did not change her mind about her subjectively improved swallowing (as underlined in her SWAL-QOL results) and resuming her oral intake. This is in line with the literature that patient-reported outcome measures usually provide distinct but complementary information about swallowing [24], and that patients' perceived swallowing function is important for quality of life.

We cannot easily explain the variability in results we observed between the patients. Adding volume is probably not always sufficient in order to restore swallowing function. Obviously, when there is no increase in tissue volume because of insufficient lipofilling, no benefit can be expected. However, despite the fact that a clear volume increase can be accomplished, the lipofilling injections nevertheless did not improve function in all of our patients. Currently, it is well acknowledged that dysphagia post-surgery and/or chemoradiotherapy is multifactorial in its physiological basis, which indicates that other factors such as fibrosis, reduced hyolaryngeal elevation, pharyngeal constrictor activity and/

or insufficient sphincter opening may also be an important factor besides volume loss[5,6]. This might explain why improving just one element was not sufficient to make significant gains for some cases, though it was for others. Hence, further research will be necessary to improve the patient selection for this procedure.

Although for all patients pre- and post-treatment MRIs were available, these were not specifically made according to a protocol enabling accurate volume measurements, but merely to show the persistence of the injected adipose tissue. In fact, the fat deposits were visualized in all patients. MRIs enabling volume measurements, however, might be interesting as part of a future study protocol to substantiate the suggested beneficial effects of lipofilling in HNC.

Adipose tissue is extremely suitable for filling tissue defects because it is autologous and homogeneous in consistency, preventing possible graft-versus-host reactions without realm of artificial fillers that may have complications[11-14]. Nevertheless, it remains difficult to predict how much fat will be resorbed and thus how long a therapeutic effect will persist[16]. With the Coleman technique absorption of fat seems to be reduced as much as possible[13,17], however, three (or more) repeats are probably necessary in order to achieve and hold a therapeutic effect. According to the literature, the favorable outcomes of autologous fat injection are not only due to the filling of soft tissue, but also to the potential regenerative effect of adipose-derived mesenchymal stem cells[12,16]. Possibly the tissue may also become less fibrotic, yet there is no clear evidence for this.

As is often the case in clinical pilot feasibility studies, the sample size of this study was limited to only six patients, and these results should be interpreted with caution. However, the positive clinical outcomes of this study warrant further extensive investigation in larger patient cohorts to study the indications for lipofilling more precisely.

CONCLUSION

In this study, we describe the use of lipofilling in six patients with chronic dysphagia following advanced HNC treatment. The procedure seems feasible and safe, and – in four out of six cases – of value for improving oropharyngeal dysfunction in this small, otherwise therapy-refractory patient cohort.

ACKNOWLEDGEMENTS

This study was made possible by a grants provided by “Stichting de Hoop”, ATOS medical, and the Verwelius Foundation.

REFERENCES

1. Pignon JP, le Maitre A, Maillard E, Bourhis J. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol. 2009;92:4-14.
2. Agarwal J, Palwe V, Dutta D, Gupta T, Laskar SG, Budrukkar A, et al. Objective assessment of swallowing function after definitive concurrent (chemo)radiotherapy in patients with head and neck cancer. Dysphagia. 2011;26:399-406.
3. Nguyen NP, Moltz CC, Frank C, Vos P, Smith HJ, Karlsson U, et al. Dysphagia following chemoradiation for locally advanced head and neck cancer. Ann Oncol. 2004;15:383-8.
4. Chen AM, Li BQ, Lau DH, Farwell DG, Luu Q, Stuart K, et al. Evaluating the role of prophylactic gastrostomy tube placement prior to definitive chemoradiotherapy for head and neck cancer. Int J Radiat Oncol Biol Phys. 2010;78:1026-32.
5. Kos MP, David EF, Aalders IJ, Smit CF, Mahieu HF. Long-term results of laryngeal suspension and upper esophageal sphincter myotomy as treatment for life-threatening aspiration. Ann Otol Rhinol Laryngol. 2008;117:574-80.
6. Lazarus C, Logemann JA, Pauloski BR, Rademaker AW, Helenowski IB, Vonesh EF, et al. Effects of radiotherapy with or without chemotherapy on tongue strength and swallowing in patients with oral cancer. Head Neck. 2007;29:632-7.
7. Metreau A, Louvel G, Godey B, Le Clech G, Jegoux F. Long-term functional and quality of life evaluation after treatment for advanced pharyngolaryngeal carcinoma. Head Neck. 2014;36:1604-10.
8. Kraaijenga SA, van der Molen L, van den Brekel MW, Hilgers FJ. Current assessment and treatment strategies of dysphagia in head and neck cancer patients: a systematic review of the 2012/13 literature. Curr Opin Support Palliat Care. 2014;8:152-63.
9. Carnaby-Mann G, Crary MA, Schmalfuss I, Amdur R. "Pharyngocise": randomized controlled trial of preventative exercises to maintain muscle structure and swallowing function during head-and-neck chemoradiotherapy. Int J Radiat Oncol Biol Phys. 2012;83:210-9.
10. Kraaijenga SA, van der Molen L, Jacobi I, Hamming-Vrieze O, Hilgers FJ, van den Brekel MW. Prospective clinical study on long-term swallowing function and voice quality in advanced head and neck cancer patients treated with concurrent chemoradiotherapy and preventive swallowing exercises. Eur Arch Otorhinolaryngol. 2014.
11. Rigotti G, Marchi A, Galie M, Baroni G, Benati D, Krampera M, et al. Clinical treatment of radiotherapy tissue damage by lipoaspirate transplant: a healing process mediated by adipose-derived adult stem cells. Plast Reconstr Surg. 2007;119:1409-22; discussion 23-4.
12. Hamza A, Lohsiriwat V, Rietjens M. Lipofilling in breast cancer surgery. Gland Surg. 2013;2:7-14.
13. Mazzola RF, Cantarella G, Torretta S, Sbarbati A, Lazzari L, Pignataro L. Autologous fat injection to face and neck: from soft tissue augmentation to regenerative medicine. Acta Otorhinolaryngol Ital. 2011;31:59-69.
14. Navach V, Calabrese LS, Zurlo V, Alterio D, Funicelli L, Giugliano G. Functional base of tongue fat injection in a patient with severe postradiation Dysphagia. Dysphagia. 2011;26:196-9.
15. van der Molen L, van Rossum MA, Burkhead LM, Smeele LE, Rasch CR, Hilgers FJ. A randomized preventive rehabilitation trial in advanced head and neck cancer patients treated with chemoradiotherapy: feasibility, compliance, and short-term effects. Dysphagia. 2011;26:155-70.
16. Tabit CJ, Slack GC, Fan K, Wan DC, Bradley JP. Fat grafting versus adipose-derived stem cell therapy: distinguishing indications, techniques, and outcomes. Aesthetic Plast Surg. 2012;36:704-13.
17. Pu LL, Coleman SR, Cui X, Ferguson RE, Jr., Vasconez HC. Autologous fat grafts harvested and refined by the Coleman technique: a

comparative study. Plast Reconstr Surg. 2008;122:932-7.

18. Rosenbek JC, Robbins JA, Roecker EB, Coyle JL, Wood JL. A penetration-aspiration scale. Dysphagia. 1996;11:93-8.

19. Logemann JA. Evaluation and treatment of swallowing disorders; Pro-ed (2nd edition). Texas, Austin. 1998.

20. Pauloski BR, Rademaker AW, Logemann JA, Stein D, Beery Q, Newman L, et al. Pretreatment swallowing function in patients with head and neck cancer. Head Neck. 2000;22:474-82.

21. Bogaardt HC, Speyer R, Baijens LW, Fokkens WJ. Cross-cultural adaptation and validation of the Dutch version of SWAL-QOL. Dysphagia. 2009;24:66-70.

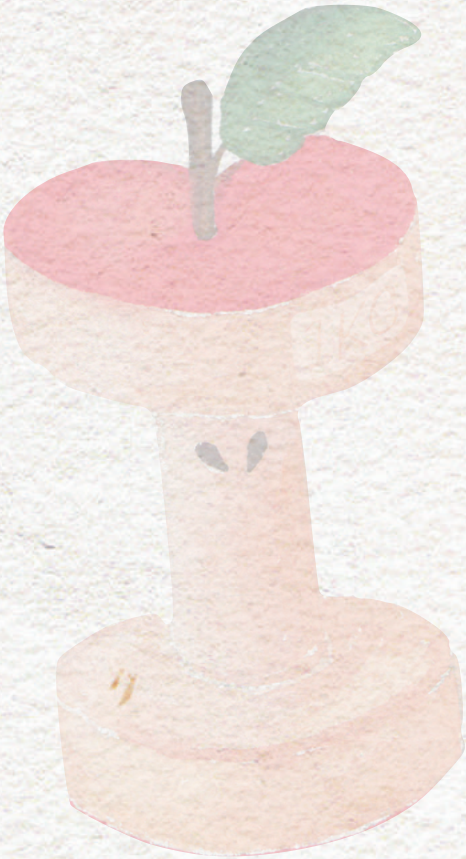
22. Rinkel RN, Verdonck-de Leeuw IM, Langendijk JA, van Reij EJ, Aaronson NK, Leemans CR. The psychometric and clinical validity of the SWAL-QOL questionnaire in evaluating swallowing problems experienced by patients with oral and oropharyngeal cancer. Oral Oncol. 2009;45:e67-71.

23. Rinkel RN, Verdonck-de Leeuw IM, van den Brakel N, de Bree R, Eerenstein SE, Aaronson N, et al. Patient-reported symptom questionnaires in laryngeal cancer: voice, speech and swallowing. Oral Oncol. 2014;50:759-64.

24. Rinkel RN, Verdonck-de Leeuw IM, de Bree R, Aaronson NK, Leemans CR. Validity of patient-reported swallowing and speech outcomes in relation to objectively measured oral function among patients treated for oral or oropharyngeal cancer. Dysphagia. 2015;30:196-204.

CHAPTER 10

General discussion and future perspectives



GENERAL DISCUSSION

As extensively discussed in the introduction and various papers of this thesis, patients with head and neck cancer (HNC) are at risk to develop substantial functional impairments after organ-preserving treatment with radiotherapy (RT) or concurrent chemoradiotherapy (CRT). Swallowing is one of the main functions in which oral, pharyngeal and laryngeal functions cooperate, and tumors in this area and treatment sequels can seriously impair swallowing function and oral intake. As many as two thirds of patients with advanced HNC are left with permanent swallowing impairments[1-3], and dysphagia can even deteriorate several years post-treatment[4-7]. Given its serious impact on quality of life[8, 9], functional swallowing assessment and treatment have become standard of care in HNC patients[10], and prevention of dysphagia has become a major focus point in HNC research. Since the radiation fields frequently encompass the larynx and/or the vocal tract, also substantial effects on laryngeal function (i.e. voice quality, speech intelligibility) have been noted. The effects are correlated to the radiation dose to these structures[11, 12], and aggravated by the combination with chemotherapy[11, 13-18].

In the past decade, improved RT protocols with intensity-modulated radiotherapy (IMRT) have been introduced to reduce the radiation dose to the muscles and structures important for swallowing (i.e. the pharyngeal constrictor muscles)[19-22]. RT is known to affect swallowing function in the short-term through mucositis and edema, and at longer-term through fibrosis with scar tissue formation within the irradiated structures[23, 24]. With the progression to IMRT treatment planning, the relevant swallowing structures can be defined as 'organs at risk', as already is done for the salivary glands to limit xerostomia, and post-treatment swallowing function can become potentially less impaired[19-21].

Although IMRT is relevant for function preservation and not without effect, more recently, the notion has evolved that part of the swallowing problems can be attributed to the 'use it or lose it' concept[25, 26]. Over the last years, the strong focus on prevention of weight loss by confining patients to tube feeding, either by clinical necessity or according to protocol, and effectively immobilizing the swallowing musculature, has inevitably resulted in non-use atrophy of these muscles and structures. Hence, after months of non-use, recovery of oral intake is extremely difficult and not-seldom impossible. And by that, prolonged dysphagia was almost pre-programmed.

At present, this notion has led to the so-called 'eat or exercise' principle[27]. This means that oral intake should be maintained as long as possible, and that preventive swallowing rehabilitation should keep the swallowing musculature 'active' as much as possible. Preventive exercise programs starting before therapy onset and being continued during and after treatment, even when tube feeding has become unavoidable, seem a valid approach to limit the dismal side effects of (C)RT. Recent studies in the Netherlands Cancer Institute

and elsewhere have shown that these programs (in particular in the short-term) actually are associated with better post-treatment swallowing function[28-35]. Thus, prescribing preventive swallowing exercises to all patients with HNC prior to definitive RT or CRT is now increasingly applied, and has become more or less standard of care.

Unfortunately, as became clear from the systematic review of the 2012-2013 literature (Chapter 2), the available studies often differ in the methodologies used and outcomes reported. There is lack of a uniform assessment method, and whether the treatment strategy applied is optimal remains uncertain too, because the performed studies about preventive or rehabilitative strategies are rather limited in size and scope[10, 24]. This literature review clearly confirmed the increasing demand for effective assessment and treatment strategies for dysphagia, in line with most of the other reviews discussed in this paper. All stressed the importance of further longitudinal studies in order to obtain much needed prospective, adequately controlled, powered and randomized data on preventive swallowing exercises[10]. Research to optimize swallowing treatment strategies regarding time, type, duration, frequency and intensity of exercises, with optimal adherence to treatment and assessment of potential long-term benefits, is currently underway at multiple centers[10, 24, 36, 37]. Further optimization of preventive efforts might come from early identification of high-risk patients through systematic assessment using instrumental examinations and complementary patient-reported outcomes[6].

Long-term evaluation

Because studies evaluating long-term functional outcomes after (C)RT for advanced HNC were quite scarce and in demand at the start of this research project, in Chapter 3 and Chapter 4 a patient population with HNC previously treated with concurrent CRT was studied for long-term swallowing, mouth opening, voice and speech outcomes at more than 10 years post-treatment. Regarding swallowing function, both observer-rated and patient-reported severe functional disorders and related morbidity problems were common in this patient cohort. The results showed occurrence of profound pharyngeal residue in all patients, and laryngeal penetration and/or aspiration in almost 70% of the 18 evaluated patients. Moreover, four of the 22 long-term HNC survivors were feeding tube dependent and/or had developed frequent aspiration pneumonias or other recurring pulmonary problems. Also functional voice and speech problems were common in this patient cohort more than ten years after organ-preservation treatment, as assessed with perceptual evaluation, automatic speech recognition, and with validated structured questionnaires. On a positive note, the impairments were significantly less profound in the patients treated with IMRT as compared to the patients treated with conventional RT. Although the patient population concerned only 22 long-term survivors, the results from this study are in line with other studies that found correlations between radiation dose to the pharyngeal structures or glottis and swallowing

or voice/speech impairments, resulting in better functional outcomes in patients treated with IMRT compared to those treated with conventional RT[38-40]. It is not exactly clear whether the poor outcomes in this patient cohort were mainly caused by the lack of preventive rehabilitation, the larger radiation fields, or the progressive fibrosis at long-term following RT. Next to preventive rehabilitation, ongoing clinical trials in HNC are currently looking into the options to optimize the IMRT process to further improve outcomes[41].

For the discussion in this thesis the published data from Chapter 3 and Chapter 4 were also combined to additionally investigate associations between swallowing and voice/speech problems, which appeared to be significantly correlated in this patient cohort more than 10 years post-treatment. In Table 1 the significant univariate Pearson correlations between swallowing function and voice and speech outcomes are shown. As can be seen, laryngeal penetration and/or aspiration, as assessed with Penetration Aspiration Scale scores obtained from videofluoroscopy, was significantly correlated with patients' perceived voice and speech handicap, based on (sub) total Voice Handicap Index (VHI) and Speech Handicap Index (SHI) scores. Also patient's perceived swallowing impairment, assessed with (sub) total SWAL-QOL scores, was significantly associated with patients' perceived voice/speech parameters on most (sub) domains. Though the problems were predominantly related to radiation technique, the phenomenon of neural plasticity might also apply here, meaning that disordered swallowing function is associated with central and peripheral sensorimotor deficits, which also cause voice and speech problems[42, 43]. This is in line with earlier studies that have examined the association between voice quality parameters and dysphagia[44-46].

In Chapter 5 the preventive rehabilitation program of van der Molen et al. (2006-2008) was further studied on long-term prospectively collected objective and subjective functional results after CRT for advanced, anatomical and functional inoperable HNC[30, 35]. With the finding that all patients of the original preventive study population prospectively followed and still alive at 6 years follow-up had maintained or regained adequate oral intake, the effectiveness of this preventive approach was further underlined. Also voice problems were limited in this rehabilitated patient cohort, despite the fact that the vast majority of patients (20/22) due to positive lymph nodes had received a radiation dose to the larynx of 43.5 Gy and higher, according to the literature the threshold value for developing chronic edema or voice problems[39, 47]. Especially when the functional outcomes of this patient cohort (n=22) are compared with the functional swallowing and mouth opening results of the IMRT-treated patients (n=10) from Chapter 3, with comparable patient and tumor characteristics, considerably lower incidence of laryngeal penetration and/or aspiration (4/18 versus 5/10), pharyngeal residue (14/18 versus 10/10), abnormal oral intake (0/22 versus 4/10), and trismus (1/22 versus 3/10) are present. Regarding voice quality, comparison of both patient cohorts is limited to the patient-reported VHI questionnaire. In Chapter 4, four of the ten IMRT-treated patients showed voice problems (VHI >15) in daily life, whereas in Chapter

5 this concerned only five out of 22 patients. Therefore, it seems likely that the favorable outcomes in Chapter 5, at least in part, can be attributed to the preventive and continued post-treatment rehabilitation program that was applied.

In the outcome analysis in dysphagia research, such as the studies described in Chapters 3 to 5, videofluoroscopy has been considered the gold standard for clinical swallowing assessment. Quantitative assessment of swallow mechanics represents probably the best means available for understanding dysphagia in various patient populations. Hence, one of the outcome parameters studied in this thesis is hyoid bone elevation and anterior excursion during swallowing. The literature suggests that reduced or delayed hyoid displacement is an important factor contributing to aspiration and pharyngeal residues in patients with dysphagia. Specifically, reduced vertical excursion of the hyolaryngeal complex may lead to incomplete airway closure with an associated risk of laryngeal aspiration, while reduced hyoid displacement in the anterior direction will lead to reduced opening of the upper esophageal sphincter, resulting in pyriform sinus residues, thus also increasing the risk of aspiration[48]. Contrary to several papers[48, 49], in the above-described rehabilitated HNC patient population, no correlations between anterior and/or superior hyoid excursion and aspiration or residue scores were found (Chapter 6). The significant association found between reduced superior hyoid movement and subjective swallowing impairment based on four study-specific questions regarding swallowing function was quite small. Possibly, other mechanical variables may have been impaired and accounted for patients' reported dysphagia. In the current patient cohort hyoid displacement did increase slightly in the superior direction for 5 cc thin liquid swallows in a subgroup of patients with a tumor at the oropharynx or hypopharynx at 10 weeks post-treatment compared to baseline. The higher values at 10 week post-treatment may reflect extra effort being exerted during these swallows, possibly as result of other issues such as poor sensation or non-hyoid mechanical impairment. This might also reflect the disappearance of the primary tumor, which impaired the mobility of the hyoid bone at baseline in these patients. Also the preventive and continued post-treatment swallowing rehabilitation program might in part explain these favorable 10 weeks hyoid elevation outcomes. However, the patient population was rather small, and other parameters such as tumor volume and/or radiation dose effects may also play a role. Hence, hyoid excursion is subject to variability from a number of sources. It is therefore not surprising that many conflicting results of association between hyoid excursion and aspiration have been published[49, 50]. Moreover, it has been acknowledged in the literature that the measurements of hyoid displacement are not always easy and reproducible, and thus are prone to measurement errors[51, 52]. Therefore, further research with larger sample sizes will be necessary to confirm possible correlation patterns. For now, this parameter seems not very valuable for clinical use in HNC patients with dysphagia.

Table 1. Overview of significant univariate Pearson correlations between swallowing and voice/speech variables in 22 head and neck cancer patients 10 years after concurrent chemoradiotherapy.

	PAS	SWAL-QOL	General burden	Food selection	Eating duration	Eating desire	Fear of eating	Communication	Mental Health	Social function	Symptom score
SHI score	.43*	.63**	.52*	.56**	.48*	.48*	.55**	.86**	.50*	.50*	.66**
Speech domain	.46*	.63**	.54**	.51*	.52*	.55**	.59**	.88**		.43	.64**
Psychosocial domain		.57**	.43*	.57**			.45*	.74**	.56**	.55**	.61**
VHI score	.51*	.70**	.55**	.59**	.61**	.53*	.60**	.81**	.51*	.60**	.67**
Physical domain		.76**	.63**	.53*	.64**	.58**	.74**	.78**	.50*	.60**	.69**
Functional domain	.49*	.57**		.54**	.54**	.46*	.43*	.72**		.49*	.57**
Emotional domain	.52*	.53*		.53*	.44*			.69**	.46*	.52*	.54*
ELIS speech intelligibility			−.43*	−.47*							
Grade							−.53*				
Roughness		−.51*			−.47*		−.57*				
Nasality			−.44*								

Abbreviations: PAS = Penetration Aspiration Scale; SWAL-QOL = Swallowing Quality of Life questionnaire; SHI = Speech Handicap Index; VHI = Voice Handicap Index; ELIS = Text-aligned Running Speech Intelligibility. Note: * means p <.05; ** means p <.01.

Despite the promising effects on pharyngeal swallowing function up to (maximum) 5 years of preventive rehabilitation published by the Netherlands Cancer Institute and others, persistent or late onset dysphagia in HNC survivors still can develop or progress beyond the first years of treatment[4-7]. While acute toxicities such as mucositis and edema commonly disrupt normal swallowing during or shortly after treatment and usually substantially improve in the subsequent months, late-radiation associated dysphagia, now commonly referred to as 'late-RAD', may develop or persist long after the completion of treatment[4, 6]. Although rare, late-RAD may develop after treatment with CRT, RT alone, and also after IMRT, as result of neuropathy, progressive fibrosis, and/or non-use atrophy of the relevant swallowing musculature. It is thought to develop after a radiation dose of 70 Gy or higher[4], especially to the superior pharyngeal constrictor muscles[6]. Often times the onset is preceded by a long interval of adequate functioning. As late-RAD frequently manifests with lower cranial neuropathy (52–83%)[6], the late effects will ultimately affect the range of motion of key swallowing structures (i.e. the hyolaryngeal complex, pharyngeal constrictors, base of tongue). This leads to a significantly inefficient swallow with profound pharyngeal residue, likely combined with progressive fibrosis, and a tendency for refractory, silent aspiration[4]. Hence, novel approaches to prevent and manage this progressive, challenging complication, with high risk of aspiration pneumonia that is frequently refractory to standard dysphagia care, are increasingly in demand for[4].

Prospective studies

Based on the above-described insights obtained with the cross-sectional studies, in the final section of this thesis different treatment strategies for persistent, therapy-refractory oropharyngeal and laryngeal dysfunction were prospectively explored. Many studies have investigated the effects of exercise therapy for improvement of swallowing function, often carried out in a preventive setting or at low level of intensity[53]. As suggested in the literature, compliance, i.e. adherence to treatment, is one of the main factors influencing outcomes, and poor compliance will clearly impact the validity of clinical trial results[54]. Consequently, although sometimes effective for preventive rehabilitation, recent studies have shown that simple, low intensity 'home exercise programs' without adequate patient monitoring are not enough to improve clinically relevant swallowing parameters (i.e. reduction of laryngeal penetration and/or aspiration, or weight gain) in patients with chronic or late onset dysphagia, as compliance in these settings is often low[55, 56]. Instead, one should aim for individualized, high-intensity exercises as recently have been trialed in dysphagia therapy programs[53]. It is important to stress that, because of their relevance for the outcomes assessment of these programs, the collection of compliance data, e.g. with daily exercise logs or time logs, is vital, and that patients should be monitored frequently with preferably weekly follow-up contacts to achieve optimal compliance.

Currently, the literature is suggesting that rehabilitative swallowing therapy that aims to strengthen the swallowing musculature can possibly compensate for 'loss' of resistive load, when acute effects of CRT cause patients with HNC to stop eating[27]. Based on the same methods used in sports medicine, repetitive exercises that address all principles of strength or endurance training (i.e. specificity, individuality, and progressive overload) are increasingly applied. In this respect, the development of medical devices supporting a therapeutic approach is promising, as was also shown in our recent feasibility study (Chapter 7), proving that senior healthy subjects are able to improve and increase suprahyoid muscle strength and volume during a 6-week period of intensive swallowing training. The exercise protocol consisted of both swallow and non-swallow exercises, which were performed with a newly developed dedicated swallow exercise device: the Swallow Exercise Aid (SEA). Exercises included chin tuck against resistance (CTAR), jaw opening against resistance (JOAR), and effortful swallow exercises. The device allows adaptation to individual subjects' capacity, and thus for applying progressive overload during the training program. The high compliance (mean 86%) found in this study certainly contributed to the positive results, which probably also in part is attributable to the biofeedback and visual feedback on the resistance level provided by the device. These results are in concordance with other studies among healthy subjects that demonstrated improved swallowing outcome parameters such as improved hyoid bone elevation, amount of upper esophageal sphincter opening, and time for pharynx passage after approximately six weeks of intensive swallowing training[57-61].

Obviously, the positive results found in our and other studies[58-61] in healthy individuals had to be confirmed and tested in patients with dysphagia, since it needs to be demonstrated whether the targeted, often atrophied and/or fibrosed muscle groups in patients with therapy-refractory dysphagia are also still trainable. And even more important question was, whether increased suprahyoid muscle strength indeed aids in opening of the upper esophageal sphincter by elevation and anterior excursion of the hyolaryngeal complex, and results in less post-swallow aspiration. This was reason to conduct a clinical trial in patients with chronic dysphagia after organ-preservation treatment for HNC (Chapter 8). In this prospective phase 2 clinical trial the feasibility, compliance, and short-term efficacy of the same SEA-based strength training protocol was studied in 18 patients with chronic, therapy-refractory dysphagia after treatment for advanced HNC. Similarly, swallow and non-swallow exercises were used for rehabilitation, including CTAR, JOAR, and effortful swallow exercises. After 6 to 8 weeks of targeted swallowing training, the feasibility and compliance again appeared to be high, and some objective and subjective effects of progressive load on muscle strength and swallowing function were demonstrated, indicating that the swallowing muscles at long-term are, up to a certain point, still trainable. Unfortunately, no major improvements such as tube removal or improved PAS scores were observed. An explanation could be that 6 to 8 weeks of strength training is not enough for achieving clinically relevant improvements

in this challenging patient population with chronic or late onset dysphagia 10 years after their oncological treatment. Another reason could be that other muscles involved in swallowing, not or less efficiently targeted with the SEA exercises, might play an important role. Also fibrosis and/or nerve dysfunction at long-term are likely to prohibit functional improvement at such short notice, in spite of improved muscle strength. And although the benefits as perceived by the patients themselves did not correlate with the objective improvements in muscle strength, the literature suggests that swallowing training 'might help patients adapt to severe levels of swallowing dysfunction, to cope and compensate better, and to live better with their problem'[53]. And as a result, patients' oral intake might hereby improve as well. And the challenge of increasing or decreasing the 'resistive load' of swallowing, recently envisaged by Langmore et al., as mentioned in the introduction, has been not been too elusive after all.

Future perspectives

To further study the efficacy and effectiveness of rehabilitative exercises in HNC patients with chronic or late dysphagia, larger, prospective, well-designed studies of longer duration ensuring adequate numbers of patients (with comparable tumor sites and stages), and structured treatment protocols (with well-defined numbers of sets and repetitions) are needed[24, 36]. Based on the established effect size for improved oral intake (Cohen's d = 0.3) obtained from Chapter 8, at least 56 patients should ideally be included. Further, probably only patients with baseline muscle strengths of 10 Newton (N) or higher should be included, because the non-responders all showed baseline muscle strengths below 10 N, and the device appeared to work better with the resistance minimally on position 2 or higher. Since significant benefits of preventive exercises during organ-preservation treatment already have been demonstrated[24, 31, 32, 35], starting rehabilitation before treatment onset, or at least as soon as possible in case of post-treatment rehabilitation, is preferable. Therefore, as a next step in the validation process of the SEA-based exercise protocol, a phase 3 randomized controlled trial in the preventive or early rehabilitation setting of HNC treatment is planned. It cannot be ruled out, however, that this subsequent trial will show that therapy effects in the field of dysphagia rehabilitation are time dependent. Already after two years, but especially more than ten years after radiation treatment, swallowing function might have become so poor that even the best therapy cannot stop the progressive deterioration[4-6]. It is therefore not unlikely that a possible critical window for post-treatment rehabilitation exists, with a threshold approximately two years after radiation[4]. This is also stated in the principle 'time matters' of neural plasticity, meaning that early implementation of interventions is hypothesized most likely to access neural plastic adaptations[42, 43].

Many factors contribute to dysphagia, aspiration and even the inability to swallow. In patients with chronic or late dysphagia who are really refractory to therapy, multiple

swallowing abnormalities are likely present. Often, due to insufficient contact between the base of tongue and posterior pharyngeal wall, the food bolus is swallowed less powerful, leading to stagnation of food ('residue'), with a high risk of aspiration of the residue. A combination of decreased tongue strength, deficient/reduced hyolaryngeal elevation, lack of pharyngeal constrictor activity, lack of oropharyngeal seal, or insufficient opening of the esophageal inlet may also play a role in aspiration[62, 63]. To address dysphagia based on volume loss or non-use muscle atrophy of the tongue or pharyngeal musculature, a feasibility study on the potential value of lipofilling as minimally invasive surgical method for the treatment of oropharyngeal dysfunction and dysphagia was carried out in Chapter 9. This study, encompassing preliminary data on seven patients, showed that the procedure was feasible and safe. Regarding effectiveness, promising results were demonstrated, with significant swallowing improvements in four of the seven patients. Two of them were confined to long-term tube feeding, but afterwards were back to oral intake, allowing removal of the feeding tube. According to the literature, the favorable outcomes of autologous fat injection are not only attributable to the filling effect of soft tissue, but possibly also to the potential regenerative effect of adipose-derived mesenchyme stem cells[64, 65]. As a result, the tissue also may become less fibrotic. These examples show that a close collaboration between the head and neck surgeon and allied health professionals is essential for progress in these functional deficit areas. Head and neck surgeons should have a keen interest, not only in HNC treatment, but also in HNC rehabilitation, since they have the armamentarium to restore or compensate functions losses. And dysphagia research is only at its infancy in this respect.

To sum up, over the last decades the increasing use of organ-preservation protocols has created new challenges for HNC rehabilitation. Besides the traditional rehabilitation after total laryngectomy, now also the functional issues caused by the compromised larynx and pharynx as result of RT or concurrent CRT have to be addressed. Multiple swallowing abnormalities are likely present in patients with chronic or late dysphagia. To better rehabilitate dysphagia in HNC patients, the following focus points for future perspectives in dysphagia rehabilitation are recommended. First, function preservation in organ-preservation protocols should be more integrated, not only through ever more clever RT treatment planning, but also through the (continued) evaluation of traditional therapy techniques (i.e. chin tuck, effortful swallow), to give speech language pathologists and head and neck surgeons the ammunition to select and apply these techniques on a best-practice basis for individual patients. Second, incorporation of structural, intensive, daily functional swallow and non-swallow exercises for dysphagia rehabilitation is required, as many swallowing difficulties are related to muscle weakness, and potential effects of these exercise-based strategies already have been demonstrated. Tools or devices that intensify the work load under a progressive-resistance model of exercise-based therapy are encouraged, in order to avoid non-use atrophy and progressive fibrosis of the relevant swallowing musculature and structures at long-term. Third, novel approaches such

as compensating existing tissue defects or tissue loss by transplantation of autologous adipose tissue (lipofilling) can sometimes restore functional outcomes in HNC patients with chronic dysphagia. Especially the combination of strategies might provide the best possible care for patients with chronic dysphagia with high risk of aspiration pneumonia that is frequently refractory to standard dysphagia care. Especially combining of SEA exercises and lipofilling is worthwhile further exploring, since both treatment modalities were explored in parallel for this thesis. First signs of an additional beneficial effect of the combination are positive. As the evidence and clinicians' skills for various strategies and tools increases, hopefully the clinical outcomes in HNC patients with dysphagia will improve as well[66].

REFERENCES

1. Lazarus CL. Effects of radiation therapy and voluntary maneuvers on swallow functioning in head and neck cancer patients. Clin Commun Disord. 1993;3:11-20.
2. Smith RV, Kotz T, Beitler JJ, Wadler S. Long-term swallowing problems after organ preservation therapy with concomitant radiation therapy and intravenous hydroxyurea: initial results. Arch Otolaryngol Head Neck Surg. 2000;126:384-9.
3. Staar S, Rudat V, Stuetzer H, Dietz A, Volling P, Schroeder M, et al. Intensified hyperfractionated accelerated radiotherapy limits the additional benefit of simultaneous chemotherapy--results of a multicentric randomized German trial in advanced head-and-neck cancer. Int J Radiat Oncol Biol Phys. 2001;50:1161-71.
4. Hutcheson KA, Lewin JS, Barringer DA, Lisec A, Gunn GB, Moore MW, et al. Late dysphagia after radiotherapy-based treatment of head and neck cancer. Cancer. 2012;118:5793-9.
5. Payakachat N, Ounpraseuth S, Suen JY. Late complications and long-term quality of life for survivors (>5 years) with history of head and neck cancer. Head Neck. 2013;35:819-25.
6. Awan MJ, Mohamed AS, Lewin JS, Baron CA, Gunn GB, Rosenthal DI, et al. Late radiation-associated dysphagia (late-RAD) with lower cranial neuropathy after oropharyngeal radiotherapy: a preliminary dosimetric comparison. Oral Oncol. 2014;50:746-52.
7. Hutcheson KA, Yuk MM, Holsinger FC, Gunn GB, Lewin JS. Late radiation-associated dysphagia with lower cranial neuropathy in long-term oropharyngeal cancer survivors: video case reports. Head Neck. 2015;37:E56-62.
8. Ackerstaff AH, Rasch CR, Balm AJ, de Boer JP, Wiggenraad R, Rietveld DH, et al. Five-year quality of life results of the randomized clinical phase III (RADPLAT) trial, comparing concomitant intra-arterial versus intravenous chemoradiotherapy in locally advanced head and neck cancer. Head Neck. 2012;34:974-80.
9. Metreau A, Louvel G, Godey B, Le Clech G, Jegoux F. Long-term functional and quality of life evaluation after treatment for advanced pharyngolaryngeal carcinoma. Head Neck. 2014;36:1604-10.
10. Kraaijenga SA, van der Molen L, van den Brekel MW, Hilgers FJ. Current assessment and treatment strategies of dysphagia in head and neck cancer patients: a systematic review of the 2012/13 literature. Curr Opin Support Palliat Care. 2014;8:152-63.
11. Lazarus CL. Effects of chemoradiotherapy on voice and swallowing. Curr Opin Otolaryngol Head Neck Surg. 2009;17:172-8.
12. Gamez M, Hu K, Harrison LB. Laryngeal Function After Radiation Therapy. Otolaryngol Clin North Am. 2015;48:585-99.
13. Fung K, Yoo J, Leeper HA, Bogue B, Hawkins S, Hammond JA, et al. Effects of head and neck radiation therapy on vocal function. J Otolaryngol. 2001;30:133-9.
14. Bibby JR, Cotton SM, Perry A, Corry JF. Voice outcomes after radiotherapy treatment for early glottic cancer: assessment using multidimensional tools. Head Neck. 2008;30:600-10.
15. Starmer HM, Tippett DC, Webster KT. Effects of laryngeal cancer on voice and swallowing. Otolaryngol Clin North Am. 2008;41:793-818, vii.
16. Agarwal JP, Baccher GK, Waghmare CM, Mallick I, Ghosh-Laskar S, Budrukkar A, et al. Factors affecting the quality of voice in the early glottic cancer treated with radiotherapy. Radiother Oncol. 2009;90:177-82.
17. Jacobi I, van der Molen L, Huiskens H, van Rossum MA, Hilgers FJ. Voice and speech outcomes of chemoradiation for advanced head and neck cancer: a systematic review. Eur Arch Otorhinolaryngol. 2010;267:1495-505.
18. Lazarus CL, Husaini H, Hu K, Culliney B, Li Z, Urken M, et al. Functional outcomes and quality of life after chemoradiotherapy: baseline and 3 and 6 months post-treatment. Dysphagia. 2014;29:365-75.

19. Feng FY, Kim HM, Lyden TH, Haxer MJ, Worden FP, Feng M, et al. Intensity-modulated chemoradiotherapy aiming to reduce dysphagia in patients with oropharyngeal cancer: clinical and functional results. J Clin Oncol. 2010;28:2732-8.

20. Roe JW, Carding PN, Dwivedi RC, Kazi RA, Rhys-Evans PH, Harrington KJ, et al. Swallowing outcomes following Intensity Modulated Radiation Therapy (IMRT) for head & neck cancer - a systematic review. Oral Oncol. 2010;46:727-33.

21. Eisbruch A, Kim HM, Feng FY, Lyden TH, Haxer MJ, Feng M, et al. Chemo-IMRT of oropharyngeal cancer aiming to reduce dysphagia: swallowing organs late complication probabilities and dosimetric correlates. Int J Radiat Oncol Biol Phys. 2011;81:e93-9.

22. Gutiontov SI, Shin EJ, Lok B, Lee NY, Cabanillas R. Intensity-modulated radiotherapy for head and neck surgeons. Head Neck. 2015.

23. Platteaux N, Dirix P, Dejaeger E, Nuyts S. Dysphagia in head and neck cancer patients treated with chemoradiotherapy. Dysphagia. 2010;25:139-52.

24. Virani A, Kunduk M, Fink DS, McWhorter AJ. Effects of 2 different swallowing exercise regimens during organ-preservation therapies for head and neck cancers on swallowing function. Head Neck. 2015;37:162-70.

25. Lee WT, Akst LM, Adelstein DJ, Saxton JP, Wood BG, Strome M, et al. Risk factors for hypopharyngeal/upper esophageal stricture formation after concurrent chemoradiation. Head Neck. 2006;28:808-12.

26. Chen AM, Li BQ, Lau DH, Farwell DG, Luu Q, Stuart K, et al. Evaluating the role of prophylactic gastrostomy tube placement prior to definitive chemoradiotherapy for head and neck cancer. Int J Radiat Oncol Biol Phys. 2010;78:1026-32.

27. Hutcheson KA, Bhayani MK, Beadle BM, Gold KA, Shinn EH, Lai SY, et al. Eat and exercise during radiotherapy or chemoradiotherapy for pharyngeal cancers: use it or lose it. JAMA Otolaryngol Head Neck Surg. 2013;139:1127-34.

28. Kulbersh BD, Rosenthal EL, McGrew BM, Duncan RD, McColloch NL, Carroll WR, et al. Pretreatment, preoperative swallowing exercises may improve dysphagia quality of life. Laryngoscope. 2006;116:883-6.

29. Carroll WR, Locher JL, Canon CL, Bohannon IA, McColloch NL, Magnuson JS. Pretreatment swallowing exercises improve swallow function after chemoradiation. Laryngoscope. 2008;118:39-43.

30. van der Molen L, van Rossum MA, Burkhead LM, Smeele LE, Rasch CR, Hilgers FJ. A randomized preventive rehabilitation trial in advanced head and neck cancer patients treated with chemoradiotherapy: feasibility, compliance, and short-term effects. Dysphagia. 2011;26:155-70.

31. Carnaby-Mann G, Crary MA, Schmalfuss I, Amdur R. "Pharyngocise": randomized controlled trial of preventative exercises to maintain muscle structure and swallowing function during head-and-neck chemoradiotherapy. Int J Radiat Oncol Biol Phys. 2012;83:210-9.

32. Kotz T, Federman AD, Kao J, Milman L, Packer S, Lopez-Prieto C, et al. Prophylactic swallowing exercises in patients with head and neck cancer undergoing chemoradiation: a randomized trial. Arch Otolaryngol Head Neck Surg. 2012;138:376-82.

33. Bhayani MK, Hutcheson KA, Barringer DA, Lisec A, Alvarez CP, Roberts DB, et al. Gastrostomy tube placement in patients with oropharyngeal carcinoma treated with radiotherapy or chemoradiotherapy: factors affecting placement and dependence. Head Neck. 2013;35:1634-40.

34. Ohba S, Yokoyama J, Kojima M, Fujimaki M, Anzai T, Komatsu H, et al. Significant preservation of swallowing function in chemoradiotherapy for advanced head and neck cancer by prophylactic swallowing exercise. Head Neck. 2014.

35. van der Molen L, van Rossum MA, Rasch CR, Smeele LE, Hilgers FJ. Two-year results of a prospective preventive swallowing rehabilitation trial in patients treated with chemoradiation for advanced head and neck cancer. Eur Arch Otorhinolaryngol. 2014;271:1257-70.

36. Burkhead LM, Sapienza CM, Rosenbek JC. Strength-training exercise in dysphagia rehabilitation: principles, procedures, and directions for future research. Dysphagia. 2007;22:251-65.

37. Langmore SE, Pisegna JM. Efficacy of exercises to rehabilitate dysphagia: A critique of the literature. Int J Speech Lang Pathol. 2015;17:222-9.

38. van Rij CM, Oughlane-Heemsbergen WD, Ackerstaff AH, Lamers EA, Balm AJ, Rasch CR. Parotid gland sparing IMRT for head and neck cancer improves xerostomia related quality of life. Radiat Oncol. 2008;3:41.

39. Nguyen NP, Abraham D, Desai A, Betz M, Davis R, Sroka T, et al. Impact of image-guided radiotherapy to reduce laryngeal edema following treatment for non-laryngeal and non-hypopharyngeal head and neck cancers. Oral Oncol. 2011;47:900-4.

40. Vainshtein JM, Griffith KA, Feng FY, Vineberg KA, Chepeha DB, Eisbruch A. Patient-reported voice and speech outcomes after whole-neck intensity modulated radiation therapy and chemotherapy for oropharyngeal cancer: prospective longitudinal study. Int J Radiat Oncol Biol Phys. 2014;89:973-80.

41. Tejpal G, Jaiprakash A, Susovan B, Ghosh-Laskar S, Murthy V, Budrukkar A. IMRT and IGRT in head and neck cancer: Have we delivered what we promised? Indian J Surg Oncol. 2010;1:166-85.

42. Robbins J, Butler SG, Daniels SK, Diez Gross R, Langmore S, Lazarus CL, et al. Swallowing and dysphagia rehabilitation: translating principles of neural plasticity into clinically oriented evidence. J Speech Lang Hear Res. 2008;51:S276-300.

43. van der Molen L, van Rossum MA, Jacobi I, van Son RJ, Smeele LE, Rasch CR, et al. Pre- and posttreatment voice speech outcomes in patients with advanced head and neck cancer treated with chemoradiotherapy: expert listeners' and patient's perception. J Voice. 2012;26:664.e25-33.

44. Ryu JS, Park SR, Choi KH. Prediction of laryngeal aspiration using voice analysis. Am J Phys Med Rehabil. 2004;83:753-7.

45. Murugappan S, Boyce S, Khosla S, Kelchner L, Gutmark E. Acoustic characteristics of phonation in "wet voice" conditions. J Acoust Soc Am. 2010;127:2578-89.

46. [46] de Bruijn MJ, Rinkel RN, Cnossen IC, Witte BI, Langendijk JA, Leemans CR, et al. Associations between voice quality and swallowing function in patients treated for oral or oropharyngeal cancer. Support Care Cancer. 2013;21:2025-32.

47. Sanguineti G, Adapala P, Endres EJ, Brack C, Fiorino C, Sormani MP, et al. Dosimetric predictors of laryngeal edema. Int J Radiat Oncol Biol Phys. 2007;68:741-9.

48. Steele CM, Bailey GL, Chau T, Molfenter SM, Oshalla M, Waito AA, et al. The relationship between hyoid and laryngeal displacement and swallowing impairment. Clin Otolaryngol. 2011;36:30-6.

49. Molfenter SM, Steele CM. Kinematic and temporal factors associated with penetration-aspiration in swallowing liquids. Dysphagia. 2014;29:269-76.

50. Steele CM, Cichero JA. Physiological factors related to aspiration risk: a systematic review. Dysphagia. 2014;29:295-304.

51. Sia I, Carvajal P, Carnaby-Mann GD, Crary MA. Measurement of hyoid and laryngeal displacement in video fluoroscopic swallowing studies: variability, reliability, and measurement error. Dysphagia. 2012;27:192-7.

52. Baijens L, Barikroo A, Pilz W. Intrarater and interrater reliability for measurements in videofluoroscopy of swallowing. Eur J Radiol. 2013;82:1683-95.

53. Hutcheson KA, Kelly S, Barrow MP, Barringer DA, Perez DP, Little LG, et al. Offering More for Persistent Dysphagia after Head and Neck Cancer: The Evolution of Boot Camp Swallowing Therapy. Downloaded online at 8th November 2015 at: http://researchposters.com/Posters/COSM/COSM2015/C058pdf.

54. Langmore SE, McCulloch TM, Krisciunas GP, Lazarus CL, Van Daele DJ, Pauloski BR, et al. Efficacy of electrical stimulation and exercise for dysphagia in patients with head and neck cancer: A randomized clinical trial. Head Neck. 2015.

55. Ahlberg A, Engstrom T, Nikolaidis P, Gunnarsson K, Johansson H, Sharp L, et al. Early self-care rehabilitation of head and neck cancer patients. Acta Otolaryngol. 2011;131:552-61.

56. Mortensen HR, Jensen K, Aksglaede K, Lambertsen K, Eriksen E, Grau C. Prophylactic Swallowing Exercises in Head and Neck Cancer Radiotherapy. Dysphagia. 2015;30:304-14.

57. Wada S, Tohara H, Iida T, Inoue M, Sato M, Ueda K. Jaw-opening exercise for insufficient opening of upper esophageal sphincter. Arch Phys Med Rehabil. 2012;93:1995-9.

58. Watts CR. Measurement of hyolaryngeal muscle activation using surface electromyography for comparison of two rehabilitative dysphagia exercises. Arch Phys Med Rehabil. 2013;94:2542-8.

59. Hughes T, Watts CR. Effects of 2 Resistive Exercises on Electrophysiological Measures of Submandibular Muscle Activity. Arch Phys Med Rehabil. 2015.

60. Mishra A, Rajappa A, Tipton E, Malandraki GA. The Recline Exercise: Comparisons with the Head Lift Exercise in Healthy Adults. Dysphagia. 2015;30:730-7.

61. Sze WP, Yoon WL, Escoffier N, Rickard Liow SJ. Evaluating the Training Effects of Two Swallowing Rehabilitation Therapies Using Surface Electromyography-Chin Tuck Against Resistance (CTAR) Exercise and the Shaker Exercise. Dysphagia. 2016.

62. Kos MP, David EF, Aalders IJ, Smit CF, Mahieu HF. Long-term results of laryngeal suspension and upper esophageal sphincter myotomy as treatment for life-threatening aspiration. Ann Otol Rhinol Laryngol. 2008;117:574-80.

63. Lazarus C, Logemann JA, Pauloski BR, Rademaker AW, Helenowski IB, Vonesh EF, et al. Effects of radiotherapy with or without chemotherapy on tongue strength and swallowing in patients with oral cancer. Head Neck. 2007;29:632-7.

64. Tabit CJ, Slack GC, Fan K, Wan DC, Bradley JP. Fat grafting versus adipose-derived stem cell therapy: distinguishing indications, techniques, and outcomes. Aesthetic Plast Surg. 2012;36:704-13.

65. Hamza A, Lohsiriwat V, Rietjens M. Lipofilling in breast cancer surgery. Gland Surg. 2013;2:7-14.

66. Groher ME, Crary MA. Dysphagia: clinical management in adults and children. St. Louis, Missouri: Elsevier; 2016.

CHAPTER 11

Summary

Summary in Dutch | Samenvatting

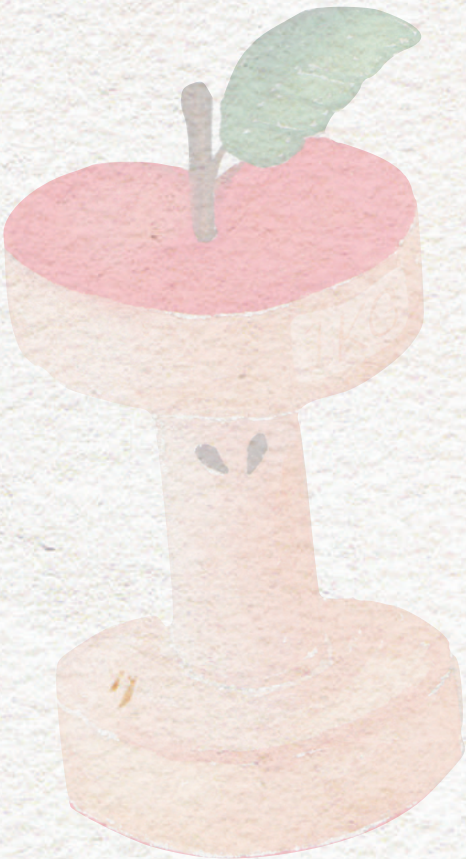
List of abbreviations

Authors and affiliations

PhD portfolio

About the author

Acknowledgement | Dankwoord



SUMMARY

This thesis describes and discusses oropharyngeal and laryngeal function following (organ-preservation) treatment for advanced head and neck cancer (HNC), including long-term results of cross-sectional cohort studies, and prospectively studied treatment strategies for chronic, therapy-refractory dysfunction.

Radiotherapy (RT) or combined chemoradiotherapy (CRT) regimens are increasingly used as primary treatment for patients with (locally) advanced HNC. Unfortunately, these organ-preserving protocols are associated with substantial adverse functional events, notably dysphagia. The result can be reduced food intake, weight loss and ultimately the need for nasogastric or percutaneous tube feeding, which negatively influences patients' quality of life. **Chapter 1** provides a general introduction into the epidemiology, treatment, and treatment-induced toxicities following organ-preservation treatment for advanced HNC. Preventive and rehabilitative strength training strategies based on the same methods applied in sports medicine are discussed. **Chapter 2** concerns a systematic review, which aims to summarize the current assessment and treatment strategies for dysphagia following HNC, and to give directions for the future. Studies were identified by a comprehensive electronic database search using Medline and Embase, and all retrieved articles were screened on title and abstract, methodological quality, and risk of bias. Dysphagia assessment is addressed with emphasis on timing and on the various tools used. Further, optimal treatment strategies are discussed with special focus on treatment goals and options. In total 11 studies or reviews that describe dysphagia assessment, and 10 studies or reviews that report on dysphagia treatment are reviewed. It became clear that there is still no uniform 'gold-standard' for either assessment or treatment strategies, despite the fact that functional swallowing assessment and treatment have become standard of care in HNC patients, given the serious impact of dysphagia on quality of life during HNC survivorship. Hence, this systematic review recommends more high quality data, adequately controlled, powered and randomized, on prophylactic and therapeutic swallowing exercises, with longer follow-up and optimal adherence to treatment, in order to better reduce toxicity of chemo- and radiotherapy, and to possibly modify surgical resections and reconstructions. In addition, frequency, timing and duration of exercise therapy need further investigation to improve swallowing function and optimize quality of life.

Long-term evaluation

Also substantial effects on laryngeal function (i.e. voice quality and speech intelligibility) are reported in the literature following organ-preservation treatment for (locally) advanced HNC. Part 1 of this thesis focuses on oropharyngeal and laryngeal function at long-term.

In **Chapter 3** and **Chapter 4** a HNC patient population previously treated with concurrent CRT is studied on functional swallowing, and voice and speech outcomes at more than 10 years post-treatment. Twenty-two disease-free survivors, treated with cisplatin-based CRT for inoperable HNC (1999–2004), were evaluated to assess long-term morbidity. The prospective assessment protocol consisted of videofluoroscopy (VFS) for obtaining Penetration Aspiration Scale (PAS), and presence of residue scores. Functional Oral Intake Scale (FOIS) scores, maximum mouth opening measurements, and (SWAL-QOL and study-specific) questionnaires were also assessed. A standard Dutch text was recorded, and perceptual analysis of voice, speech, and articulation was conducted by two expert listeners. Additionally, an experimental expert system based on automatic speech recognition was used. Patients' perception of voice and speech and related quality of life was assessed with the Voice Handicap Index (VHI) and Speech Handicap Index (SHI) questionnaires. Regarding oropharyngeal functional outcomes, 10 patients (45%) were able to consume a normal oral diet without restrictions (FOIS score 7), whereas 12 patients (55%) had moderate to serious swallowing issues, of whom 3 (14%) were feeding tube dependent. VFS evaluation showed 15/22 patients (68%) with penetration and/or aspiration (PAS ≥3). Fifty-five percent of patients (12/22) had developed trismus (mouth opening ≤35 mm), which was significantly associated with aspiration (p =.011). Subjective swallowing function (SWAL-QOL score) was impaired across almost all quality of life domains in the majority of patients. Patients treated with IMRT showed significantly less aspiration (p =.011), less trismus (p =.035), and less subjective swallowing problems than those treated with conventional RT. Voice quality and speech intelligibility were also affected. Perceptual evaluation showed abnormal scores in up to 64% of cases, depending on the outcome parameter analysed. Automatic assessment of voice and speech parameters correlated moderately to strongly with perceptual outcome scores. Patient-reported problems with voice (VHI >15) and speech (SHI >6) in daily life were present in 68% and 77% of patients, respectively. Again, patients treated with IMRT showed significantly less impairment compared to those treated with conventional RT.

The aim of **Chapter 5** was to report the long-term functional outcomes >5 years after concurrent CRT in a patient cohort that was previously also treated with preventive rehabilitation. Primary endpoints were swallowing function, mouth opening and voice quality. The original trial involved 55 patients with advanced HNC who received CRT and were randomized to one of two preventive rehabilitation programmes for 1 year: standard logopaedic swallowing exercises or an experimental swallowing rehabilitation program. Since the results were generally similar in the two treatment groups, this analysis used combined data from all 22 participants who were disease-free and evaluable at >5 years post-treatment. Swallowing function was assessed by investigating laryngeal penetration and aspiration, oral intake and nutritional status, mouth opening, pain and quality of life. Voice quality was assessed using acoustic voice parameters. At a mean follow-up period of 6 years,

the frequency of most swallowing problems remained low and was similar to that observed at baseline or after 2 years of follow-up. The exceptions were increases in the frequency of xerostomia from 18% at baseline to 68% at 6 years (p =.003), and of mild pain in the head and neck region, from 9% at 2 years to 32% (p =.06). In the 7 patients with tumours located below the hyoid bone, acoustic voice analysis showed they had less voicedness, a higher fundamental frequency, and increased vocal effort at 6 years than those with tumours above the hyoid bone. Overall, the patients' subjective perceptions of their vocal function at 6 years were good, although 50% perceived their voice as different from that at baseline. In conclusion, few surviving patients with advanced HNC who received concurrent CRT and took part in a preventive rehabilitation program had problems with either swallowing or voice quality at 6 years post-treatment.

Chapter 6 provides quantitative data pertinent to one of the mechanical features of fluoroscopic swallow studies, i.e. anterior and superior hyoid bone displacement. This study reports on temporal and kinematic measures of hyoid displacement, with the additional goal to investigate correlations with persisting (clinical) swallowing impairment in the rehabilitated patient population. A single-blind analysis of data collected as part of the above-described larger prospective study (Chapter 5) was performed at three time points before and after CRT. Twenty-five HNC patients are evaluated. Patients had undergone clinical swallowing assessments at baseline, at 10 weeks, and at 1 year post-treatment. VFS analysis was done on different swallowing consistencies of varying amounts. The VFS studies were independently reviewed frame-by frame by two clinical researchers to assess temporal (onset and duration) and kinematic (anterior and superior movement) measures of hyoid displacement (ImageJ), PAS scores, and presence of more than normal vallecula or pyriform sinus residues. Patient-reported FOIS scores and swallowing function (study-specific questionnaire) were also evaluated. Results show that the mean maximum hyoid displacement ranged from 9.4 mm (23% of C2-4 distance) to 12.6 mm (27%) anteriorly, and from 18.9 mm (41%) to 24.9 mm (54%) superiorly, depending on bolus volume and consistency. Hyoid elevation start time and maximum hyoid elevation time did not differ significantly over time. In accordance with the literature, hyoid bone displacement seems subject to variability from a number of sources. Further research with larger sample sizes will be necessary to confirm possible correlation patterns.

Prospective studies

Part 2 of this thesis describes prospective studies on non-surgical or minimal invasive treatment strategies for oropharyngeal and laryngeal dysfunction, based on the insights obtained with the cross-sectional studies in Part 1. Since dysphagia in HNC patients may develop due to muscle weakness (as result of fibrosis or atrophy) following CRT, strengthening of the swallowing muscles through therapeutic exercise is potentially effective for improving

swallowing function. In **Chapter 7** the feasibility and effectiveness of strengthening exercises with a dedicated swallowing exercise aid (SEA) is studied on suprahyoid musculature and function in senior healthy subjects. It was hypothesized that this tool, developed for isometric and isokinetic strengthening exercises against resistance, can help to functionally strengthen the suprahyoid musculature (i.e. the mylohyoid, geniohyoid, and digastric muscles), which in turn can improve swallowing function. Ten senior healthy volunteers performed chin tuck against resistance (CTAR), jaw opening against resistance (JOAR), and effortful swallow exercises 3 times per day for 6 weeks. Multidimensional assessment consisted of measurements of maximum chin tuck and jaw opening strength, maximum tongue strength/endurance, suprahyoid muscle volume, hyoid bone displacement, swallowing transport times, occurrence of laryngeal penetration/aspiration and/or contrast residue, maximum mouth opening, feasibility and compliance (questionnaires), and subjective swallowing complaints (SWAL-QOL questionnaire). After 6 weeks exercise, mean chin tuck strength, jaw opening strength, anterior tongue strength, suprahyoid muscle volume, and maximum mouth opening significantly increased (p <.05). Feasibility and compliance (median 86%, range 48–100%) of the SEA exercises were good. To summarize, this prospective feasibility and effectiveness study on the effects of CTAR/JOAR isometric and isokinetic strengthening exercises on swallowing musculature and function showed that senior healthy subjects are able to significantly increase suprahyoid muscle strength and volume after a 6-week training period.

These positive results warranted further investigation of efficacy and effectiveness of these SEA exercises in HNC patients with chronic dysphagia. Therefore, in **Chapter 8** this dedicated treatment regimen is explored in a phase-2 clinical trial among patients with chronic, therapy-resistant dysphagia. A prospective clinical study was carried out in 18 HNC patients with chronic dysphagia, who performed swallow and non-swallow exercises 3 times daily for 6-8 weeks. The exercises were performed with the SEA allowing for progressive muscle overload, including chin tuck and jaw opening against resistance, and effortful swallow exercises. Outcome parameters were feasibility, compliance, and short-term effect parameters. After 6 to 8 weeks of intensive swallowing training, the overall and specific compliance in terms of the 3 daily sessions were 89% and 97%, respectively. At the end of the training period, median chin tuck and jaw opening strength had substantially improved. Ninety-four percent of patients reported to benefit from the exercises. In conclusion, feasibility and compliance were high. Some objective and subjective effects of progressive load on suprahyoid muscle strength and swallowing function were demonstrated.

In **Chapter 9**, the feasibility and potential value of an experimental treatment (lipofilling) is prospectively studied in patients with post-treatment oropharyngeal dysfunction, to address chronic dysphagia and aspiration in HNC patients who are really therapy-refractory. It was hypothesized that, if intensive swallowing therapy offers no further improvement, and

the functional problems persist, transplantation of autologous adipose tissue (lipofilling) might restore functional outcomes by compensating the existing tissue defects or tissue loss. In total seven patients with chronic dysphagia were included. The procedure was carried out under general anesthesia in several sessions using the Coleman technique. Swallowing outcomes were evaluated with standard VFS for obtaining objective PAS and residue scores. Subjective FOIS scores and SWAL-QOL questionnaires were also completed. MRI was used to evaluate the post-treatment injected fat. Five patients completed the intended three lipofilling sessions, while two completed two injections. One patient dropped out of the study after two injections because of progressive dysphagia requiring total laryngectomy. Four of the six remaining patients showed improved PAS scores on post-treatment VFS assessments, with two patients no longer showing aspiration for a specific consistency. Two patients were no longer feeding tube dependent. Patient-reported swallowing and oral intake improved in four out of six patients. Based on the results, the lipofilling technique seems safe and – in selected cases – of potential value for improving swallowing function in this small therapy-refractory HNC patient cohort.

Finally, in **Chapter 10**, the results obtained in the current thesis are discussed, and future perspectives are outlined.

SAMENVATTING

Dit proefschrift richt zich op orofaryngeale en laryngeale functies zoals slikken, mondopening en stem/spraak na (orgaan-sparende) behandeling voor vergevorderde hoofd-halskanker. In het eerste deel van dit proefschrift komen enkele cross-sectionele studies naar de functionele gevolgen op de lange termijn aan de orde. In het tweede deel wordt in prospectieve studieopzet gezocht naar niet-chirurgische of minimaal invasieve behandelmodaliteiten voor chronische/persisterende functionele problemen.

Vergevorderde hoofd-halskanker wordt veelal orgaan-sparend behandeld middels radiotherapie (RT) of door radiotherapie te combineren met chemotherapie (CRT). Met deze behandelmodaliteiten worden regelmatig goede resultaten bereikt, echter helaas nog al eens ten koste van aanzienlijke functionele bijwerkingen, zoals het optreden van slikproblemen (dysfagie). Dysfagie kan leiden tot verminderde orale intake, gewichtsverlies en zelfs tot het permanent via een voedingssonde gevoed moeten worden. Als gevolg hiervan is de kwaliteit van leven vaak ernstig gestoord. **Hoofdstuk 1** van dit proefschrift geeft een overzicht van de epidemiologie, behandeling en functionele bijwerkingen na orgaan-sparende behandeling voor vergevorderde tumoren in het hoofd-halsgebied. Ook wordt aandacht besteed aan de mogelijke rol van preventieve slikrevalidatie en intensieve krachtrevalidatie gebaseerd op principes uit de sportgeneeskunde. In **Hoofdstuk 2** wordt een systematisch literatuuroverzicht gegeven over de huidige diagnostische en therapeutische mogelijkheden voor dysfagie na behandeling voor hoofd-halskanker. Met behulp van een uitgebreide zoekactie in de elektronische databases Medline en Embase zijn alle artikelen uit 2012 en 2013 op basis van titel en samenvatting gescreend op relevantie, methodologische kwaliteit en het risico op bias. In totaal konden 11 studies of reviews geselecteerd worden, waarin verschillende diagnostische testen voor dysfagie worden beschreven. Eveneens worden 10 studies of reviews besproken waarin wordt gerapporteerd over verschillende behandelmogelijkheden voor dysfagie. Dit literatuuroverzicht heeft duidelijk gemaakt dat er geen evidente gouden standaard bestaat voor diagnostische en/of therapeutische strategieën. Ondanks dat dysfagie bij hoofd-halskanker patiënten, gezien de zeer negatieve impact van slikklachten op de kwaliteit van leven, standaard wordt geëvalueerd en behandeld, is het nog steeds onduidelijk welke behandeling (met name met betrekking tot type, frequentie, duur en intensiteit van oefeningen) moet worden toegepast. Dit systematische literatuurreview maakt het mogelijk enkele aanbevelingen te doen voor het uitvoeren van prospectieve, gerandomiseerd en gecontroleerde studies. Daarbij is het essentieel dat er gestreefd wordt naar optimale therapietrouw (compliance), lange termijn follow-up en doelgerichtere therapieën om de slikproblemen te verminderen, om daarmee de kwaliteit van leven te verbeteren.

Lange-termijn evaluatie

Naast slikproblemen worden in de literatuur eveneens aanzienlijke stem- en spraakproblemen beschreven na orgaan-sparende behandeling voor vergevorderde hoofd-halskanker. Deel 1 van dit proefschrift richt zich op de functionele gevolgen op de lange termijn. In **Hoofdstuk 3** en **Hoofdstuk 4** worden functionele uitkomsten zoals slikfunctie, mondopening en stem/spraak beschreven in een populatie hoofd-halskanker patiënten na eerdere behandeling met gecombineerde CRT (1999–2004). Ruim 10 jaar na behandeling werden 22 patiënten geëvalueerd om de lange termijn morbiditeit vast te stellen. Alle patiënten hadden een primaire tumor uitgaande van de mond- of keelholte (mondholte, orofarynx of hypofarynx). De patiënten werden onderzocht aan de hand van een gestructureerd multidimensionaal protocol, te weten: röntgenslikvideo's, stemopnames, lichaamsgewicht, maximale mondopening en gestructureerde vragenlijsten met betrekking tot de slikfunctie, orale intake, stem- en spraakfunctie en algemene kwaliteit van leven. De vragenlijsten betroffen de gevalideerde 'Swallowing Quality of Life Questionnaire' (SWAL-QoL) en een studie-specifieke vragenlijst. Op basis van de röntgenslikvideo's werden de Penetratie Aspiratie Schaal (PAS) en contrast residu scores bepaald. Daarnaast werd de Functionele Orale Intake Schaal (FOIS) toegepast. Perceptieve stemanalyses werden uitgevoerd door twee ervaren luisteraars (logopedisten) en met behulp van een geavanceerd computerprogramma (ASISTO), gebaseerd op automatische spraakherkenning. Dit onderzoek liet zien dat 10 patiënten (45%) een normale orale intake hadden (FOIS score 7) ruim 10 jaar na behandeling, terwijl 12 patiënten (55%) matig tot ernstige slikproblemen hadden, waarvan 3 patiënten (14%) zelfs sondevoeding afhankelijk waren. De röntgenslikvideo's toonden laryngeale penetratie of aspiratie (PAS ≥3) in 15 patiënten (68%). Twaalf patiënten (55%) hadden trismus ontwikkeld (mondopening ≤35 mm), wat geassocieerd was met het optreden van aspiratie (p=0.011). Het merendeel van de patiënten rapporteerde (op basis van de SWAL-QoL scores) een aan de slikproblemen gerelateerde, gestoorde kwaliteit van leven. De patiënten die behandeld waren met IMRT lieten significant minder aspiratie (p=0.011), minder trismus (p=0.035) en minder subjectief ervaren slikproblemen zien dan de patiënten die behandeld waren met conventionele RT. De stemkwaliteit en spraakverstaanbaarheid waren eveneens vaker aangedaan in de conventioneel bestraalde patiëntengroep. Perceptieve stem- en spraakanalyses lieten abnormale scores zien oplopend tot 64%, afhankelijk van de geanalyseerde uitkomstparameter. De uitkomsten van de automatische stem- en spraakanalyse correleerde matig tot sterk met de perceptieve beoordelingen van de ervaren luisteraars. De patiënten rapporteerden dagelijkse stem- (VHI >15) en spraak- (SHI >6) stoornissen in 68% en 77% van de gevallen, respectievelijk. Ook hierbij gold dat de door IMRT behandelde patiënten minder stoornissen rapporteerden.

Het doel van **Hoofdstuk 5** was om de lange termijn functionele uitkomsten te rapporteren ruim 5 jaar na behandeling met gecombineerde CRT in een cohort hoofd-halskanker patiënten

dat had meegedaan aan een gerandomiseerd klinisch onderzoek naar de effecten van preventieve slikrevalidatie. De primaire uitkomstmaten waren slikfunctie, mondopening en stemkwaliteit. Initieel waren er 55 patiënten met een vergevorderde tumor in de mondholte, orofarynx, hypofarynx, nasofarynx of larynx in deze preventieve revalidatiestudie geïncludeerd. De patiënten waren behandeld met IMRT en (gelijktijdige) intraveneuze chemotherapie (cisplatin). Voorafgaand aan de behandeling werden de patiënten gerandomiseerd in een standaard logopedische oefengroep of een experimentele oefengroep. Alle patiënten hadden tijdens de behandeling preventieve slikoefeningen uitgevoerd, die zij hadden gecontinueerd tot 1 jaar na behandeling. Doordat de resultaten in beide oefengroepen op de korte termijn gelijk waren, werden de gegevens gecombineerd voor analyse op de lange termijn. De slikfunctie werd vastgesteld aan de hand van laryngeale penetratie of aspiratie (PAS scores), contrast residu scores, orale intake en voedingsstatus (FOIS scores, gewicht, BMI), maximale mondopening, pijn en kwaliteit van leven. De stemkwaliteit werd gemeten aan de hand van verschillende akoestische stemparameters. Na een mediane follow-up van 6 jaar bleken de 22 overlevende patiënten slechts weinig slikproblemen te hebben. De meeste functionele en kwaliteit van leven aspecten waren niet significant veranderd ten opzichte van de uitgangssituatie of van de situatie na 2 jaar follow-up. Uitzonderingen waren xerostomie, die significant was toegenomen van 18% vóór de behandeling tot 68% na 6 jaar (p=0.003) en milde pijn in het hoofd-halsgebied, die was toegenomen van 9% na 2 jaar tot 32% na 6 jaar (p=0.06). In de 7 patiënten met een tumor distaal van het tongbeen (larynx, hypofarynx) lieten de akoestische stemanalyses minder stemhebbendheid, een hogere toonhoogte en meer vocale inspanning zien vergeleken met de patiënten met een tumor craniaal van het tongbeen (mondholte, orofarynx, nasofarynx). De patiënten ervoeren weinig stemklachten 6 jaar na behandeling, ondanks dat 50% van de patiënten aangaf dat de stem veranderd was ten opzichte van de uitgangssituatie. Concluderend zijn er beperkte functionele slik- en stemproblemen in dit patiëntencohort 6 jaar na behandeling met CRT, mogelijk vanwege de preventieve slikrevalidatie programma's die tijdens en na de behandeling zijn toegepast.

Hoofdstuk 6 verschaft kwantitatieve gegevens over de slikfunctie aan de hand van temporele en spatiele variabelen die betrekking hebben op de verplaatsing van het tongbeen (als maat voor larynxheffing) tijdens het slikken. Het doel van de studie was een beter inzicht te verkrijgen in de pathofysiologie van het slikken in de gerevalideerde hoofd-halskanker patiëntenpopulatie en om correlaties te onderzoeken met objectieve en subjectieve klinische slikproblemen. De gegevens werden geanalyseerd aan de hand van eerder verzamelde röntgenslikvideo's in het kader van de hierboven beschreven prospectieve studie (Hoofdstuk 5). Een gestandaardiseerd videofluoroscopie protocol was toegepast in 25 hoofd-halskanker patiënten die röntgenslikvideo's hadden ondergaan op drie verschillende meetmomenten vóór en na CRT (uitgangssituatie, 10 weken en 1 jaar na behandeling). De analyses werden verricht op verschillende (dun en dik vloeibare) consistenties contrastmiddel van verschillende

hoeveelheden. De slikstudies werden onafhankelijk, frame per frame door twee klinisch onderzoekers beoordeeld. Informatie werd verkregen over transporttijden, de verplaatsing van het tongbeen in zowel de anterieure als de craniale richting (met behulp van het beeldanalyse programma ImageJ), PAS scores en contrast residu scores. De eerder verzamelde FOIS scores en gegevens over de subjectief ervaren slikfunctie (studie-specifieke vragenlijst) werden eveneens in de analyse meegenomen. De gemiddelde maximale verplaatsing van het tongbeen varieerde van 9.4 mm (23% van de afstand tussen de cervicale nekwervels C2-C4) tot 12.6 mm (27%) in de anterieure richting en van 18.9 mm (41%) tot 24.9 mm (54%) in de craniale richting, afhankelijk van bolus volume en consistentie. De transporttijden tijdens het slikken verschilden niet significant over de tijd. Zoals verondersteld in de literatuur, werd door middel van dit onderzoek duidelijk dat er meerdere oorzaken lijken te zijn voor de variabele verplaatsing van het tongbeen. Verder onderzoek met een grotere patiëntenpopulatie is aldus gewenst om mogelijke correlaties te bevestigen.

Prospectieve studies

Deel 2 van dit proefschrift beschrijft prospectieve studies over niet-chirurgische of minimaal invasieve behandelstrategieën voor orofaryngeale en laryngeale dysfunctie, mede op basis van de inzichten verkregen met het literatuurreview en de cross-sectionele studies uit Deel 1. Aangezien hoofd-halskanker patiënten dysfagie kunnen ontwikkelen door spierzwakte (als gevolg van fibrose en spieratrofie) na CRT, kan versterking van de slikspieren middels therapeutische krachtoefeningen mogelijk effectief zijn voor het verbeteren van de slikfunctie. In **Hoofdstuk 7** wordt de haalbaarheid en effectiviteit van spierversterkende (slik-)oefeningen gericht op de suprahyoidale spiergroep bestudeerd in oudere, gezonde proefpersonen. De oefeningen werden uitgevoerd met een speciaal daarvoor ontwikkeld hulpmiddel; de zgn. 'Swallow Exercise Aid' (SEA). Met dit apparaat is het mogelijk om progressieve spierbelasting te realiseren doordat de weerstand tijdens de oefeningen kan worden opgehoogd. Verondersteld werd dat dit instrument, ontwikkeld voor zowel isometrische als isokinetische krachtoefeningen, kan helpen om de suprahyoidale spieren te versterken en daarmee het slikken functioneel kan verbeteren. Tien gezonde vrijwilligers hebben gedurende 6 weken 3 keer per dag verschillende oefeningen uitgevoerd, te weten: 'chin tuck against resistance' (CTAR; kin op de borst), 'jaw opening against resistance' (JOAR; mond opening) en 'effortful swallow' (krachtig slikken) oefeningen. Met behulp van een multidimensionaal evaluatieprotocol werden de volgende uitkomstmaten vooraf en achteraf geëvalueerd: maximale 'chin tuck' en maximale 'jaw opening' kracht (met behulp van een speciaal ontwikkelde testopstelling met een dynamometer), maximale tongkracht en uithoudingsvermogen gemeten met de 'Iowa Oral Performance Instrument' (IOPI), suprahyoidale spiervolume (d.w.z. het volume van de musculus mylohyoideus, de musculus geniohyoideus en de musculus digastricus tezamen, gemeten met behulp van MRI

opnames), anterieure en craniale tongbeen verplaatsing (op basis van röntgenslikvideo's), maximale mondopening (in mm), haalbaarheid/therapietrouw (door middel van een studie-specifieke vragenlijst) en subjectief ervaren slikklachten gebaseerd op SWAL-QoL scores. Na de 6-weekse oefenperiode met de SEA lieten de resultaten significante verbeteringen zien in maximale 'chin tuck' en maximale 'jaw opening' kracht, maximale tongkracht, suprahyoidale spiervolume en maximale mondopening (p <0.05). De haalbaarheid en therapietrouw (mediaan 86%; range 48-100%) van de SEA oefeningen waren goed. Samenvattend toont deze prospectieve haalbaarheids- en effectiviteitsstudie aan dat de isometrische en isokinetische spierversterkende oefeningen met de SEA slikspiervolume en spierkracht bij oudere gezonde proefpersonen aanzienlijk kan verhogen na een oefenperiode van 6 weken.

Deze positieve resultaten rechtvaardigden verder onderzoek naar de werkzaamheid en effectiviteit van deze SEA oefeningen bij hoofd-halskanker patiënten met chronische dysfagie. Daarom werd in **Hoofdstuk 8** deze behandeling in een fase 2 klinische studie prospectief onderzocht bij patiënten met chronische, therapieresistente dysfagie. Gedurende 6 tot 8 weken hebben 18 hoofd-halskanker patiënten met chronische slikklachten 3 keer per dag geoefend met de SEA. De primaire uitkomstmaten waren haalbaarheid, therapietrouw en korte termijn effect parameters. Na 6 tot 8 weken intensieve sliktraining was er sprake van een algemene en specifieke (op basis van de 3 dagelijkse oefensessies) therapietrouw van 89% en 97%, respectievelijk. Aan het eind van de oefenperiode was er wederom sprake van een significante verbetering in mediane maximale 'chin tuck' en 'jaw opening' kracht, met uitzondering van een drietal patiënten met een uitgangskracht van minder dan 10 Newton. Bijna alle patiënten (94%) hadden het gevoel beter te kunnen slikken na de oefenperiode. Concluderend was er sprake van een hoge haalbaarheid en therapietrouw en werden er een aantal objectieve en subjectieve effecten van progressieve spierbelasting op de slikspierkracht en functie aangetoond.

In **Hoofdstuk 9** wordt de haalbaarheid en potentiële waarde van een experimentele behandeling (lipofilling) prospectief onderzocht bij patiënten met chronische, ernstig invaliderende orofaryngeale dysfunctie, waarbij eerdere reguliere of intensieve (logopedische) sliktherapie onvoldoende resultaat heeft geboden. Lipofilling werd toegepast bij functionele slikproblemen als gevolg van volumeverlies of atrofie van de tongbasis of farynxachterwand na eerdere chirurgische of (chemo-)radiatie behandeling voor vergevorderde hoofd-halskanker. De hypothese was dat transplantatie van autoloog vetweefsel uit de buikwand mogelijk de klachten van dysfagie en aspiratie kan verminderen door compensatie van de langer bestaande weefseldefecten/volumeverlies. In totaal werden zeven patiënten met langdurig bestaande slikproblemen geïncludeerd voor deelname aan de studie. De procedure werd uitgevoerd onder algehele narcose in een drietal sessies. De uitkomsten werden geëvalueerd middels röntgenslikvideo's voor het verkrijgen van objectieve PAS en contrast residu scores. Subjectieve FOIS scores en SWAL-QoL scores werden ook meegenomen in de analyse. MRI

opnames werden gebruikt om de postoperatieve hoeveelheid geïnjecteerd vet te evalueren. Vijf patiënten hadden de geplande procedure van 3 lipofilling sessies voltooid, terwijl twee patiënten slechts twee vetinjecties hadden ondergaan. Eén patiënt viel uit de studie na twee vetinjecties vanwege progressieve dysfagie waardoor een totale laryngectomie noodzakelijk werd. Vier van de zes overige patiënten lieten na behandeling verbeterde PAS scores zien tijdens videofluoroscopie, waarbij twee patiënten niet langer aspireerden bij het slikken van een specifieke dun of dik vloeibare consistentie. Twee patiënten waren niet langer sondevoeding afhankelijk. De subjectief ervaren (patiënt-gerapporteerde) slikfunctie en orale intake verbeterde in vier van de zes patiënten. Op basis van deze resultaten lijkt de lipofilling techniek dus veilig en – in geselecteerde gevallen – ook van potentiële waarde voor verbetering van de slikfunctie en orale intake bij hoofd-halskanker patiënten met chronische, therapieresistente dysfagie.

Tot slot worden de resultaten van dit proefschrift in **Hoofdstuk 10** besproken en worden enkele toekomstperspectieven geschetst.

LIST OF ABBREVIATIONS

1RM	1-Repetition Maximum
3D	3-Dimensional
ASISTO:	Automatic Speech analysis In Speech Therapy for Oncology
AVQI:	Automatic Voice Quality Index
BMI:	Body Mass Index
CRT:	Chemoradiotherapy
CT:	Chemotherapy
CTAR:	Chin Tuck Against Resistance
FEES:	Fiberoptic Endoscopic Examination of Swallowing
FOIS:	Functional Oral Intake Scale
HNC:	Head and Neck Cancer
ICC:	Intraclass Correlation Coefficient
IA:	Intra-Arterial
IMRT:	Intensity-Modulated Radiation Therapy
IV:	Intravenous
JOAR:	Jaw Opening Against Resistance
MIO:	Maximum Interincisor Opening
MRI:	Magnetic Resonance Imaging
NMES:	Neuro Muscular Electrical Stimulation
NPO:	Nothing Per Oral
OS:	Overall Survival
PES:	Pharyngo-Esophageal Sphincter
PAS:	Penetration Aspiration Scale
RT:	Radiotherapy
SD:	Standard Deviation
SEA:	Swallow Exercise Aid
SHI:	Speech Handicap Index
SLP:	Speech Language Pathologist
SPSS:	Statistical Package for Social Sciences
SWAL-QOL:	Swallowing Quality of Life Questionnaire
TL:	Total Laryngectomy
TNM:	Tumor Node Metastasis
UES:	Upper Esophageal Sphincter
VAS:	Visual Analog Scale
VFS:	Videofluoroscopy of Swallowing
VHI:	Voice Handicap Index
QOL:	Quality of Life

AUTHORS AND AFFILIATIONS

A. Al-Mamgani, MD, PhD. Department of Radiation Oncology, The Netherlands Cancer Institute – Antoni van Leeuwenhoek, Amsterdam, The Netherlands.

M.W.M. van den Brekel, MD, PhD. Department of Head and Neck Oncology and Surgery, The Netherlands Cancer Institute – Antoni van Leeuwenhoek, Amsterdam, The Netherlands; Institute of Phonetic Sciences, University of Amsterdam, Amsterdam, The Netherlands; Department of Oral and Maxillofacial Surgery, Academic Medical Center, Amsterdam, The Netherlands.

W.D. Heemsbergen, PhD. Department of Radiation Oncology, The Netherlands Cancer Institute – Antoni van Leeuwenhoek, Amsterdam, The Netherlands.

F.J.M. Hilgers, MD, PhD. Department of Head and Neck Oncology and Surgery, The Netherlands Cancer Institute – Antoni van Leeuwenhoek, Amsterdam, The Netherlands; Institute of Phonetic Sciences, University of Amsterdam, Amsterdam, The Netherlands

O. Hamming-Vrieze, MD. Department of Radiation Oncology, The Netherlands Cancer Institute – Antoni van Leeuwenhoek, Amsterdam, The Netherlands.

I. Jacobi, PhD. Department of Head and Neck Oncology and Surgery, The Netherlands Cancer Institute – Antoni van Leeuwenhoek, Amsterdam, The Netherlands.

O. Lapid, MD, PhD. Department of Plastic Reconstructive and Hand Surgery, Academic Medical Center, Amsterdam, The Netherlands.

L. van der Molen, SLP, PhD. Department of Head and Neck Oncology and Surgery, The Netherlands Cancer Institute – Antoni van Leeuwenhoek, Amsterdam, The Netherlands.

I.M. Oskam, MD. Department of Head and Neck Oncology and Surgery, The Netherlands Cancer Institute – Antoni van Leeuwenhoek, Amsterdam, The Netherlands.

G.B. Remmerswaal, MD. Department of Head and Neck Oncology and Surgery, The Netherlands Cancer Institute – Antoni van Leeuwenhoek, Amsterdam, The Netherlands.

L.E. Smeele, MD, PhD. Department of Head and Neck Oncology and Surgery, The Netherlands Cancer Institute – Antoni van Leeuwenhoek, Amsterdam, The Netherlands; Department of Oral and Maxillofacial Surgery, Academic Medical Center, Amsterdam, The Netherlands.

R.J.J.H. van Son, PhD. Department of Head and Neck Oncology and Surgery, The Netherlands Cancer Institute – Antoni van Leeuwenhoek, Amsterdam, The Netherlands.

M.M. Stuiver, PT, PhD. Department of Physical Therapy, The Netherlands Cancer Institute – Antoni van Leeuwenhoek, Amsterdam, The Netherlands; Department of Clinical Epidemiology Biostatistics and Bioinformatics, University of Amsterdam, The Netherlands.

R.P. Takes, MD, PhD. Department of Otorhinolaryngology-Head and Neck Surgery, Radboud University Medical Center, Nijmegen, The Netherlands.

H.J. Teertstra, MD. Department of Radiology, The Netherlands Cancer Institute – Antoni van Leeuwenhoek, Amsterdam, The Netherlands.

PhD PORTFOLIO

Name PhD student:	Sophie Anne Charlotte Kraaijenga
PhD period:	September 2012 – March 2016
Name PhD supervisors:	Prof. dr. M.W.M. van den Brekel
	Prof. dr. F.J.M. Hilgers

Courses

2010	Global Health Course, University Medical Center, Utrecht
2012	Clinical Epidemiology, AMC graduate school, Amsterdam
2012	GPRA Post-Laryngectomy Rehabilitation Course, NKI-AVL, Amsterdam
2013	Dysphagia Diagnosis and Prevention, University Hospital, Antwerp
2013	Multidisciplinary treatment in Head and Neck Cancer, Free University, Brussels
2013	'Basis Regelgeving en Organisatie voor Klinisch onderzoekers' (BROK), AMC graduate school, Amsterdam
2013	Developing a Systematic Review, AMC graduate school, Amsterdam
2013	Practical Biostatistics, AMC graduate school, Amsterdam
2014	Oral Presentation in English, AMC graduate school, Amsterdam
2014	Scientific Writing in English for Publication, AMC graduate school, Amsterdam
2015	Fundamental Critical Care Support (FCCS), Society of Critical Medicine, Bilthoven

Seminars, workshops, and master classes

2012–2016	Monthly 'Werkgroep Hoofd-Hals Tumoren' (WHHT), NKI-AVL, Amsterdam
2012–2016	Monthly 'Heelkundige Oncologische Disciplines' (HOD) seminars, NKI-AVL, Amsterdam
2013–2014	Yearly Head and Neck Cancer Dysphagia Workshop, NKI-AVL, Amsterdam
2014	Three-day Medical Business Masterclass, Masterclass Foundation, Amsterdam

(Inter)national conferences attended

2012–2016	KNO-ledenvergadering (Nieuwegein, Maastricht UMC)
2013–2016	NWHHT Jonge Onderzoekersdag (UMC Utrecht, NKI-AVL, Radboudumc)
2013–2014	NWHHT Researchdag (Erasmus MC, NKI-AVL)
2013	NVMKA najaarsvergadering (Assen)
2014	NVPC regionale refereeravond (Amsterdam)

2014	IFHNOS 5th world congress (New York)
2015	Duitse Vereniging voor Dysfagie vergadering (München)
2015	Dysphagia Research Society (Chicago)
2015	NVMKA najaarsvergadering (Amersfoort)
2015	IAOO world congress (Sao Paulo)
2015	European Society for Swallowing Disorders (Barcelona)

Supervising

2014	G.B. Remmerswaal (medical student), scientific internship
2015	S. Verheijen (diagnostic radiographic student), scientific internship

Oral presentations

'13-'14 **Kraaijenga SA**, van den Brekel MW. Surgical treatments for oropharyngeal dysphagia in advanced head and neck cancer. Annual Head and Neck Cancer Dysphagia Rehabilitation Course. Antoni van Leeuwenhoek, Amsterdam, 26 april 2013; 4 oktober 2013; 25 april 2014

Nov '13 **Kraaijenga SA**, van der Molen L, van Tinteren H, Hilgers FJ, Smeele LE. Behandeling van myogene temporomandibulaire dysfunctie; een gerandomiseerd klinisch onderzoek met de TheraBite en standaard fysiotherapie. Mond-, kaak- en aangezichtschirurgie (NVMKA) 57e najaarsvergadering. Assen, 8 november 2013

Juni '14 **Kraaijenga SA**, Smeele LE, van den Brekel MW, Lapid O. Lipofilling injecties in de keelholte bij hoofd-hals kanker patiënten vanwege ernstige therapie- resistente slik- of stemklachten. Plastische Chirurgie AMC & VUmc regionale refereeravond. Amsterdam, 11 juni 2014

Juli '14 **Kraaijenga SA**, van der Molen L, Jacobi I, van den Brekel MW, Hilgers FJ. Long term swallowing function and voice quality in advanced head and neck cancer patients treated with chemoradiotherapy and preventive swallowing rehabilitation. Int. Federation Head Neck Oncology Society (IFHNOS) 5th world congress. New York, 30 juli 2014

Nov '14 **Kraaijenga SA**, van der Molen L, Jacobi I, van den Brekel MW, Hilgers FJ. Prospectief klinisch onderzoek naar de lange termijn (5-jaar+) slik- en stemfunctie bij hoofd-halskanker patiënten behandeld met chemoradiatie en preventieve slikrevalidatie. 225e KNO-ledenvergadering. Nieuwegein, 21 november 2014

Mrt ‘15 **Kraaijenga SA**, van der Molen L, Stuiver MM, Teertstra HJ, Hilgers FJ, van den Brekel MW. Effects of strengthening exercises on swallowing musculature and function in senior healthy subjects; a prospective effectiveness and feasibility study. Dysphagia Research Society (DRS) annual meeting. Chicago, 12 maart 2015

Mrt ‘15 **Kraaijenga SA**, van der Molen L, Stuiver MM, Teertstra HJ, Hilgers FJ, van den Brekel MW. Het effect van spierversterkende oefeningen op volume en functie van slikspieren bij gezonde proefpersonen. 5e Nederlandse Werkgroep Hoofd-Hals Tumoren (NWHHT) jonge onderzoekersdags. Nijmegen, 24 maart 2015

Mrt ‘15 **Kraaijenga SA**, van der Molen L. Prevention and rehabilitation of swallowing function in head and neck cancer patients; results of a randomized controlled trial. Deutsche Gesellschaft für Dysphagie, jahrestagung. München, 27 maart 2015

April ’15 **Kraaijenga SA**, van der Molen L, Stuiver MM, Teertstra HJ, Hilgers FJ, vd Brekel MW. Een prospectieve effectiviteits- en haalbaarheidsstudie naar spierversterkende oefeningen op slikspiervolume en -functie in gezonde proefpersonen (posterpresentatie). 226e KNO-ledenvergadering. Nieuwegein, 24 april 2015

Juli ’15 **Kraaijenga SA**, Oskam IM, van der Molen L, Hilgers FJ, vd Brekel MW. Evaluation of long-term (10-years+) dysphagia and trismus in patients treated with concurrent chemo-radiotherapy for locally advanced head and neck cancer. Int. Academy of Oral Oncology (IAOO) 5th world congress. Sao Paulo, 10 juli 2015

Sept ’15 **Kraaijenga SA**, van der Molen L, Hilgers FJ, vd Brekel MW. Long-term outcomes of swallowing, voice and speech following organ-preservation treatment for advanced head and neck cancer. Chirurgische Oncologie (sectie XI) bespreking. Antoni van Leeuwenhoek, Amsterdam, 16 september 2015

Okt ’15 **Kraaijenga SA**, van der Molen L, Heemsbergen WD, Remmerswaal G, Hilgers FJ, vd Brekel MW. Hyoid bone displacement as parameter for swallowing impairment in patients treated for advanced head and neck cancer. European Society for Swallowing Disorders (ESSD). Barcelona, 3 oktober 2015

Okt ’15 **Kraaijenga SA**, Oskam IM, van der Molen L, Hilgers FJ, vd Brekel MW. Evaluation of long-term (10-years+) dysphagia and trismus in patients treated with concurrent chemo-radiotherapy for locally advanced head and neck cancer. European Society for Swallowing Disorders (ESSD). Barcelona, 3 oktober 2015

Nov ’15 **Kraaijenga SA**, Lapid O, van der Molen L, Hilgers FJ, Smeele LE, van den Brekel MW. Hertel van slikfunctie en orale intake met behulp van lipofilling in de mond- of keelholte na behandeling voor hoofd-halskanker. Mond-, kaak- en aangezichtschirurgie (NVMKA) 59e najaarsvergadering. Amersfoort, 5 november 2015

Nov ’15 **Kraaijenga SA**, van der Molen L, Stuiver MM, Hilgers FJ, vd Brekel MW. Chronische slikproblemen bij hoofd-halskanker patiënten: nieuwe (oefentherapie) mogelijkheden? Symposium Logopedische & Audiologische Wetenschappen. Leuven, 14 november 2015

Nov ’15 **Kraaijenga SA**, Lapid O, van der Molen L, Hilgers FJ, Smeele LE, van den Brekel MW. Hertel van slikfunctie en orale intake met behulp van lipofilling in de mond- of keelholte na behandeling voor hoofd-halskanker. 227e KNO-ledenvergadering. Nieuwegein, 19 november 2015

Jan ’16 **Kraaijenga SA,** van der Molen L, Hilgers FJ, van den Brekel MW. Chronische slikproblemen bij hoofd-halskanker patiënten: nieuwe (oefentherapie) mogelijkheden? Jaarvergadering Logopedie landelijke werkgroep Hoofd-Hals tumoren. Nijmegen, 15 januari 2016

List of publications

Kraaijenga SA, van der Molen L, Stuiver MM, Takes RJ, Al-Mamgani A, van den Brekel MW, Hilgers FJ. Efficacy of a novel swallowing exercise program for chronic dysphagia in long-term head and neck cancer survivors. Submitted.

Kraaijenga SA, van der Molen L, Heemsbergen WD, Remmerswaal GB, Hilgers FJ, van den Brekel MW. Hyoid bone displacement as parameter for swallowing impairment in patients treated for advanced head and neck cancer. Eur Arch Otorhinolaryngol. Online 2016 Apr 16.

Kraaijenga SA, Lapid O, van der Molen L, Hilgers FJ, Smeele LE, van den Brekel MW. Feasibility and potential value of lipofilling in post-treatment oropharyngeal dysfunction. Laryngoscope. Online 2016 Apr 14.

Kraaijenga SA, Oskam IM, van Son RJJH, Hamming-Vrieze O, Hilgers FJ, van den Brekel MW, van der Molen L. Assessment of voice, speech, and related quality of life in advanced head and neck cancer patients 10-years+ after chemoradiotherapy. Oral Oncol. 2016 Apr;55:24-30.

Kraaijenga SA, Oskam IM, van der Molen L, Hilgers FJ, van den Brekel MW. Evaluation of long-term (10-years+) dysphagia and trismus in patients treated with concurrent chemo-radiotherapy for locally advanced head and neck cancer. Oral Oncol. 2015 Aug;51(8):787-94.

Kraaijenga SA, van der Molen L, Stuiver MM, Teertstra HJ, Hilgers FJ, van den Brekel MW. Effects of strengthening exercises on swallowing musculature and function in senior healthy subjects; a prospective effectiveness and feasibility study. Dysphagia. 2015 Aug;30(4):392-403.

Kraaijenga SA, van der Molen L, Jacobi I, van den Brekel MW, Hilgers FJ. Prospective clinical study on long-term swallowing function and voice quality in advanced head and neck cancer patients treated with concurrent chemoradiotherapy and preventive swallowing exercises. Eur Arch Otorhinolaryngol. 2015 Nov;272(11):3521-31.

Kraaijenga SA, Smeele LE, van den Brekel MW, Lapid O. Herstel van slik- en stemfunctie met behulp van lipofilling in de mond- of keelholte na behandeling voor hoofd-hals kanker. Nederlands Tijdschr voor Plastische Chirurgie. 2015 Jan;6(1):33-38.

Kraaijenga SA, van der Molen L, van den Brekel MW, Hilgers FJ. Current Assessment and treatment strategies of dysphagia in head and neck cancer patients: a systematic review of the 2012/13 literature. Curr Opin Support Palliat Care. 2014 Jun;8(2):152-63.

Heres Diddens H, **Kraaijenga SA**, van der Molen L, Hilgers FJ, Smeele LE, Retèl VP. A cost-effectiveness analysis of using the TheraBite compared to standard physical therapy exercise in a prospective randomized clinical trial for treating myogenic temporomandibular disorder. Submitted.

Kraaijenga S, van der Molen L, van Tinteren H, Hilgers FJ, Smeele LE. Treatment of myogenic temporomandibular disorder: a prospective randomized clinical trial, comparing a mechanical stretching device (TheraBite) with standard physical therapy exercise. Cranio. 2014 Jul;32(3):208-16.

Winters SM, Klis SFL, **Kraaijenga SA**, Kool ACM, Tange RA, Grolman W. Peri-operative bone-conducted Vestibular Evoked Myogenic Potentials in otosclerosis patients. Otol Neurotol. 2013 Aug;34(6):1109-14.

ABOUT THE AUTHOR

Sophie Kraaijenga was born on October 3th, 1986 in Utrecht, the Netherlands. She grew up with her parents and three sisters in Geldrop (Noord-Brabant). In 2005 she graduated from secondary school and started her medical study at the University of Utrecht. During that time she worked as a medical student at the department of Oncology and Haematology, was an active member of her students' union (U.V.S.V./N.V.V.S.U), and became chairmen of the masters' medical education committee. She spent a period of 3 months (2010) in India and 2 months (2011) at Curacao for clinical internships. After obtaining her medical degree at the end of 2012, she started her PhD project at the department of Head and Neck Oncology and Surgery of the Netherlands Cancer Institute, under the supervising of prof. dr. F.J.M. Hilgers and prof. dr. M.W.M. van den Brekel. During this period she worked at the outpatient clinic for two years, she organized a 2-day annual meeting of the Dutch Head and Neck Society, and she participated with 99 colleagues at the national cycling event 'Alpe d'HuZes' to raise money for cancer research. In August 2015 she started working as a surgical resident at the Netherlands Cancer Institute, while finishing her PhD project. The results are described in this thesis.

ACKNOWLEDGEMENT | DANKWOORD

Een half jaar voor mijn afstuderen, tijdens mijn keuze co-schap op de afdeling hoofd-hals oncologie en chirurgie van het Antoni van Leeuwenhoek, stond ik op de OK te assisteren tot er ineens werd gebeld. Of de co-assistent even naar Michiel wilde komen? Nietsvermoedend liep ik naar het toenmalige H-gebouw, waar ik niet alleen Michiel, maar ook Frans en Lisette in enigszins formele setting aantrof, met de vraag of ik fulltime wilde gaan promoveren. “Iets met slikken” was het enige dat ik onthouden had.. Ondanks dat Michiel zei dat ik hier eigenlijk een week over moest nadenken, zei ik meteen ja. Het was het begin van een nieuw avontuur, wat achteraf gezien veel te snel voorbij is gegaan. Het Antoni van Leeuwenhoek is een fantastisch instituut en ik kijk met heel veel plezier terug op de afgelopen jaren dat ik deel heb mogen uitmaken van de hoofd-hals afdeling. Uiteraard heb ik gedurende deze jaren van velen begeleiding en ondersteuning gehad. Iedereen die een bijdrage heeft geleverd aan de totstandkoming van dit proefschrift ben ik dan ook veel dank verschuldigd. Een aantal personen zou ik hier graag in het bijzonder noemen.

Mijn promotor prof. dr. M.W.M. van den Brekel. Beste Michiel, ik heb ontzettend veel bewondering voor de hoeveelheid energie en interesse die jij hebt en hoe je altijd zoveel verschillende klinische, wetenschappelijke en overige zaken met elkaar weet te combineren. Je gaf me de vrijheid om zelfstandig te werk te gaan, maar was ook kritisch wanneer dat nodig was. Ook wil ik je enorm bedanken voor het mogelijk maken van verschillende congresbezoeken naar o.a. New York, Chicago en Sao Paulo. Zolang je de trap naar de 5e verdieping op blijft sprinten en Marion of Henny je agenda en afspraken beheert, weet ik zeker dat het goed met je zal gaan. Ik wens je het allerbeste voor de toekomst!

Mijn promotor, prof. dr. F.J.M. Hilgers. Beste Frans, het is me gelukt; ik ben (toch nog) tot één van jouw promovendi gaan horen! De snelheid van de totstandkoming van dit proefschrift is deels te danken aan jouw snelle en zorgvuldige begeleiding, met altijd zeer laagdrempelig (whatsapp) contact. Waar je je ook ter wereld bevond, jij reageerde altijd binnen enkele uren en het tijdsverschil zorgde er vaak voor dat we des te efficiënter konden samenwerken. Ik wil je enorm bedanken voor je enthousiasme en betrokkenheid en voor alle mogelijkheden die je mij geboden hebt.

Mijn co-promotor, dr. L. van der Molen. Lieve Lisette, jij was vanaf het eerste moment mijn directe begeleider en ik denk dat we zo goed konden samenwerken doordat ik mezelf vaak in jou herkende. Jouw proefschrift was de basis voor het mijne en met name op al die internationale congressen, waar werkelijk iedereen jou kende, was ik enorm trots jouw opvolger te mogen zijn. De vele uren die we samen achter de computer hebben doorgebracht

om alle slikvideo's te beoordelen zal ik niet snel vergeten, evenals onze weekendjes naar Malmö, Brussel/Antwerpen en Leuven. Ik heb veel bewondering voor hoe je al je verschillende werkzaamheden weet te combineren met ook nog een druk privé leven. Ik wens je nog een hele fijne tijd in het AVL toe!

De leden van mijn promotiecommissie, prof. dr. A.J.M. Balm, prof. dr. J.J. de Lange, prof. dr. C.R.N. Rasch, prof. dr. H.A.M. Marres en dr. L.W.J Baijens, ik wil u allen hartelijk danken voor de tijd die u heeft vrijgemaakt om mijn manuscript te beoordelen en om zitting te nemen in de oppositie tijdens de verdediging van mijn proefschrift. Ik hoop u allen te blijven tegenkomen in de (steeds veranderende) medische wereld, waarin de vraag naar kritische blikken en innovatieve oplossingen van groot belang is.

Prof dr. L.E. Smeele, beste Ludi, mijn allereerste project over temporomandibulaire dysfunctie was deels onder jouw begeleiding, gevolgd door ons gezamenlijke lipofilling project. Ik kijk met plezier terug op deze samenwerking, maar misschien nog wel meer op het samen opereren op zaterdag of op onze vele wielertochten in zowel binnen- als buitenland. Hoe snel jij de berg op fietst is uniek en ik hoop ooit weer samen een rondje te maken!

Dr. W.M. Klop, beste Martin, hartelijk bedankt voor het begeleiden van mij als co-assistent, arts-assistent en zelfs op de tennisbaan. Naast al je humor en gezelligheid ken ik maar weinig mensen die zo didactisch zijn als jij. Gaan we snel weer een potje tennissen?

(Oud) hoofd-hals chirurgen uit het Antoni van Leeuwenhoek, Bing Tan, Fons Balm, Lotje Zuur, Baris Karakullukçu en Peter Lohuis, ik ben zeer trots dat ik deel mocht uitmaken van jullie fantastische team en ik wil jullie enorm bedanken voor de fijne samenwerking op de polikliniek, afdeling, operatiekamer of U-gebouw.

Alle co-auteurs die hebben meegeschreven aan een of meerdere hoofdstukken uit dit proefschrift, veel dank voor jullie tijd en positieve feedback. In het bijzonder dr. M.M. Stuiver, beste Martijn, enorm bedankt voor alle inhoudelijke opmerkingen over de rol van intensieve krachtrevalidatie en de nodige statistiek uitleg! Dr. R.P. Takes, beste Robert, veel dank voor de prettige samenwerking met Nijmegen. En Gawein, heel veel dank voor al het (saaie!) werk dat jij verzet hebt!

Alle gezonde proefpersonen die ruim 6 weken hebben geoefend met de Swallow Exercise Aid in het kader van mijn studie over intensieve slikspiertraining, Peter, Wim, Rob, Rien, George, Govert, Cees, Bing, Michiel en Frans, enorm bedankt voor jullie inzet! Wim, heel veel dank voor het vervaardigen van de apparaten. En Cees, wat fijn dat jij het mogelijk maakte om op zaterdag MRI's te verrichten.

Marion van Zuilen en Henny Buis, heel veel dank voor het regelen, versturen, boeken, mailen, bellen of declareren van allerlei zaken.

De AVL logopedisten, Anne, Merel en Klaske, bedankt voor de fijne samenwerking in de kliniek en rondom mijn onderzoek. Ik kan me voorstellen dat het niet altijd uit kwam om onverwachts een slikvideo 'volgens SEA protocol' te moeten uitvoeren, maar voor mij was heel fijn dat jullie zo flexibel waren. Jullie zijn een gouden team en onmisbaar voor de afdeling!

Alle overige mensen met wie ik als arts-onderzoeker of-assistent heb samengewerkt, zoals de medewerkers van de hoofd-hals poli, de secretaressen en verpleegkundigen van de 5e etage, de radiotherapeuten, chirurgen, tandartsen en hoofd-hals internisten. Dr. J.P. de Boer en dr. M.E.T. Tesselaar, veel dank voor alle consulten over nierfunctiestoornissen bij RADPLAT patiënten. Peter Seerden, jij was nooit te beroerd om langs te komen op zaal en altijd zo geïnteresseerd, veel dank daarvoor! Dr. J van der Hage, hartelijk bedankt voor het begeleiden van mij op zaal, maar bovenal voor het vele lachen op de fiets, op de piste of op de schaatsbaan. Ik wens je het allerbeste voor de toekomst.

De AVL fellows FLEUS, RDIRV en ook X-BEM, veel dank voor alle gezelligheid op de piste en tijdens de borrels en vooral ook veel dank voor alle onderwijs momenten op de OK of afdeling.

De Sao Paulo congres groep, Hester, Caro, Simone, Charlotte, Ellen, Saar, Steven, Baris en Pim, wat een fantastische week hebben wij gehad! Gaan we snel weer samen ergens heen!?

(Oud-) arts-onderzoekers uit het O-, U- en hoofdgebouw, veel dank voor alle leuke lunches, wintersporten (4x!), festivals, squash avonden en vrijdagmiddagborrels. Rosa, het was heel fijn om af en toe weer helemaal bij te kletsen. Marieke, dank voor de leuke wintersport! Matthijs, Tjeerd en Roel, de Alpe d'Huez was onze eerste ervaring in de bergen en daarna volgden steeds meer bergtochten. Ik vind het heel bijzonder dat we nog steeds regelmatig samen fietsen. Lieve Hannah, Liset, Marije, Jos en Ann-Jean, ik wens jullie veel succes en plezier verder in het U-gebouw!

(Oud-) arts-assistenten chirurgie en KNO, lieve Anne, Bas, Caro, Danique, Gawein, Jacq, Jantien, Jasper, Martijn, Michel, Nick, Niels Noor, Pep, Piet & Piet, Rens, Roos, Tessa, Thijs en Steef, het was altijd een dolle boel op de afdeling, tijdens wintersport, op de borrel, op de schaatsbaan en op de racefiets. Dank voor de fijne samenwerking! Met pijn in mijn hart heb ik ons weekend Renesse moeten missen. Maar ik hoop binnenkort op een herkansing!?

Al mijn lieve vriendinnetjes uit Eindhoven, Utrecht, Amsterdam of elders, in het bijzonder Wen, Janna, Emma, Cres, Kaar, Wil, Griet, Mayo, Yvette, Siets, Saar, Ell, Nyn en Geer, heel veel dank voor alle gezelligheid, sportiviteit, borrels, diners en gesprekken buiten het werk om. Ik ben blij dat we zo'n hechte band hebben! Lieve Wen, we kennen elkaar nog geen 5 jaar maar het voelt zo veel langer en altijd zo vertrouwd! Lieve Janna, wat ben ik trots dat jij zo'n grote carrièreswitch hebt durven maken. Lieve Emma, sommige vriendinnetjes hoef je niet dagelijks te spreken :) Lieve Ro en Naad, ik ben stiekem heel erg blij dat jullie voorlopig nog in Nederland blijven! En Griet en Mayo, gaan we snel weer zeilen, schaatsen, skiën (haute route!) of lekker eten?

Mijn schoonfamilie. Lieve Ben, Margreet en Bente, wat bof ik met jullie als schoonouders en schoonzus. Veel dank voor jullie interesse, steun en gezelligheid. Ik kijk uit naar alle gezamenlijke diners en vakanties die nog zullen volgen!

Mijn paranimf en lieve vriendin, Caroline Bambach. Lieve Caro, wat ben ik blij dat wij elkaar in Amsterdam weer helemaal gevonden hebben! Door niet alleen vriendinnetjes maar ook collega's te zijn, is onze band alleen maar versterkt. En door het vele tennissen zijn nu zelfs onze vriendjes goede vrienden geworden. Ik ben enorm trots op jouw positieve instelling, kritische blik en doorzettingsvermogen. Zodra er iets is sta je voor me klaar. Ik ben daarom erg blij dat je vandaag naast me staat! En lieve Jel, wat fantastisch dat jij vanavond de DJ wilt zijn. De voetjes gaan van de vloer!

Mijn paranimf en kleine zusje Veronique. Lieve Veer, onze band was van jongs af aan al ijzersterk doordat we enorm veel op elkaar lijken en op dezelfde manier in het leven staan. Door onze gedeelde interesse voor de KNO-heelkunde is deze band voor mijn gevoel alleen maar sterker geworden. Ik was vroeger jouw grote voorbeeld maar straks zal jij mij vermoedelijk voor gaan. Ik ben super trots op je! En Yannick, wat super fijn dat jij bij ons in de familie bent gekomen!

Mijn andere lieve zus, Charlotte. Lieve Char, gelukkig zorg jij ervoor dat niet alle zusjes exact hetzelfde zijn. Waar wij al wat eerder op zoek waren naar enige structuur en houvast, was jij nog wel eens zoekende naar wat je nu precies wilt. Inmiddels ben je ook bijna aan het werkende leven toe en ik heb er alle vertrouwen in dat het je goed af zal gaan. Er is maar een zus die zo goed kan inschatten hoe het met me gaat en met wie ik zo goed kan praten, dus ik weet zeker dat elk kind straks ontzettend blij zal zijn met jouw behandeling en begeleiding! En Pieter, welkom in de familie-app ;-)

Mijn grote zus, Juliette, Lieve Juul, als er iemand is die altijd voor me klaar staat, dan ben jij het wel. Ik zou me geen betere zus en voorbeeld kunnen wensen dan jij. Samen met Rogier ben je inmiddels de trotse ouder van Boele, die nu met 6 maanden al volop geniet van jouw onvoorwaardelijke liefde en zorgzaamheid. Als die kleine lacht dan smelt ik gewoon! Lieve Rogier, ook jij bent na bijna 10 jaar niet meer weg te denken uit onze familie. Ik vind het enorm bijzonder om straks op jullie huwelijk als getuige te mogen optreden. Ik kijk uit naar onze toekomst samen met hopelijk veel geluk en samenzijn. Ik hou van jullie!

Mijn ouders, lieve papa en mama, wat ben ik blij met jullie onvoorwaardelijke steun, liefde en vertrouwen. Door jullie was het mogelijk om een huis te kopen in Amsterdam, iets waar ik enorm dankbaar voor ben. Frank, onze gedeelde liefde voor sport bracht ons dicht bij elkaar en ik hoop nog vaak samen op de fiets te stappen. Karien, wij delen een passie voor lekker en gezond koken en ik hoop nog vele dinertjes samen te organiseren. Papa, dank voor alle mogelijkheden die je me gegeven hebt. Ik hoop nog veel samen in Friesland te zijn om te genieten van het zeilen. Mama, bedankt dat je altijd voor me klaar staat – no matter what. Ik hou zo veel van jullie!

Tot slot.. mijn liefde voor altijd. Lieve Wiebe, wat ben ik gelukkig met jou. Ik ben zo blij dat wij elkaar hebben ontmoet. Onze gedeelte passies en interesses zorgen ervoor dat wij ons nooit vervelen. Waar ik nog wel eens twijfel, help jij me om de juiste keuze te maken. Ik hou heel erg veel van jou en verheug me enorm op onze toekomst samen!