Improving dysphagia care in head and neck cancer patients treated with radiotherapy

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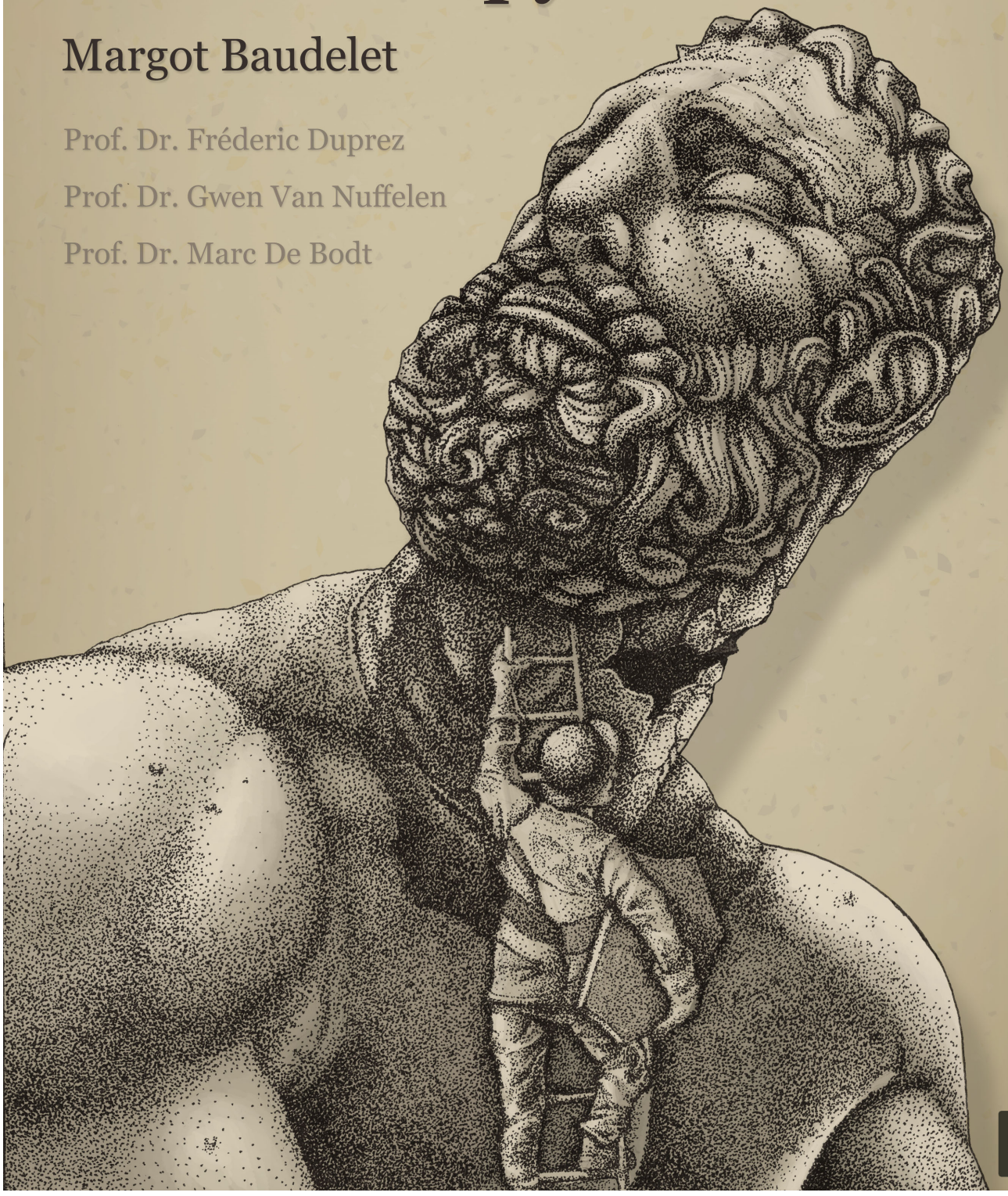

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Improving dysphagia care in head and neck cancer patients treated with radiotherapy

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Publications

This thesis is based on the following articles published in or submitted to international peer reviewed journals:

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2. **Baudelet, M.**, Van den Steen, L., Duprez, F., De Bodt, M., Deschuymer, S., Goeleven, A., Hutsebaut I., Mariën S., Meersschout S., Nevens D., Nuyts S., Peeters M., Specenier P., Van den Brekel M., van der Molen L., Vandenbruaene C., Vanderveken O., Van Dinther J., Van Laer C., Vauterin T., Verstraete H. and Van Nuffelen, G. Study protocol for a randomized controlled trial: prophylactic swallowing exercises in head-and-neck cancer patients treated with (chemo) radiotherapy (PRESTO trial). *Trials*. 2020;21(1), 1-10.

3. **Baudelet M.**, Van den Steen L., Wouters S., De Bodt M., Vanderveken O., Duprez F., Van Nuffelen G. Supportive care among head and neck cancer patients: validation of the Dutch version of the Oral Mucositis Weekly Questionnaire-Head and Neck Cancer (D-OMWQ-HN). *B-ENT.* 2022; 18: 254-261.

4. **Baudelet M.**, Duprez F., Van den Steen L., Nuyts S., Nevens D., Goeleven A., Vandenbruaene C., Massonet H., Vergauwen A., Bollen H., Deschuymer S., Wouters K., Peeters M., Van Laer C., Mariën S., Van den Brekel M., van der Molen L., Vauterin T., van Dinther J., Verstraete H., Hutsebaut I., Meersschout S., Vanderveken O., De Bodt M., Van Nuffelen G. Increasing adherence to prophylactic swallowing exercises during head and neck radiotherapy: the multicenter, randomized controlled PRESTO-trial. *Dysphagia*. 2022; 1-10.

5. **Baudelet M.**, Van den Steen L., Duprez F., Goeleven A., Nuyts S., Nevens D., Vandenbruaene C., Massonet H., Vergauwen A., Vauterin T., Verstraete H., Wouters K., Vanderveken O., De Bodt M., Van Nuffelen G. Prophylactic swallowing therapy during head and neck cancer radiotherapy: effect of service-delivery mode and overall adherence level on swallowing function and muscle strength. The PRESTO trial. *Manuscript submitted in Dysphagia*.

List of abbreviations

1RM: 1-repetition maximum

CRT: chemoradiotherapy

CTAR: chin tuck against resistance

D-OMWQ-HN: Dutch oral mucositis weekly questionnaire-head and neck cancer

HNC: head and neck cancer

HPV: human papillomavirus

IMRT: intensity-modulated radiotherapy

OM: oral mucositis

OMWQ: oral mucositis weekly questionnaire

PRESTO: **PR**ophylactic **E**xercises in **S**wallowing **T**herapy for **O**ropharyngeal cancer patients treated with (chemo)radiotherapy

PROM: patient-reported outcome measure

PSE: prophylactic swallowing exercises

QoL: quality of life

RAD: radiation-associated dysphagia

RCT: randomized controlled trial

RT: radiotherapy

RT/CRT: (chemo)radiotherapy

SLP: speech and language pathologist

SWOT: strengths, weaknesses, opportunities and threats

TLM: transoral laser microsurgery

TORS: transoral robotic surgery

TSE: tongue strengthening exercises

Chapter 1

Introduction

Chapter 1: Introduction

Radiation-associated dysphagia (RAD) in head and neck cancer (HNC) patients is very common both during and (long) after radiotherapy [1-4]. The medical and psychosocial consequences such as malnutrition, tube feeding dependency and depression, have an immense impact on the patients' quality of life (QoL) [5-7]. Therefore, monitoring, prevention and treatment of this burdensome side-effect is paramount. Whilst prophylactic swallowing exercises have already demonstrated beneficial effects on post-treatment swallowing function and QoL, adherence to these therapy programs remains however low [2; 8-11]. This low adherence hampers the positive impact these exercises have.

Current research aims to improve healthcare in HNC patients by monitoring and evaluating dysphagia and by seeking ways to prevent this debilitating side-effect. The primary aim of this thesis was **to develop an optimized, patient-tailored and evidence-based prophylactic swallowing program that increases adherence** to swallowing exercises and can be easily used in daily clinical practice in HNC patients undergoing radiotherapy.

Marc is 56 years old and diagnosed with head and neck cancer. His life is turned upside down when the treatment, including chemoradiotherapy lasting 7 weeks and its possible side-effects, are explained by his doctor. A few days after his diagnosis, Marc is offered participation in an ongoing trial: extra guidance and support towards the possible development of swallowing problems will be given and preventive swallowing therapy will be started. Marc does not hesitate for a moment. The strenuous weeks of radiotherapy slowly pass while the side-effects of the treatment begin to sink in. In spite of all this, Marc continues the swallowing therapy with dedication, even though he can no longer manage to eat solid food.

Three months after the intensive radiotherapy, Marc is able to enjoy eating and drinking again. He is grateful and very satisfied that he had the opportunity to participate in the proposed trial and states: "I think this swallowing therapy should be a part of the whole package during radiotherapy. It will help a lot of people, in the same way it helped me. This therapy must simply be a part of it." (free translation).

(Dutch) "Ik vind dat deze sliktherapie een onderdeel moet zijn van het gehele pakket tijdens de radiotherapie. Het zal heel veel mensen helpen, op dezelfde manier als het mij geholpen heeft. Deze therapie hoort er gewoon bij."

Chapter 2

Background

Chapter 2: Background

Head and neck cancer

Head and neck cancer (HNC) is a collective term for cancers arising from the oral cavity, nasal and paranasal cavities, nasopharynx, oropharynx, hypopharynx and larynx as well as the salivary glands (Figure 1) [12; 13]. It is the sixth most common cancer worldwide with annually approximately 830 000 new diagnoses resulting in more than 430 000 deaths every year [14]. In Belgium, 2682 patients were diagnosed with HNC in 2017. This number is expected to rise to more than 3000 by 2025. Males are significantly more affected than females, with a ratio ranging from 2:1 to 4:1, depending on the age [15; 16]. In more than 90% of the cases the main histologic type is squamous cell carcinoma [14; 17]. The consumption of tobacco and alcohol are the most important risk factors of HNC, but recently, many studies have highlighted the role of human papillomavirus (HPV), especially for oropharyngeal tumors [18]. These HPV-related carcinomas mostly affect a younger population and are characterized by a favorable prognosis [19].

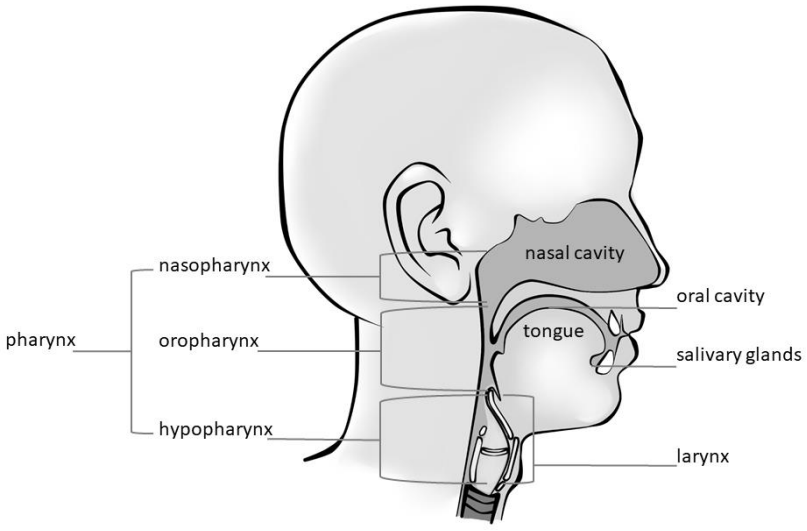

Figure 1: Head and neck cancer regions

Treatment strategies for HNC

Options for a curative treatment of HNC include surgery, radiotherapy (RT) and chemotherapy or a combination of these modalities [14]. Radiotherapy is a commonly used treatment method, that uses high doses of ionizing radiation to damage the DNA of tumor cells with the intention to eradicate the tumor [20]. Over the last decade, intensity-modulated radiotherapy (IMRT) has become the standard of care for curative radiotherapy of HNC patients. IMRT is an advanced form

of conformal radiotherapy permitting excellent radiation dose conformity to complex target volumes thereby reducing the risk of toxicity to normal tissues [21-24].

Radiotherapy is often combined with chemotherapy since it works synergistically in inducing tumor responses and it is known to bring a survival advantage [25; 26]. The survival benefit of the addition of chemotherapy in locoregional treatment for non-metastatic head and neck squamous cell carcinoma is 8% at two and five years [22]. In head and neck cancer with curative treatment intent, chemotherapy is mostly administered in parallel with radiotherapy (concomitant). In some cases, it is given preceding (chemo)radiation or surgery, then called induction chemotherapy [22]. Radiotherapy, whether or not in combination with chemotherapy, has the benefit of organ preservation, resulting in function preservation [27].

Surgery is also often used as a treatment strategy for HNC. The intervention can however be limited by the anatomical extent of the tumor and the wish to preserve organs [13]. Minimally invasive surgical treatment options, e.g. transoral robotic surgery (TORS) and transoral laser microsurgery (TLM), have improved drastically over the past 30 years and have become treatment options with far fewer morbidities than open surgery.

The choice of treatment modality requires a multidisciplinary approach and depends on different factors, including tumor site and stage, oncological and functional outcomes, overall health and patient preference [13; 21]. Early stage disease (stage I/II) should be treated with a single modality strategy (surgery or radiotherapy), while multimodality treatment will usually be offered for locally advanced or high risk early stage head and neck cancer [13].

This thesis focuses on HNC patients treated with primary (chemo)radiotherapy (RT/CRT).

Acute and late toxicity after RT/CRT

Despite innovations in RT/CRT, such as the introduction of static beam and rotational IMRT in the last two decades, the development of acute and late toxicity, impacting on functioning and quality of life (QoL), is still very common. Frequent acute complications during RT/CRT are radiation dermatitis, oral mucositis, xerostomia, loss of taste, fatigue, swallowing disorders (dysphagia) and dysphonia [28-30]. Late RT/CRT complications, generally defined as occurring >90 days after treatment, significantly affect long-term HNC survivors [31-33]. It has been shown that late effects decrease during the

first 2 years after RT/CRT with a more prominent improvement during the first year [23; 34]. However, the impact of these complications on QoL continues to be substantial [35].

Oral mucositis (OM) refers to an inflammation/ulceration of the oral mucosa and can occur as a dose-limiting and dose-delaying toxicity during radiotherapy [36-38]. It results in pain, bleeding and infections which contributes to the development of dysphagia and nutritional intake impairment [38; 39]. Since OM has a significant impact on QoL, clinical evaluation and assessment of this complication is necessary to establish a proper management plan and allowing for follow-up [29; 40]. However, clinical evaluation does not provide information on the impact of OM on patients' well-being and QoL, making the use of patient-reported outcome measures (PROMs) of great importance.

Besides OM, one of the widely reported complications during and after RT/CRT for HNC is radiation-associated dysphagia (RAD) which can persist for a long period of time. Fifty to 60% of HNC patients experience dysphagia during or after RT/CRT due to radiotherapy associated fibrosis, neuropathy, edema and muscle atrophy which causes muscle weakness and damages the range of motion of the swallowing musculature [1-4]. Some studies even report dysphagia rates from 76 to 86% after treatment [41; 42]. The medical and psychosocial consequences of dysphagia, e.g. feeding tube dependency, aspiration pneumonia, social deprivation and depression, have a major impact on daily functioning and health-related QoL and can even be life-threatening [7; 43].

To comprehend the pathophysiology of (radiation-associated) dysphagia, one must fully understand the physiology of a normal swallowing act.

Normal and impaired swallowing function

Swallowing is defined as the entire act of deglutition, from the placement of food in the mouth, to the oral, pharyngeal and esophageal phases of the swallowing act until the food arrives in the stomach via the gastro-esophageal sphincter [44]. The aim is to transport food safely and efficiently from mouth to stomach and thus targeting two important purposes: food passage and airway protection [45].

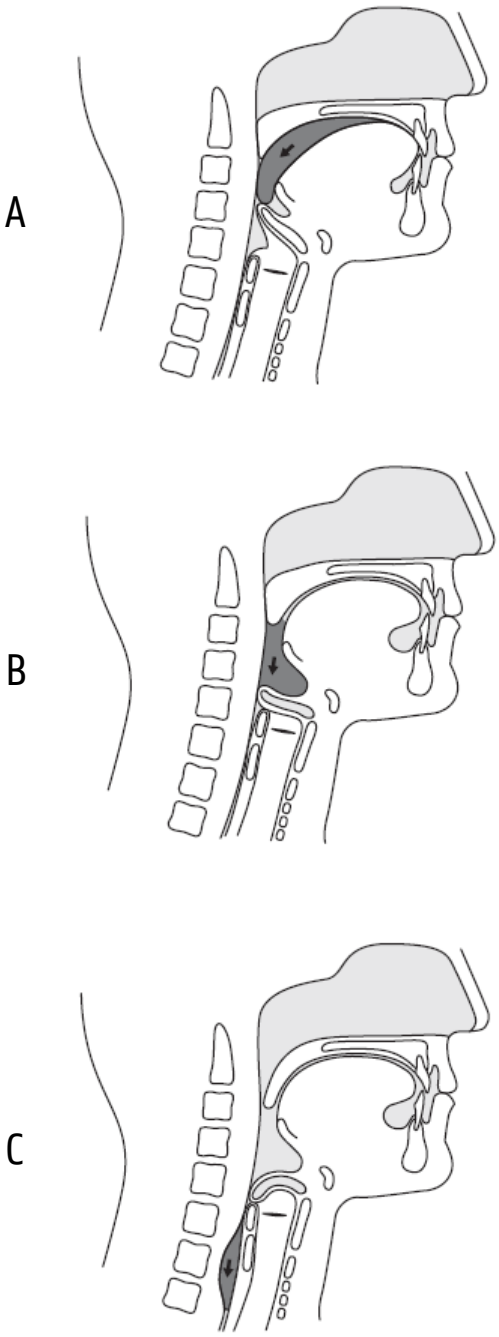

Figure 2: phases of swallowing (De Bodt et al. 2015 [44])

The swallowing act can be divided into different phases, namely the oral, pharyngeal and esophageal phase which are shown in figure 2. The oral phase (A, figure 2) consists of a *preparatory stage* and a *propulsive stage*. During the preparatory phase, liquids or food are taken into the mouth and a cohesive bolus is formed. Food will be chewed and mixed with saliva after which the tongue will make an up- and backward movement to push the food to the oropharynx. The tongue movement and strength thus have an important role in this process. This first phase of swallowing is under voluntary control. The pharyngeal phase (B, figure 2), which is under involuntary neuromuscular control, starts when the food bolus reaches the oropharynx (the exact location is quite variable), and triggers the swallowing reflex. During this second phase, different airway protection mechanisms, preventing food and liquids from entering the airway, and bolus transport mechanisms are set in motion. First, the velopharyngeal closure ensures prevention of food from entering the nose and causes apnea. In combination with the tongue base retraction, a negative pressure is created and the bolus moves downwards. Glottic closure follows the apnea and is situated at the level of the true vocal folds, false vocal folds and aryepiglottic folds. Epiglottic retroversion is the next protection mechanism during the swallowing process. The hyoid bone and larynx will move superiorly and anteriorly to shorten and enlarge the pharynx. This stimulates the upper esophageal sphincter to relax and creates a negative hypopharyngeal pressure. This pressure, together with the tongue driving force, the contraction of the pharynx constrictors and gravity, are the four factors working together to transport the bolus towards the esophagus. The

esophageal phase (C, figure 2) starts when the upper esophageal sphincter relaxes, and thus opens, and the bolus is transported to the stomach [45-48].

During these three phases, sensory input via different pathways is vital, triggering the reflexes, informing the neural control centers and modulating the motor activity. This is coordinated by the brainstem and central nervous system [49].

Dysphagia

The word dysphagia derives from the Greek 'dys' and 'phag-', meaning 'bad' or 'disordered' and 'eat' respectively. Generally speaking, dysphagia is an impaired functioning of structures, muscles or nerves in the oral, pharyngeal or esophageal area resulting in transport and/or safety disorders, therefore causing the impossibility, difficulty or unsafety of transporting a bolus (one or more consistencies) from mouth to stomach. This causes the risk of malnutrition, dehydration and aspiration pneumonia.

Residue, penetration and aspiration are key words in defining the presence and severity of dysphagia. Residue means that (part of) the bolus remains in the mouth, larynx or pharynx after swallowing. The term penetration indicates the entry of (part of) the bolus into the larynx, above or on the level of the vocal folds. Aspiration means that (part of) the bolus enters the trachea. When there is a reduced sensibility and no cough reflex is initiated, this is called silent aspiration. Figure 3 shows these events [45; 50].

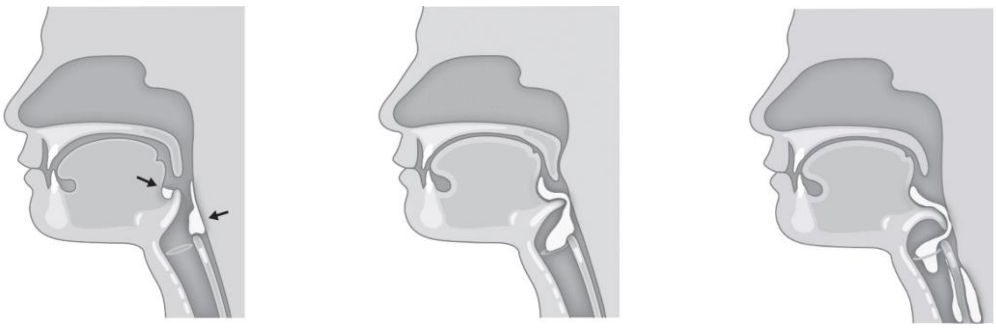

Figure 3: residue, penetration, aspiration (De Bodt et al. 2015 [45])

There are different classifications for dysphagia, and one of them is the classification according to etiology. Besides neurologic, iatrogenic dysphagia and presbyphagia, structural dysphagia is also recognized in this classification. The latter includes swallowing disorders caused by a structural change, for example a carcinoma in the head and neck region or the treatment for it [45].

Radiation-associated dysphagia

Pathophysiology

The concept of radiotherapy is the disruption of tissue homeostasis by damaging DNA of rapidly proliferating cells. Although the intention is to destroy only tumor cells, the radiation also damages healthy cells, which negatively affects their functioning. Within several minutes after radiation, bioactive molecules are numerous and an inflammation in the submucosa is induced. This results in a cascade of pro-inflammatory cytokines and chemokines, pro-fibrotic growth factors, increases in vascular permeability, decreases in stem cell proliferation and progressive epithelial breakdown, which, altogether suppresses the resolution of inflammation and inhibits normal cell repopulation [20; 51]. Patients may develop unintentional radiation toxicities such as mucositis, radiation dermatitis, edema and xerostomia, contributing to acute dysphagia [48]. Fibrosis and atrophy develop consequently from the first radiotherapy session, exist for a long period of time and also contribute to the development of (long-term) RAD [20]. The pathophysiological characteristics of dysphagia are muscle weakness and a limited range of motion at different levels, leading to, amongst others, a reduced retraction of the base of the tongue, a prolonged pharyngeal transit time, a reduced laryngeal elevation and closure and reduced epiglottic inversion [10]. Since these characteristics are often accompanied by oral mucositis (causing pain), fatigue and nausea, the desire and motivation to eat decreases even more [5; 6; 43]. Nevertheless, there are ongoing effects on tissue secondary to radiation due to the cascade of cytokines, resulting in fibrotic and rigid tissues leading to a loss of function. Murphy et al. indicate that even long after radiotherapy, continued hypoxia and chronic oxidative stress may perpetuate tissue damage and thus impairment of the swallowing musculature [48; 52]. Together with late lymphedema and damage to neural structures, this may explain why RAD develops or worsens even years after treatment [48].

Consequences

The medical consequences of RAD, e.g. weight loss, malnutrition, dehydration and aspiration pneumonia can increase mortality in cured patients [5; 43]. Tube feeding often becomes necessary to counter malnutrition and dehydration, carrying an important financial burden [53]. Furthermore, the psychological consequences should not be underestimated. Dysphagia can result in a decreased self-esteem, changes in social behavior, anxiety, stress and depression [7; 54; 55]. These consequences can persist for years after RT/CRT treatment, and have an immense impact on the patients' QoL [48; 56-58].

Prevention

The high prevalence and major consequences of dysphagia emphasize the importance of prevention, monitoring and treatment of the problem and this especially now, since the number of surviving patients is increasing due to improvements in diagnostics, treatment modalities and an increasing number of HPV-related oropharyngeal cancer patients. The latter ones also having a very good prognosis which makes management of late complications in this group even more important as more patients will survive for long periods. The swallowing function has become an important factor in treatment planning and delivery [6; 59]. Rutten et al. (2011) indicate that monitoring the swallowing function with early intervention techniques and rehabilitation can optimize outcomes [60]. Since the treatment of late dysphagia after HNC radiotherapy is strenuous, prevention strategies are highly recommended [4]. Patients should be encouraged to continue swallowing and perform and maintain swallowing exercises through the period of treatment. Avoiding periods of *nil per os* (e.g. feeding tube dependency) as long as possible is important during and after treatment as well as performing swallowing exercises in order to keep the involved musculature strong, both preventing disuse atrophy. Previous research indicates that the continued use of the swallowing muscles, both via continued eating/drinking and performing strength exercises, leads to better swallowing function after RT/CRT [2; 61; 62]. However, despite increased attention to early treatment of dysphagia, accessibility to therapy programs often remains a hurdle for patients in most countries [2; 10].

Prophylactic swallowing exercises (PSE)

Prophylactic swallowing exercises in HNC patients are exercises initiated before or at the start of RT/CRT. The last decade, PSE is gaining more attention, with positive effects on swallowing after RT/CRT treatment demonstrated in several studies. Research has shown that it can lead to better tongue base retraction, better maintained epiglottic inversion, better oral intake and shorter duration of feeding tube dependency [63-65]. Furthermore, research indicated significantly less muscle atrophy and improved dysphagia-related QoL with less aspiration, less feeding tube dependency and less hospitalization post-treatment [1; 2; 8; 66-68]. Implementing swallowing exercises during RT/CRT helps to maintain the swallowing function during and after treatment [6]. A battery of exercises have already been developed in the field of dysphagia, including both compensation and rehabilitation [69-71]. Compensatory techniques focus on a safe swallow by means of adjustments in patient (e.g. posture), food or swallowing without the aim of changing swallowing physiology. In contrast,

rehabilitation strategies intend to address the physiology of swallowing and improve swallowing function [71]. Strength training (e.g. tongue strength training), functional swallowing training (e.g. McNeill Dysphagia Therapy Program) and neural stimulation (e.g. neuromuscular electrical stimulation) are rehabilitation techniques [71-73]. Both compensatory and rehabilitation techniques have already been applied in HNC patients as prophylactic strategy and increase muscle strength, swallowing function and recovery and QoL in this patient population [1; 8; 66; 67; 74].

The feasibility of completing swallowing exercises during radiotherapy has already been demonstrated in previous research, however Hutcheson and Van den Steen et al. indicated that it decreases during the last weeks of radiotherapy [9; 75].

(Non-) adherence to prophylactic swallowing exercises

Despite the promising results concerning the impact of PSE on post-treatment swallowing function, these positive effects are threatened by the generally moderate to low adherence rates [2; 11; 76]. Adherence can be defined as "the extent to which a patient's behavior corresponds with recommendations from a health care provider" [77]. Virani et al. and Messing et al. showed that the percentage of performed PSE decreases rapidly during radiotherapy weeks, and drops to very low levels by the end of radiotherapy [10; 78]. Moreover, throughout the six training weeks in the study of Wall et al., adherence was 27% and declined even further from week 4 of CRT to 16% at week 6 [11].

It is generally accepted that low adherence rates for PSE are due to the additional demand the exercises put on the patients during an already very burdensome therapy period [9]. However, Shinn et al. [79] and Wells et al. [80] indicated that the etiology of low adherence can be multifactorial; for example forgetfulness, the absence of supervision or the not yet experiencing the problem at the start of the exercises. Within physiotherapy, it has also been suggested that patients experiencing pain during exercising are less likely to adhere to therapy protocols [81].

Clear instructions, continuous supervision, feedback and a close relationship between the patient and therapist have already been shown to have a significant positive effect on adherence in physical therapy research [82-84]. This indicates that the way the exercises are delivered, the service-delivery mode, can have an impact on patients' adherence. And although scarcely studied in HNC patients, service-delivery mode might also impact on adherence to PSE in this population [11; 85]. Therefore, the development of an effective PSE program, augmented with adherence-improving measurements

based on service-delivery mode, is needed. During the development of a new PSE program for patients during RT/CRT, it is important to properly assess and track not only swallowing ability, but also other side-effects that may impact swallowing function, the execution of the exercises or the adherence to PSE.

Chapter 3

Research problems, hypotheses and outline of this thesis

Chapter 3: Research problems, hypotheses and outline of this thesis

Research problems

Radiation-associated dysphagia is a prevalent problem in HNC patients treated with RT/CRT, impacting on patients' health-related QoL and survival and therefore increasing the burden on our healthcare systems. Although the prevalence of acute dysphagia during and shortly after RT/CRT is widely studied, little has been described concerning very late side-effects. In order to gain insight in the epidemiology of late RAD, it is important to analyze the **evolution of RAD years after radiotherapy (Chapter 4)**. It was hypothesized that the presence of severe late RAD in long-term survivors after radiotherapy for HNC might be higher than commonly thought and might worsen with increasing follow-up time.

During the last decade, there has been increasing evidence for the positive effects of PSE during radiotherapy on muscle strength, swallowing function post-treatment and QoL. Nevertheless, since low adherence rates are threatening this positive impact, there is an urgent and crucial need for **the development of an optimized, patient-tailored and evidence-based PSE program improving adherence** to be used in daily clinical practice **(Chapter 5)** [2; 78; 86].

Since OM results in pain and affects swallowing function, it can have an impact on the execution of and adherence to PSE. **The Oral Mucositis Weekly Questionnaire (OMWQ)** was designed to assess the impact of OM on a patient's well-being and QoL, but has never been translated into the Dutch language. Therefore, it was necessary to **translate and validate this PROM (Chapter 6)**. The hypothesis was that the Dutch version of the OMWQ is valid and reliable, what enables the use of this tool in clinical practice and research.

The main aim of the development of the new PSE program was to counter the reasons for low (or non-)adherence with the goal of increasing the positive effect of these exercises. This was done by adding different adherence improving measures to this program, based on three different service-delivery modes (paper-, app-, and therapist-supported PSE). **A thorough comparison between these three modes** should determine how to increase adherence rates in patient undergoing RT/CRT for HNC **(Chapter 7)**. We hypothesized that there would be a significant difference in adherence between the three groups, with the highest adherence rates in the therapist-supported group and the lowest rates in the paper-supported group.

Finally, after implementing this program in a group of HNC patients treated with RT/CRT, it is necessary to assess **the effect of service-delivery mode and overall adherence on swallowing function and muscle strength post-treatment (Chapter 8)**. Better swallowing function and muscle strength was expected in the patients with higher adherence rates.

Table 1 shows the outline and aims of this doctoral thesis.

Outline and aims of this doctoral thesis

Table 1: outline and aims of this doctoral thesis with objectives, methods and conclusions per research question

Research goal 1: increasing insight in the presence of dysphagia in HNC patients treated with RT/CRT			
Study	**Objective**	**Method**	**Conclusion**
Research question 1: what is the evolution of xerostomia, dysphagia and neck fibrosis 3 to 8 years after head and neck radiotherapy?			
Chapter 4 (p.23): *Very late xerostomia, dysphagia, and neck fibrosis after head and neck radiotherapy*	To gain insight into the presence and severity of very late dysphagia, xerostomia, and neck fibrosis, 3-8 years after (chemo)radiotherapy in HNC patients.	Retrospective study investigating toxicity in survivors after intensity-modulated radiotherapy for squamous cell carcinoma of the oropharynx, hypopharynx, larynx and oral cavity. (descriptive group: n = 265 and GEE group: n = 60)	Decreasing severity rates of dysphagia during the first five years of follow-up and increasing rates thereafter were observed. The presence and severity of xerostomia decreased and of neck fibrosis increased until 8 years of follow-up.
Research goal 2: developing an evidence-based PSE protocol that improves adherence ***PR****ophylactic* ***E****xercises in* ***S****wallowing* ***T****herapy for* ***O****ropharyngeal cancer patients treated with (chemo)radiotherapy:* ***PRESTO****-trial*			
Research question 2: can we develop an optimized, patient-tailored and evidence-based PSE program for head and neck cancer patients treated with (chemo)radiotherapy?			
Chapter 5 (p.38): *Study protocol for a randomized controlled trial: prophylactic swallowing exercises in head-and-neck cancer patients treated with (chemo)radiotherapy (PRESTO trial)*	To develop an optimized, patient-supported and patient-tailored evidence-based PSE program to be used in daily clinical practice in HNC patients.	Multicenter prospective randomized controlled trial to investigate the effect of specific adherence improving measures.	There is an internationally recognized need to develop an efficient PSE protocol in which the adherence rates are maximized.
Research question 3: is the Dutch version of the Oral Mucositis Weekly Questionnaire a valid PROM to assess oral mucositis in head and neck cancer patients treated with CRT?			
Chapter 6 (p.52): *Validation of the Dutch version of the Oral Mucositis Weekly Questionnaire-Head and Neck Cancer (D-OMWQ-HN)*	To translate and validate a patient-reported outcome measure (PROM) assessing the impact of OM in HNC patients.	Prospective study to translate and validate the English PROM: OMWQ-HN. (n = 35)	The Dutch version of the OMWQ-HN is a valid, reliable and feasible instrument to assess patient-reported OM in HNC patients treated with (adjuvant) RT/CRT.

<u>Research question 4</u>: what is the effect of service-delivery mode on actual patient adherence to PSE?			
Chapter 7 (p.68): *Increasing adherence to prophylactic swallowing exercises during head and neck radiotherapy: the multicenter, randomized controlled PRESTO-trial*	To increase adherence to PSE in HNC patients treated with RT/CRT.	We investigated the effect of three different service-delivery modes on patients' actual adherence to PSE. (n = 148)	Increasing the face-to-face contact with a SLP improves the adherence to PSE in HNC patients treated with CRT.
<u>Research question 5</u>: what is the effect of improved adherence to PSE on swallowing function and muscle strength?			
Chapter 8 (p.83): *Prophylactic swallowing therapy during head and neck cancer radiotherapy: effect of service-delivery mode and overall adherence level on swallowing function and muscle strength – the PRESTO trial*	To examine the effect of improved adherence to PSE in HNC patients.	We investigated the effect of service-delivery mode and overall adherence level to PSE on swallowing function and muscle strength. (n = 148)	Service-delivery mode did not have an impact on patients' swallowing function or muscle strength. However, patients practicing ≥75% of the prescribed exercises showed better swallowing function post RT/CRT. Moreover, muscle strength gain was higher compared to patients practicing <75%.

Chapter 4

Very late xerostomia, dysphagia, and neck fibrosis after head and neck radiotherapy

This chapter has been published in

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Chapter 4: Very late xerostomia, dysphagia, and neck fibrosis after head and neck radiotherapy

Abstract

Background. Acute and late toxicity after intensity-modulated radiotherapy (IMRT) for head-and-neck cancer (HNC) impacts on patient quality of life, yet very late toxicity data remain scarce. This study assessed dysphagia, xerostomia and neck fibrosis 3-8 years after IMRT.

Methods. A retrospective analysis using generalized estimated equations was performed on 60 HNC patients treated with fractionated IMRT between 2000-2015 who had a follow-up ≥8 years. Toxicity was scored using LENT-SOMA scales.

Results. A trend towards a non-linear global time effect (p=0.052) was noted for dysphagia with a decrease during the 5 years post-treatment and an increase thereafter. A significant decrease in xerostomia (p=0.001) and an increase in neck fibrosis (p=0.040) was observed until 8 years.

Conclusions. Dysphagia, xerostomia and neck fibrosis do not appear stable over time and remain highly prevalent in the very late follow-up. Our findings support the need for prospective trials investigating very late toxicity in HNC patients.

Introduction

In the last decade, intensity-modulated radiotherapy (IMRT) has become standard of care for patients with head-and-neck cancer (HNC). Although associated with less acute xerostomia and an improved quality of life (QOL) as compared to conventional radiotherapy[23; 87], IMRT unfortunately still significantly impacts QOL via acute and late toxicity[88-90]. Long-term HNC survivors especially are significantly affected by late toxicities[32; 33]; yet the data on very late toxicity (VLT) (≥3 years after radiotherapy) remains sparse[88].

Late toxicity - generally defined as occurring >90 days after radiotherapy[31] - has been shown to decrease during the first two years after IMRT[23; 34; 91; 92], with a more prominent improvement during the first year[34]. Nonetheless, the impact of these late toxicities on QOL remains substantial[35; 93-95]. Multiple studies, for example, have shown that xerostomia is a chronic condition, highly prevalent at six months after IMRT and notably affecting QOL[96]·[28; 97]. Also dysphagia has been found to be one of the most commonly reported late side effects after radiotherapy[28; 96], with 45% of patients reporting it two years after IMRT[95]. Since QOL in oropharyngeal cancer (OPC) patients at six and 12 months follow-up is correlated with objective swallowing function and, to a lesser extent, with xerostomia, the hypothesis has emerged that reducing these two toxicities could improve QOL[34].

Limited studies have assessed toxicity >2 years after therapy[98-101]. Motz et al. observed the highest incidence of dysphagia, airway obstruction and pneumonia in the first year after treatment, but without a significant decrease in the subsequent four years[101]. The study by Kirsh et al. assessed very late dysphagia (>3 years after IMRT) and saw that 23% of the patients still required a modified diet after a mean follow-up time of 4.55 years[99]. Furthermore, Patterson et al. found that 71% of patients six years post-IMRT reported swallowing problems, of whom one fifth suffered from aspiration[3]. Concerning xerostomia, stimulated saliva production has been shown to decrease profoundly during the three months following IMRT, with a subsequent improvement at six months post-IMRT, yet, unfortunately, without reaching the baseline values at three years follow-up[23; 102-104].

Based on the limited available data and clinical experience, toxicity >5 years after IMRT for HNC seems to be highly prevalent and severe. Since literature in this area is still scarce, the current study retrospectively investigated toxicity in survivors after IMRT for squamous cell carcinoma of the oropharynx, hypopharynx, larynx and oral cavity. The aim of this study is to gain insight into the presence and severity of very late dysphagia, xerostomia and neck fibrosis, 3-8 years after

(chemo)radiotherapy (CRT) in long-term survivors of HNC. The hypothesis is that the presence of severe VLT in long-term survivors after IMRT for HNC might be higher than commonly thought and might worsen with increasing follow-up time.

Materials and methods

The study was approved by the Ghent University Hospital's Ethical Commission. Written informed consents were obtained from all patients. Very late toxicity, defined as 3-8 years after radiotherapy, was scored by experienced radiation oncologists using the Late Effects of Normal Tissues (LENT)-Subjective, Objective, Management, and Analytic (SOMA) system[105], a validated toxicity scoring system incorporating patients' complaints and clinical evaluation. Xerostomia, dysphagia and neck fibrosis were prospectively scored at each patient visit (i.e. every 3 and 4 months during the first and second year of follow-up respectively, every 6 months for years 3-5, and annually thereafter). Dysphagia was assessed by means of patient-reported outcomes (PROs), xerostomia was assessed clinically and by means of PROs, and neck fibrosis was evaluated through clinical examination. Table 1 summarizes the different parts that were scored and used for analysis.

Only patients with clinical follow-up data ≥3 years and without recurrent disease were included, as they were considered as "long-term survivors". Since follow-up was not always planned exactly one year after the previous follow-up due to clinical or practical circumstances, it was rounded to the nearest year. Three years of follow-up was defined as 33-42 months – 1 day, four years was defined as 42-54 months – 1 day, etc. In 49/60 patients, LENT-SOMA scales were filled out more than once a year; in this case the worst toxicity scoring was used for analysis.

Table 1: LENT-SOMA SCALES for head and neck cancer patients [105]: dysphagia, xerostomia and neck fibrosis

	Grade 1	Grade 2	Grade 3	Grade 4
Dysphagia (subjective)	Difficulty eating solid food	Difficulty eating soft food	Can take liquids only	Totally unable to swallow
Xerostomia (subjective)	Occasional dryness	Partial but persistent dryness	Complete dryness, non-debilitating	Complete dryness, debilitating
Saliva (objective)	Normal moisture	Scant saliva	Absence of moisture, sticky, viscous saliva	Absence of moisture, coated mucosa
Fibrosis/scar (objective)	Present/ asymptomatic	Symptomatic	Secondary dysfunction	Total dysfunction

(score = 0 if there are no toxicities)

Abbreviation: LENT-SOMA, Late Effects of Normal Tissues-Subjective, Objective, Management, and Analytic scales.

Influencing factors

The influence of concurrent chemotherapy, T classification (T0-2 vs. T3-4) and tumor site (oropharynx vs. other) on the evolution of dysphagia were investigated; as well as the influence of chemotherapy and tumor site on the evolution of

xerostomia, and the influence of chemotherapy and pre-IMRT lymph node dissection (LND) on the evolution of neck fibrosis[42; 94; 103; 106-110].

Radiotherapy

All patients were treated with fractionated IMRT, five fractions per week with a minimal fraction dose to the high-risk planning target volume (PTV) of 2.00 Gy using a simultaneously integrated boost. Standard dose prescriptions from 2003 onwards were: 32 x 2.16 Gy (primary CRT or after incomplete surgical resection (n=153)); 33 x 2.00 Gy after complete surgery (n=35) and 25 x 2.00 Gy for cancers of unknown primary (CUP) after neck dissection (n=2). Fifty-six patients were treated with a hypofractionation protocol in prospective trials (30-32 fractions); 46 of these patients received a decreased biological equivalent elective neck dose of 40 Gy (instead of 50 Gy in all other patients). All patients received bilateral elective neck irradiation.

Before 2003, varying dose prescriptions were used with fraction doses of 2.00-2.19 Gy for a total of 31-35 fractions (n=15). In four patients, a brachytherapy boost was given after IMRT (i.e. 56-60 Gy in 2.00 Gy fractions combined with a 15-19Gy pulsed dose rate brachytherapy boost, respectively).

Statistical analysis

Statistical analyses were performed using SPSS Statistics version 25 (IBM, Armonk, NY, USA). Descriptive statistics were utilized to assess the evolution of VLT until eight years follow-up in the total patient cohort (the "descriptive group"). Also toxicity data from year 1 and 2 of follow-up are reported.

Ordinal logistic generalized estimating equations (GEE) was used to assess the evolution of VLT between one and eight years after radiotherapy. This test was applied to the subgroup of patients that survived and had a follow-up of ≥8 years (the "GEE group"). Generalized estimating equations was chosen because we assumed completely missing at random (CMAR) data since all deceased patients were excluded and since other missing data (n = 9/1275 = <1%) are due to a missed chance of data collection (e.g. patient forgot appointment). If no toxicity scores were available at eight years, but available >8 years, the values at eight years were considered missing values. Post hoc analyses were performed, corrected by means of Sequential Bonferroni-Holm; and odds ratios were calculated. For each model, time was regarded as a categorical (to account for non-linear changes) or continuous (to account for linear changes) variable, based on Akaike Information

Criterion (AIC). The statistical significance level was set at 0.05. Ordinal logistic GEE, both in univariate and multivariate models, was used to determine whether the evolution of dysphagia, xerostomia and neck fibrosis was influenced by different variables.

Results

Patient characteristics

Between 2000 and 2015, 747 patients with non-metastatic squamous cell carcinoma of the oropharynx (n=275), larynx (n=161) (except cT1-2 N0 M0 glottic carcinoma), hypopharynx (n=129), oral cavity (n=120) or lymph node metastases from a CUP (n=62) were treated with IMRT at Ghent University Hospital. Patients with previous head and neck radiotherapy were excluded from this analysis (n=3). Follow-up ≥3 years was available in 343 patients. Locoregional or distant relapse was observed in 41 patients. For 37 of the remaining 302 patients (12%), no scoring of late dysphagia, xerostomia or fibrosis was available at any time-point, resulting in a patient cohort of n=265 (figure 1).

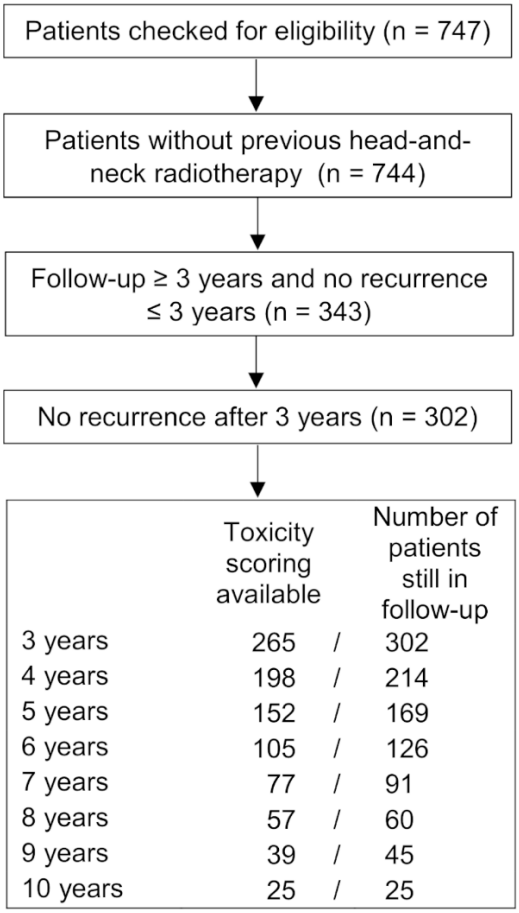


Figure 1 Flowchart of patients included in the study

GEE group

Sixty patients had a follow-up of ≥8 years and were assigned to the GEE group. Among them, 57 had toxicity scoring available at eight years. The other three patients were still in follow-up, but the LENT-SOMA scale was only completed at nine and/or ten years follow-up. In these three patients, scoring at eight years was considered as missing.

Twenty-six of these 60 patients had oropharyngeal cancer, of whom seven were human papillomavirus (HPV) positive, six were HPV negative and 13 had an unknown HPV status.

Eighteen patients received surgical resection of the primary tumor (total laryngectomy [n=7], pharyngo-laryngectomy [n=1], oropharyngeal tumor resection [n=5], hypopharyngeal tumor resection [n=1], oral cavity tumor resection [n=3], and diagnostic resection for CUP [n=1]). Among the resections for oral cavity carcinoma, two were local resections of the floor of mouth, which were done using resection and reconstruction with a free radial forearm flap. Besides water and saliva substitutes in individual patients, patients did not systematically receive any medication or intervention to reduce xerostomia. No patients received fibrosis interventions. Recurrent and life-threatening aspiration pneumonia and permanent grade 2 dysphagia mandated permanent tracheostomy and esophageal dilatation occurred in 3/60 and 1/60 patients, respectively.

Demographic, tumor and treatment characteristics of both the descriptive group (n=265) and the GEE (n=60) group are presented in table 2.

Patterns of failure

Median follow-up in the descriptive group (n=265) was 69 months (range 33-181). Of these patients, 44 (17%) died during follow-up. Cause of death was second primary cancer (n=24), intercurrent disease (n=7), toxicity (n=3; aspiration pneumonia at 49, 80 and 91 months follow-up) or unknown (n=10).

Table 2: Demographic, tumor and treatment characteristics of both descriptive and GEE group

		Descriptive group (n = 265) (%)	GEE group* (n = 60) (%)
Age at diagnosis (y)	Median	60	70
	Mean	61	70
	Range	43-93	54-89
Sex	Male	227 (86)	54 (90)
	Female	38 (14)	6 (10)
Tumor site	Oropharynx	112 (42)	26 (43)
	Larynx	56 (21)	13 (22)
	Hypopharynx	35 (13)	8 (13)
	Oral cavity	30 (11)	4 (7)
	Cancer of Unknown Primary	32 (12)	9 (15)
Karnofsky Performance Status	100	7 (3)	2 (3)
	90	154 (58)	41 (68)
	80	69 (26)	12 (20)
	70	24 (9)	1 (2)
	60	3 (1)	1 (2)
	50	1 (<1)	0 (0)
	Unknown	7 (2)	3 (5)
Surgery	Yes	63 (24)	18 (30)
	No	202 (76)	42 (70)
Concomitant systemic therapy	None	168 (63)	37 (62)
	Cisplatin	91 (34)	23 (38)
	Cetuximab	6 (2)	0 (0)

Abbreviation: GEE group, Generalized Estimating Equations group

Late toxicity

Figure 2 shows the presence of grade 0-4 dysphagia, xerostomia and neck fibrosis. Toxicity data at year 1-2 are included for completeness. In the GEE group, the effects of time were analyzed using GEE (table 3).

Dysphagia

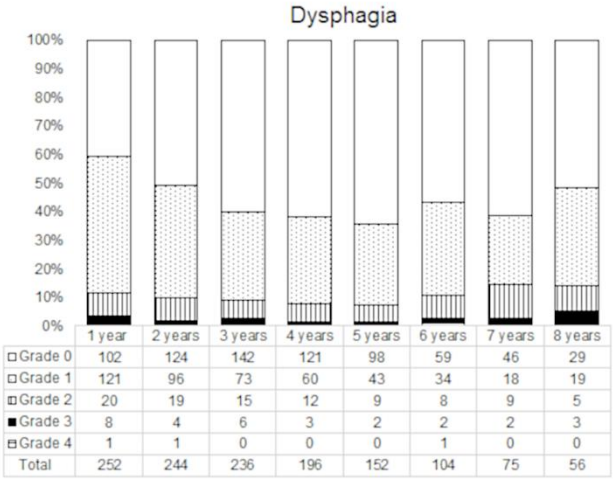
Sixty percent of the descriptive group experienced dysphagia (grade 1-4) at 1 year, decreasing to 36% at five years and increasing back to 48% after eight years of follow-up. Figure 2 shows the increase in grade 2-3 dysphagia during the 5-8 year follow-up period. Analysis using GEE demonstrated a tendency towards a non-linear global effect of time ($p = 0.052$). Dysphagia severity rates decreased during the 1-5 year follow-up and increased thereafter (table 3). Post hoc analyses, corrected by means of sequential Bonferroni-Holm, show significant effects between 1 and 4 year follow-up ($p = 0.035$, odds ratio (OR_{4-1}) = 0.43) and 1 and 5 year follow-up ($p = 0.035$, $OR_{5-1} = 0.44$).

Xerostomia

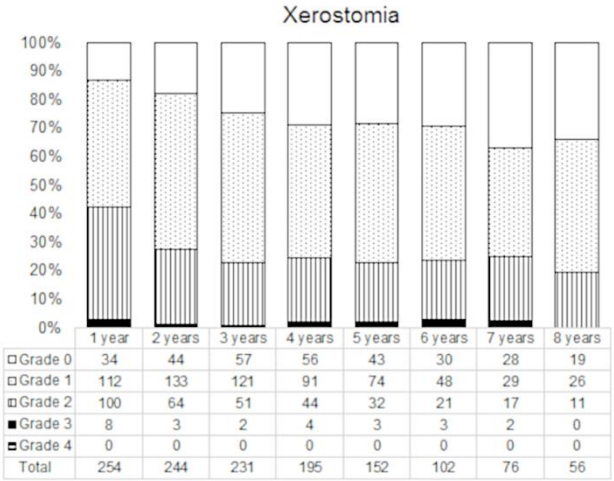
Grade 1-3 xerostomia was observed in 87% of the descriptive group at 1 year follow-up, decreasing to 65% at eight years after IMRT. One year after radiotherapy, the rate of grade 2 xerostomia decreased and after year 2, the severity remained more or less stable (figure 2). Generalized estimating equations demonstrated a significant linear effect of time ($p = 0.001$) on the evolution of xerostomia. The severity of xerostomia decreased during year 1 to 8 after radiotherapy. Every year, patients were less likely to have higher xerostomia scores ($OR_{time} = 0.88$).

Neck fibrosis

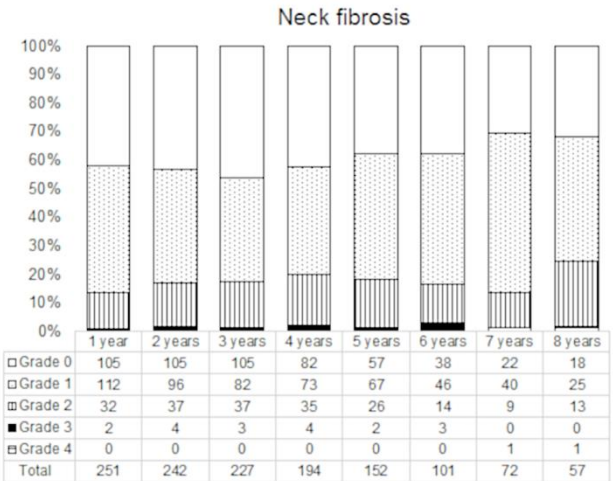
In 58% of the descriptive group, neck fibrosis was observed at 1 year after radiotherapy, decreasing slightly to 54% at three years follow-up and increasing again to 68% at eight years post-radiotherapy. Figure 2 shows the increase in grade 2 neck fibrosis over time. Analysis on the GEE group demonstrated a significant linear effect of time ($p = 0.040$) on the evolution of neck fibrosis. The severity of neck fibrosis increased during year 1 to 8 follow-up. Every year, patients were more likely to have higher neck fibrosis scores ($OR_{time} = 1.10$).



	1 year	2 years	3 years	4 years	5 years	6 years	7 years	8 years
Grade 0	102	124	142	121	98	59	46	29
Grade 1	121	96	73	60	43	34	18	19
Grade 2	20	19	15	12	9	8	9	5
Grade 3	8	4	6	3	2	2	2	3
Grade 4	1	1	0	0	0	1	0	0
Total	252	244	236	196	152	104	75	56



	1 year	2 years	3 years	4 years	5 years	6 years	7 years	8 years
Grade 0	34	44	57	56	43	30	28	19
Grade 1	112	133	121	91	74	48	29	26
Grade 2	100	64	51	44	32	21	17	11
Grade 3	8	3	2	4	3	3	2	0
Grade 4	0	0	0	0	0	0	0	0
Total	254	244	231	195	152	102	76	56



	1 year	2 years	3 years	4 years	5 years	6 years	7 years	8 years
Grade 0	105	105	105	82	57	38	22	18
Grade 1	112	96	82	73	67	46	40	25
Grade 2	32	37	37	35	26	14	9	13
Grade 3	2	4	3	4	2	3	0	0
Grade 4	0	0	0	0	0	0	1	1
Total	251	242	227	194	152	101	72	57

Figure 2 Percentage of patients (descriptive group) with grade 0-4 dysphagia, xerostomia, and neck fibrosis through 8 years of follow-up, evaluated by the Late Effects of Normal Tissues-Subjective, Objective, Management, and Analytic scales

Factors predicting late toxicity

In the GEE group, multivariate GEE was used to analyze clinical predictive factors on late toxicity, illustrated in table 4.

Dysphagia

The severity of dysphagia was significantly higher in patients having T classification 3-4 compared to patients with T classification 0-2 (p = 0.014, OR = 3.85). Older patients had higher dysphagia scores (p = 0.023).

Xerostomia

The severity of xerostomia was significantly higher in oropharynx patients as compared to the other patients (p = 0.001, OR = 5.26).

Neck fibrosis

Neck fibrosis severity rates were significantly higher in patients who underwent an LND, as compared to patients who did not (p < 0.001, OR = 5.45).

Table 3: Effect of time on the evolution of dysphagia, xerostomia and neck fibrosis between 1-8 years, n = 60

Parameter					
Dysphagia[b]	***p*-value**	**$p_{bonf\ holm}$[a]**	**OR**	**95% CI**	
1 year after IMRT			1		
2 years after IMRT	0.176	1	0.71	[0.857-2.316]	
3 years after IMRT	0.012	0.084	0.45	[1.189-4.080]	
4 years after IMRT	0.005	0.035	0.43	[1.291-4.106]	
5 years after IMRT	0.005	0.035	0.44	[1.283-4.083]	
6 years after IMRT	0.008	0.056	0.42	[1.256-4.548]	
7 years after IMRT	0.054	0.387	0.52	[0.988-3.713]	
8 years after IMRT	0.643	1	0.87	[0.631-2.106]	
Xerostomia[c]					
Time (per year)	0.001		0.88	0.807	0.950
Neck fibrosis[c]					
Time (per year)	0.040		1.10	1.004	1.207

GEE is modeling the probability for a lower score

Abbreviations: CI, confidence interval; GEE, generalized estimating equations; OR, odds ratio.

[a]Corrected by means of Bonferroni-Holm

[b]Dysphagia shows a tendency towards a non-linear global effect of time

[c]Xerostomia and neck fibrosis show a linear effect of time

Table 4: Impact of the influencing factors on the evolution of dysphagia, xerostomia and neck fibrosis, adjusted odds ratios were mutually adjusted for all analyzed influencing variables depending on the parameter, n = 60

		Unadjusted estimates			Adjusted estimates		
		p-value	OR	95% CI	*p*-value	OR	95% CI
Parameter	**Influencing factor**						
Dysphagia	Age	0.418	1.02	[0.969-1.079]	**0.023**	1.06	[1.009-1.122]
	Chemotherapy	0.887	1.06	[0.455-2.488]	0.207	1.87	[0.708-4.919]
	Tumor site[a]	0.359	1.49	[0.636-3.489]	0.736	1.15	[0.517-2.541]
	T classification[b]	0.071	0.46	[0.197-1.067]	**0.014**	0.26	[0.086-0.755]
Xerostomia	Age	0.796	0.99	[0.942-1.047]	0.906	0.10	[0.953-1.043]
	Chemotherapy	0.100	0.50	[0.214-1.146]	0.316	1.53	[0.668-3.481]
	Tumor site[a,c]	< 0.001	5.63	[0.230-14.188]	**0.001**	0.19	[0.076-0.489]
Neck fibrosis	Age	0.063	0.95	[0.893-1.003]	0.538	0.98	[0.935-1.036]
	Chemotherapy	0.450	0.74	[0.336-1.623]	0.461	1.32	[0.628-2.786]
	LND[d]	< 0.001	0.17	[0.081-0.367]	**<0.001**	5.45	[2.425-12.238]

GEE is modeling the probability for a lower score

Abbreviations: CI, confidence interval; GEE, generalized estimating equations; OR, odds ratio.

[a] Hypopharynx, larynx, oral cavity and unknown primary vs. oropharynx

[b] T0-2 vs. T3-4 (higher dysphagia severity in T3-4)

[c] higher xerostomia severity in oropharynx patients

[d] higher neck fibrosis severity in patients who underwent an LND

Discussion

Especially for the ±50% survivors after CRT for HNC, VLT is of utmost importance for their QOL[111; 112]. In the first two years after therapy, the main emphasis of patients and physicians is put on disease control and survival, as the risk of recurrence is highest during this period. Hereafter, the chances for recurrent disease decrease, and patients need to settle themselves in their new status with sometimes important permanent side effects following therapy.

Late toxicity is generally defined as occurring ≥90 days after CRT[31]. 'Early' late side effects until two years post-therapy have been described widely showing decreasing toxicities and increasing QOL up to two years of follow-up[23; 91; 92; 113; 114]. In contrast, a relatively small number of studies reported on VLT, probably due to the relatively low survival rates and lack of interest in the period before 2010. The emphasis of this study is put on VLT, defined as 3-8 years after CRT aiming at the description of incidence and evolution of very late dysphagia, xerostomia and neck fibrosis, which are the toxicities impacting QOL most[5; 115-117]. Decreasing severity rates of dysphagia during the 1-5 years follow-up and increasing rates thereafter were observed. Presence and severity of xerostomia decreased and of neck fibrosis increased until eight years follow-up.

Our findings of decreasing xerostomia severity corroborate with current literature[102; 103; 118], but in contrast to others, concomitant cisplatin did not correlate with the incidence of very late xerostomia[103; 108; 119]. Yet, we acknowledge that

our study was not designed nor powered to detect such difference. The effect of chemotherapy on the development and evolution of xerostomia and dysphagia therefore needs to be assessed in future studies.

Regarding the observed increasing severity of neck fibrosis, our findings are in line with others and, as expected, toxicity was more pronounced in patients who underwent an LND[110; 120].

Concerning xerostomia and neck fibrosis, our patients did not use medication, nor did they receive an intervention. For xerostomia, only in some cases water and saliva substitutes were used. All patients were counseled during and after treatment by a multidisciplinary team. Despite the fact that no interventions were used, this does not mean patients' QOL was unaffected. Unfortunately, QOL data of our patients are not available. Other studies have however found that in the first two years after treatment xerostomia is one of the main causes in deteriorating QOL[5; 28; 89]. The study of Tribius et al. concluded that QOL deteriorated in all domains during treatment. Many domains recovered after one year, but problems with dry mouth and sticky saliva remained high[121]. Up to five years after treatment, some evidence regarding late toxicity and the impact on QOL is available, with some studies showing a worsening in dry mouth and sticky saliva from baseline to five years follow-up[122-124]. Unfortunately, little is known about the impact of late toxicity on QOL more than five years after treatment. The high prevalence of VLT shown in this study indicates the need for studies assessing QOL after five years of follow-up. It is important to identify the aspects impacting on QOL in the long-term, to be able to improve QOL and inform patients about it.

We observed decreasing severity of very late dysphagia during 1-5 years follow-up and an increase in severity thereafter. This decrease in dysphagia severity between 1-5 years follow-up is concordant with the findings of Gujral et al.[118] Yet, as previously stated, the current study did not demonstrate a correlation between very late dysphagia and the use of chemotherapy that was previously described by many others[42; 96; 103; 106; 107], probably pointing to a lack of power in our study cohort to demonstrate such correlation. Carmignani et al. found better post-therapy swallowing function in patients with hypopharynx or larynx cancer as compared to oral cavity and oropharyngeal cancer[125]. The current study was not able to show any difference in dysphagia determined by the tumor site. Increasing T classification on the other hand, seemed to correlate with dysphagia severity.

Even though dysphagia severity decreases after radiotherapy until five years follow-up, a large portion of HNC patients still present with dysphagia years after radiotherapy (descriptive group, figure 2), with almost half (48%) of the patients in the GEE group showing dysphagia after eight years follow-up (34% grade 1, 9% grade 2, 5% grade 3). Our findings of increasing incidence of late dysphagia five years after radiotherapy are concordant with a growing amount of studies assessing late dysphagia after radiotherapy and its impact on QOL[4; 28; 126]. Up to 71% of patients continue to report swallowing difficulties at six years follow-up with one fifth having persistent aspiration[3]. Nilsen et al. found that HNC survivors who were more than six years from treatment completion, reported an increase in swallowing dysfunction[111].

Only in the last years, care-givers in head-and-neck oncology have emphasized aspects of QOL and dysphagia >5 years after treatment. Studies assessing the impact of late dysphagia on QOL remain however scarce; novel prospective trials in this area still need to be undertaken. Nevertheless, it is known that the consequences of dysphagia, e.g. malnutrition, dehydration and aspiration pneumonia, have a negative impact on daily functioning and QOL and can be life-threatening[5; 29; 43]. Preventive as well as curative swallowing therapy programs, both during and after radiotherapy, have been shown to result in better swallowing function[4; 8; 63; 66; 78; 126]. We therefore initiated two prospective trials, one investigating the effect of tongue strengthening exercises on long-term dysphagia in HNC patients (ISRCTN14447678), the other assessing the effect of three different prophylactic swallowing programs on post-treatment swallowing function as well as determining the adherence to these programs in patients undergoing primary CRT for oropharyngeal squamous cell carcinoma (ISRCTN98243550).

Limitations of our study include its retrospective character. Even though all data were scored prospectively by experienced radiation oncologists, a lost-to-follow-up bias cannot be ruled out, as this is a known issue in HNC research[127-129]. Moreover, historically, toxicity was prospectively scored using the LENT-SOMA scales in our hospital[105]. Even though this scale is a reliable instrument to measure late toxicity after radiation[130], it only counts five gradations (0-4) of which grade 4 signifies the total inability to swallow, complete dryness or total dysfunction (fibrosis). This definition is however considerably general, and validated QOL-measurements might more adequately describe a patient's problems.

Altogether, our findings are concordant with previous studies indicating persistent long-term toxicity in survivors of head and neck CRT. Without major changes in CRT modalities, patients will continue to suffer from these late side effects, and preventive and curative measures need to be investigated to support this fragile population.

This study showed the evolution of VLT in a clinical population that has not been widely studied in current literature. It was hypothesized that the presence and severity of dysphagia, xerostomia and neck fibrosis could be higher than expected in patients receiving CRT for HNC. Based on our results, it is expected that the severity of dysphagia, caused by radiotherapy for HNC, decreases in the first five years of follow-up but might increase thereafter. Although 48% of the patients who survived ≥8 years have persistent dysphagia at eight years of follow-up, a significant global effect was not demonstrated. A significant global effect of time with decreasing severity of xerostomia through the years and increasing severity of neck fibrosis in the very late follow-up was observed. Prospective trials are needed to support these findings, but will require a very high number of patients and long follow-up. Since the QOL of these patients can be affected, it is important to find new strategies to minimize and prevent these late toxicities. Further prospective research should focus on QOL more than three years after finishing CRT and prophylactic and therapeutic measures to support this patient population.

Chapter 5

Study protocol for a randomized controlled trial: prophylactic swallowing exercises in head-and-neck cancer patients treated with (chemo)radiotherapy (PRESTO trial)

This chapter has been published in

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Chapter 5: Study protocol for a randomized controlled trial: prophylactic swallowing exercises in head-and-neck cancer patients treated with (chemo)radiotherapy (PRESTO trial)

Abstract

Background

Dysphagia is a common and serious complication after (chemo)radiotherapy (CRT) for head-and-neck cancer (HNC) patients. Prophylactic swallowing exercises (PSE) can have a significant positive effect on post-treatment swallowing function. However, low adherence rates are a key issue in undermining this positive effect. Current randomized trial will investigate the effect of adherence improving measures on patients' swallowing function, adherence and Quality of Life (QOL).

Methods

This ongoing trial will explore the difference in adherence and swallowing related outcome variables during and after PSE in HNC patients performing the same therapy schedule, receiving different delivery methods. One hundred fifty patients treated in various hospitals will be divided into three groups. Group 1 performs PSE at home, group 2 practices at home with continuous counseling of an app and group 3 receives face-to-face therapy by a speech-and-language pathologist. The exercises consist of tongue strengthening exercises and chin tuck against resistance with effortful swallow. The Iowa Oral Performance Instrument and the Swallowing Exercise Aid are used for practicing. Patients are evaluated before, during and after treatment by means of strength measurements, swallowing and QOL-questionnaires.

Discussion

Since low adherence rates undermine the positive impact of PSE on post-treatment swallowing function, there is need to develop an efficient PSE protocol maximizing adherence rates.

Background

Dysphagia is a common and widely reported complication after (chemo)radiotherapy (CRT) for head-and-neck cancer (HNC) patients, which can persist for a long period of time[4; 28; 126; 131; 132]. Fifty to sixty percent of the HNC patients undergoing CRT may experience significant post-treatment dysphagia involving both muscle weakness and incoordination/timing issues[1; 10; 133]. The medical consequences (e.g. feeding tube dependency, malnutrition, aspiration pneumonia) have a major negative impact on daily functioning and health-related quality of life (QOL) and can even be life-threatening[5; 29; 40; 43; 134-136]. These consequences and the high prevalence of swallowing disorders in HNC patients stress the importance of prevention, monitoring and management of this problem[60].

Based on literature and clinical experiences, it can be concluded that nowadays there is no 'gold-standard' in the assessment nor treatment of dysphagia in HNC patients[137; 138]. An increasing number of studies show that prophylactic swallowing exercises (PSE) can have a significant positive effect on post-treatment swallowing function, can lead to significant less muscle atrophy and can improve dysphagia-related QOL in HNC patients treated with CRT[1; 2; 8; 9; 63; 66; 78]. However, low adherence rates are a key issue in undermining these positive effects. Reported adherence rates, with adherence defined as "the extent to which patient behavior corresponds with recommendations from a healthcare provider", range from 13 to 64%[2; 11; 77; 79; 80; 86; 139; 140]. A possible reason for low adherence rates is the additional demand PSE-programs put on the patient, during an already burdensome period[9]. Furthermore, Shinn et al.[79] and Wells & King[80] showed that the etiology can be multifactorial, e.g. forgetting, absence of supervision or the fact that patients do not experience the problem at the start of the exercises.

The indications that PSE can improve patients' swallowing function and swallowing related QOL, show the crucial, urgent and internationally recognized need for an effective PSE-program augmented with measures that may add to adherence[1; 2; 8; 9; 63; 66; 78; 79; 86]. Apart from patient characteristics and disease related aspects, several studies show the impact of different measures on adherence: therapist-supervised exercises, regular counseling and reinforcement sessions, clear and repeated instructions, feedback on successful performance, target setting (e.g. number of repetitions/days) and limited duration[1; 75; 80; 83; 86]. Also, therapist supervision and a close relationship with a therapist play a crucial role in patients' satisfaction, compliance and individual belief in personal skills[80].

Up to now, studies comparing standard PSE with a PSE program augmented with adherence improving measures are lacking. The randomized controlled trial (RCT) of Wall et al.[11] included 79 patients and investigated whether therapy adherence to prophylactic swallowing exercises was influenced by the delivery method of the exercises. Three different methods were compared. The first group received face-to-face therapy by a speech and language pathologist (SLP), the second group used a telepractice application and the third group practiced independently at home. Adherence was calculated based on the completion of all prescribed exercises. Significantly better adherence rates were found in the group receiving face-to-face therapy and a trend towards better results was found in the group using the application.

Current multicenter randomized trial will investigate the effect of adherence improving measures on actual patient compliance, swallowing function and QOL. The patient adherence to a prophylactic swallowing therapy protocol will be examined across 3 models, similar to the delivery methods in the RCT of Wall et al.: (1) self-help standard PSE (control group), (2) self-help app-supported PSE (app-group) and (3) speech-and-language pathologist (SLP)-supported PSE (therapist-group). Our study differs from the above-mentioned study in the type of exercises given, the number of patients included and the adherence specific measures. The goal of the proposed randomized trial is to develop an optimized PSE-program, incorporating patient tolerance and support for the exercise program. The findings of this project will be helpful to set up future guidelines and directions. The final patient benefit will be improved swallowing function and QOL.

This study aims to

- conduct a prospective randomized trial investigating the effect of specific adherence measures on patients' actual compliance, wellbeing, muscle strength, swallowing function and quality of life during and following CRT
- increase insight in the underlying reasons for (non-)adherence in this patient population

Methods

Study population

Patients with a stage III or IVA-B (TNM7) newly diagnosed squamous cell carcinoma of the oropharynx are considered as possible participants. Inclusion criteria are: patients treated with radiotherapy or concomitant CRT (CCRT) with or without induction chemotherapy and demonstrating sufficient cognitive and language abilities. The presence of a recurrent carcinoma or metastasis from another carcinoma and previous CRT or surgery in head-neck region with possible impact

on swallowing function are exclusion criteria. The patients will be recruited by a radiation oncologist and SLP. The SLP explains the study protocol and study design and assigns participants to the interventions.

Minimization

All subjects who give consent for participation and who fulfill the inclusion criteria are randomly assigned to one of the 3 groups with a 1:1:1 allocation by means of the program QMinim. It is an online minimization service supported by the ICT-unit of the Antwerp University Hospital. Minimization factors are age (20-60 years vs. ≥60 years), treating center, presence of baseline dysphagia and treatment (radiotherapy vs. CCRT).

As this is an open label trial, the minimization procedure and outcome assessment will not be blinded.

Study design

The study will be a multicenter, randomized controlled trial. All patients will be training 5 times a week during the first 4 weeks of CRT. Baseline measurements will be done before the start of CRT. Every week during the training, immediately after CRT and 1 and 3 months following treatment, patients will be evaluated by radiation therapists and SLP's. Table 1 shows an overview of the study visits and evaluations during the study. Prophylactic swallowing exercises are the same in all groups and comprise evidence based exercises targeting the main muscle groups involved in swallowing, namely muscles involved in tongue strength, pharyngeal contraction and laryngeal elevation/upper esophageal sphincter opening. These strengthening exercises include tongue strengthening exercises (TSE) and chin tuck against resistance (CTAR) combined with an effortful swallow. First, TSE will be performed since tongue strength is the main bolus driving force and reduced tongue strength can cause oral and pharyngeal residue and aspiration[47; 141; 142]. Second, CTAR exercises are used since they have a significant impact on the suprahyoid muscles, with a positive effect on laryngeal elevation and upper esophageal sphincter opening[143; 144]. The third exercise consists of effortful swallows in combination with the chin tuck. Effortful swallows have been shown to improve the tongue base posterior motion and can increase tongue base-pharyngeal wall pressures[145]. It is hypothesized that the chin tuck in combination with an effortful swallow stimulates the pharyngeal musculature[144].

Table 1: study visits and evaluations

	STUDY PERIOD						
	Enrolment	Allocation	Post-allocation				Close-out
TIMEPOINT	*Pre RT*	*Between enrolment and start RT*	*Week 1 – 4 of RT*	*Week 5 – 7 of RT*	*End of RT*	*1 month after RT*	*3 months after RT*
ENROLMENT:							
Eligibility screen	X						
Informed consent	X						
Allocation		X					
INTERVENTIONS:							
PSE – control group			X				
PSE – app-group			X				
PSE – therapist group			X				
ASSESSMENTS:							
Patient, disease and therapy characteristics	X						
Swallowing function	X		X		X	X	X
Muscle strength	X		X		X	X	X
Impact of mucositis	X		X		X	X	X
Quality of life	X				X	X	X
Attitudes towards exercises			X				
Overall fatigue	X		X				

RT radiotherapy, PSE prophylactic swallowing exercises

The different exercises described above alternate during the sessions: all subjects start their first session with TSE and perform CTAR exercises and effortful swallow the next session. Tongue strengthening exercises consist of 120 tongue presses and are divided into 12 sets of 10 repetitions with 30 seconds rest between sets and with the target level set at 80% of 1 repetition maximum (1RM, i.e., the maximum amount of pressure that can be generated in one repetition)[47] [146-150]. The next session CTAR exercises and effortful swallows are performed. Each CTAR-session consists of 150 chin tucks against resistance at a target level of 60-70%[151] of the 1RM (i.e., in this study, the maximum chin tuck strength that can be generated, see below). These chin tucks are divided into 30 sets of 5 repetitions with an effortful swallow at every fifth repetition. In both tongue and chin tuck exercises, a successful repetition was defined as reaching the target level and hold the contraction for 3 seconds, using the green light (TSE) as biofeedback or tactile biofeedback (CTAR). According to the principle of progressive overload, maximal tongue strength and strength of the suprahyoid muscles and correspondent levels of resistance are measured at baseline and recalculated subsequently every week[150].

All subjects will be randomly assigned into the previously defined groups: control group, app-group and therapist-group. The groups differ in degree and kind of adherence improving measures. All groups have some of these measures in common. Restricting the duration to the first four weeks of CRT is a first method to increase compliance since literature shows that the last 2-3 weeks of therapy the feasibility of completing exercises decreases[9; 75]. Receiving visual and tactile feedback on their performance via the therapeutic devices is a second method. The differences in adherence improving measures between the groups are illustrated in table 2. The first group (control group) will perform the exercises at home, without supervision of a SLP but with a counseling session of 10 minutes every week. Group 2 (app-group) practices at home but receives continuous counseling and gets instructions by videos via an application on a tablet, developed in collaboration with Cyborn, Antwerp, Belgium (www.cyborn.be). Generally, mobile health applications are considered to be possible tools to improve traditional health care[152]. By means of gamification, the app helps, supports and motivates the patients to practice. The app registers when the patients practice, how many repetitions they do and when they succeed in doing the exercises. Group 3 (therapist-group) gets face-to-face therapy and will be counseled by a SLP 5 times per week. All patients will complete the first session with supervision of the SLP, irrespective of their group. The intervention will be discontinued on participant request or in case of worsening disease, requiring major changes in treatment. Reasons for discontinuing will be stored in a database.

Table 2: study design

Inclusion		**n = 150**	
Stratified randomization	n = 50 Control group	n = 50 App-group	n = 50 Therapist-group
Therapy schedule	- 5x/week (30-40 min) - 4 weeks - Home practice	- 5x/week (30-40 min) - 4 weeks - Home practice but app supported	- 5x/week (30-40 min) - 4 weeks - Therapist supervised
Exercises	- TSE - CTAR - Effortful swallow	- TSE - CTAR - Effortful swallow	- TSE - CTAR - Effortful swallow
Adherence measurements			
- **Supervision**	No (home practice)	No (home practice –app)	Yes (face-to-face therapy)
- **Counseling**	Counseling 1x/week by SLP (10')	Counseling 1x/week by SLP (10') & continuous counseling via app	Counseling by SLP 5x/week
- **Feedback on performance**	Yes – instrumental	Yes – instrumental	Yes – instrumental & by SLP
- **Clear and repeated instructions**	- Introduction session - Written instructions	- Introduction session - Instructions via app: animation videos	- Each session by the SLP
- **Target setting**	Yes	Yes	Yes
- **Limited duration**	Yes – first 4 weeks of CRT	Yes – first 4 weeks of CRT	Yes – first 4 weeks of CRT

TSE tongue strengthening exercises, CTAR chin tuck against resistance, SLP speech language pathologist, CRT (chemo)radiotherapy

Instrumentation

Maximal tongue strength is measured by the Iowa Oral Performance Instrument (IOPI) Pro, model 3.1 (IOPI Medical LLC, Woodinville, WA). This is a small portable instrument connected to an air-filled bulb. Maximal isometric pressure can be measured anteriorly and posteriorly, MIP_a and MIP_p respectively. The digital display shows the amount of pressure the tongue produces (in kilopascal, kPa) when squeezing the bulb against the palate. In anterior position, the proximal end of the bulb is placed immediately behind the upper teeth at the midline of the palate. In posterior position, the bulb is placed at the level of the transition from the hard to the soft palate. The subjects are instructed to push the bulb as hard as possible against the palate. The highest value of three trials is considered the MIP. Tongue strengthening exercises are done using the IOPI Trainer, model 3.2 (figure 1), which is similar to model 3.1. The device allows the therapist to set a target manually. There is a vertical series of small lights providing visual feedback: the upper light becomes green when the subject reaches the target. The TSE only consists of anterior tongue presses since previous research shows that the increase in tongue strength depends on the localization of the bulb: higher increases of anterior and posterior tongue strength are

obtained when training exclusively anteriorly[153]. Patients are instructed to squeeze the bulb against the hard palate until the upper light becomes green and are asked to hold this effort for 3 seconds[154].

Fig. 1 Iowa Oral Performance Instrument, model 3.2 (IOPI Medical LLC, Woodinville, WA, USA)

Maximal chin tuck strength (in Newton, N) is measured by means of a dynamometer (Microfet™, Biometrics, Almere, the Netherlands) (figure 2). Patients are asked to place their chin on the chin bar and keep their mouth and teeth closed. A fixed belt stabilizes the patients' head. They are instructed to press their chin down as hard as possible. The highest value of 3 trials is considered the maximal isometric chin tuck strength. Based on this value, the resistance level can be assessed using the conversion table from Kraaijenga et al (value from 1 to 6)[144; 151]. The CTAR exercises are performed using the Swallowing Exercise Aid (SEA) (figure 3). It is a medical device remodeled by a technician of the Netherlands Cancer Institute by adding a chest bar to one of the mouthpieces of the commercially available TheraBite Jaw Mobilization device (Atos Medical, Hörby, Sweden)[144]. The ActiveBand can be placed at various, marked positions depending on the desired resistance. The minimal resistive load is 4 Newton (position 1) and the maximal resistive load is 50 Newton (position 6). Subjects are asked to hold the device with 1 hand, place the chest bar against the chest and put their chin on the chin bar. They are instructed to press the chin bar towards the chest bar and hold this effort for 3 seconds. At every fifth repetition, patients are asked to press the chin bar against the chest bar and swallow as hard as they can (effortful swallow).

Fig. 2 Examination frame and dynamometer (MicrofetTM, Biometrics, Almere, The Netherlands)

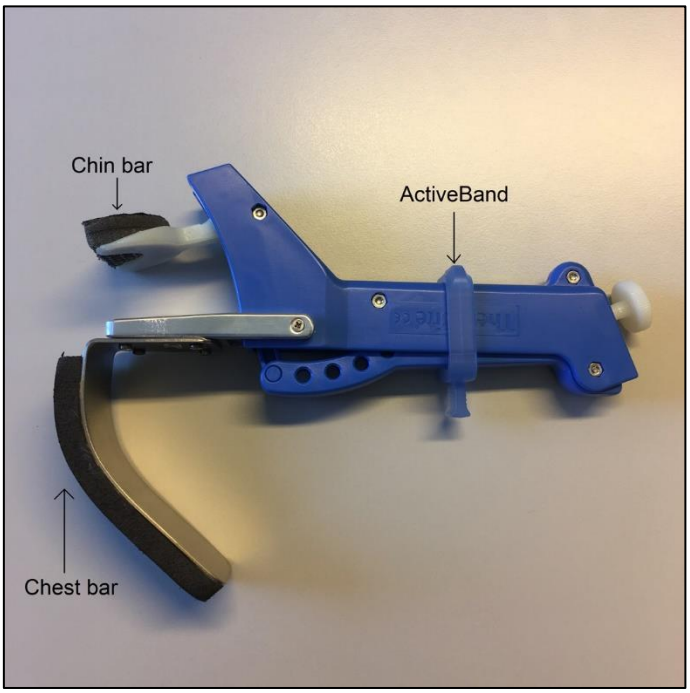

Fig. 3 Swallowing Exercise Aid (SEA)

Outcome measures

The primary outcome measure of this study is the swallowing function, based on scores of the Mann Assessment of Swallowing Ability-Cancer (MASA-C)[155]. Next to this measurement, patients are asked to fill out the Eating Assessment

Tool-10[156] and a Visual Analogue Scale. The Functional Oral Intake Scale[157] is filled in by a SLP. The swallowing function is assessed at baseline, weekly during the weeks of exercise, immediately after CRT and 1 and 3 months after CRT (table 1).

There are 3 secondary outcome measures: (1) degree of compliance, (2) muscle strength and (3) quality of life.

The degree of compliance is expressed as the total number of exercises performed per week, based on daily patient (group 1 and 2) and therapist (group 3) registration. The number of performed tongue strengthening exercises is recorded automatically by means of the IOPI. In group 2, the degree of compliance is also expressed by the time spent on the app, which is registered automatically. The compliance is assessed during the first four weeks of CRT. MIP_a, MIP_p and strength of the suprahyoid muscles are examined at the same time as the swallowing function (table 1) and are measured using IOPI and a dynamometer. The Swallowing Quality-of-Life Questionnaire[158] and the Dysphagia Handicap Index[159] examine the swallowing-related QOL and are assessed at baseline, at the end of CRT and 1 and 3 months after CRT (table 1).

All these evaluations are performed by a speech and language pathologist.

Confounders

Patient, disease and therapy characteristics

Patient and situational characteristics are questioned at baseline and include age, gender, educational level, social status, experience with mobile phones, tablets, etc. and the presence of support from family or friends. The question about the experience with mobile phones and tablets is an open question that allows the patients to answer extensively. The question about the support is a closed question: yes/no and who. The NEO Five Factor Inventory is used to examine the personality of the patient[160]. The disease and therapy characteristics include location of the carcinoma, stage, treatment, fractionation, TNM classification (TNM7) and human papillomavirus (HPV) status. This information is gained by radiation oncologists, head and neck surgeons and otolaryngologists.

Evaluation of the impact of mucositis

The Oral Mucositis Weekly Questionnaire[37] is used to measure the symptoms of mucositis and the impact on the patient well-being and function.

Evaluation of attitudes towards exercising, motivation and fatigue

The attitudes on exercises are surveyed by the questionnaire of Sluijs, Kok & Van der Zee[82] and the overall fatigue of the patients are evaluated by the Multidimensional Fatigue Inventory[161] (table 1).

Data management and monitoring

The datasets generated during the study will be stored in a non-publicly available repository. All clinical record forms are collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at Ghent University Hospital[162]. It is a secure, web-based application designed to support data capture for research studies. All patient information (except identifying information), questionnaires and measurements are stored for 20 years. The researchers from each participating institution have access to the data of their patients. All data are pseudonymized and patients' details are encoded. The principle investigator and the researcher at the University Hospital in Ghent manage the entire database.

In order to avoid introducing bias, no interim analyses will be performed. As the experimental interventions caries minimal risks, no data monitoring committee will be implemented, nor will there be a stopping procedure.

There is no anticipated harm and compensation for trial participation. After completing the trial, participants will be followed by the radiation oncologist and head and neck surgeon or otolaryngologists and if necessary, they will be referred to any other specialist.

Serious adverse events will be reported to the Ethical Committee of the central study center by means of a yearly line listing system.

Statistical analysis

Sample size calculation

The sample size calculation is performed using GLIMMPSE32 and based on published data on MASA-C scores[155]. A total sample size of 111 participants (37 per group), is needed to demonstrate a different evolution over time in the experimental groups and control group at a significance level of 0.05 and a power of 0.8 when using repeated measures with Geisser-Greenhouse correction (3 groups x 4 time points). Based on previous research on prophylactic swallowing exercises by Carnaby-Mann and colleagues[8], we expect a baseline MASA-C score of 195, with a decay in the first 6 weeks to 171 in the

control group, 177 in the app-group and 180 in the therapist-group. After 6 weeks we assume no further decline. A standard deviation of 11 is considered for the MASA-C scores at each time point, this is also based on the SDs reported in Carnaby-Mann et al[8]. First-order auto-regressive correlation (AR(1)) is assumed for the covariance structure between the repeated measures, with a base correlation of 0.4 and a decay rate of 0.5. The targeted total sample size, taking into account more than 20% dropouts, is 150 (n=50/group).

Data analysis

Patients will be analyzed in the groups to which they are assigned (intention-to-treat). Descriptive statistics will be used to summarize patient characteristics per treatment group. Data will be analyzed using linear mixed effects models with group, time and group by time interaction as fixed effects. A random intercept will be added to account for correlation between measurements coming from the same individual. When one or more overall effects are significant, post-hoc pairwise testing with Bonferroni-Holm correction for multiple testing will be performed. Missing data is assumed to be missing at random (MAR) and thus will be ignored in the analyses. By using mixed effects models for the analysis, we can incorporate all information on the available time points. If more than 15% of the data is missing, a sensitivity analysis will be conducted by using multiple imputation. Results of the original analysis of the available cases will be interpreted in the context of sensitivity analysis.

Additionally, the impact of adherence, HPV status, dosimetry and mucositis on the different functional endpoints will be studied in exploratory linear mixed effects models. Fixed main effects and interactions with group for all these factors will be evaluated.

More details on the primary, secondary and exploratory analyses can be found in the statistical analysis plan.

A p-value of less than 0.05 will be considered statistically significant. All analyses will be conducted using SPSS Statistics version 25 (IBM, Chicago, IL) and R software (R Foundation, Auckland, New Zealand).

Patient and public involvement

Pre-recruitment there has been a try-out with a small number of patients. They were questioned about the feasibility of the exercise protocol. Also, during the study all participants are asked about their experiences regarding the exercises. In the context of the application, all patients are questioned about their familiarity with smartphones, tablets and computers. Before the start of the study, the application has been tested by a number of people from different age groups.

Study sites

This multicenter study will be conducted at following sites: Antwerp University Hospital, Ghent University Hospital, University Hospital Leuven, Academic Hospital Sint-Jan Bruges, Sint-Augustinus Antwerp and other partners of the Iridium Cancer Network.

All participating centers have extensive experience in research on head-and-neck cancer and dysphagia. Data collection in these hospitals enables the study to include enough patients and gives the study sufficient power.

Discussion

An increasing number of studies showed a significant positive effect of PSE on swallowing function in HNC patients treated with CRT. However, low adherence rates are a major issue, preventing clinical implementation of PSE. There is an internationally recognized need to develop the most efficient PSE protocol in which the adherence rates are maximized. This multicenter randomized trial will investigate the effect of adherence improving measures on actual patient compliance, swallowing function, muscle strength and QOL. It is expected that this study will result in an optimized, patient supported and evidence based PSE-program improving patient compliance.

Chapter 6

Supportive care among head and neck cancer patients: validation of the Dutch version of the Oral Mucositis Weekly Questionnaire-Head and Neck Cancer (D-OMWQ-HN)

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Chapter 6: Supportive care among head and neck cancer patients: validation of the Dutch version of the Oral Mucositis Weekly Questionnaire-Head and Neck Cancer (D-OMWQ-HN)

Abstract

Objective. Oral mucositis (OM) is one of the most profound toxicities during (chemo)radiotherapy (CRT) for head-and-neck cancer (HNC), impacting a patients' quality of life (QoL). To measure the effect of OM on one's QoL, the use of patient-reported outcome measures (PROM) is of utmost importance. Since Dutch validated PROMs assessing the impact of OM are lacking, the aim of this study was to translate the Oral Mucositis Weekly Questionnaire-Head Neck Cancer (OMWQ-HN) into Dutch and to validate this version.

Methods. The OMWQ-HN was translated according to the internationally described cross-cultural adaptation process. Thirty-five HNC patients were asked to complete the D-OMWQ-HN, together with the Functional Assessment of Cancer Therapy and the Swallowing Quality-of-Life Questionnaire for 5 times during the first 5 weeks of CRT. The Toxicity criteria of the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer was completed by the radiation oncologist at the same time points. Factor analysis was done for psychometric validation and reliability was tested using Cronbach's alpha. Convergent and discriminant validity were calculated and clinical validity was assessed.

Results. 91% of the questionnaires were completed. Internal consistency was high, after removing items 1, 2 and 4F. Test-retest reliability was high, convergent and discriminant validity were demonstrated. The D-OMWQ-HN can successfully detect differences in the impact of OM and is sensitive to detect changes in time.

Conclusions. The D-OMWQ-HN is a valid and reliable instrument to assess the impact of OM in HNC patients treated with CRT.

Introduction

Radiotherapy is, along with surgery, the most frequently used treatment modality for patients with head and neck cancer (HNC). Unfortunately, radiotherapy in the head and neck area impacts on the quality of life (QoL) of patients via acute and late toxicity [29; 163; 164]. Most common acute complications during radiotherapy are radiation dermatitis, oral mucositis, xerostomia, loss of taste, fatigue, dysphagia and dysphonia [28; 29; 36; 165-167]. Oral mucositis (OM) refers to an inflammation/ulceration of the oral mucosa and is seen as the most impacting, dose-limiting and dose-delaying toxicity during radiotherapy [36-38; 168]. The severity and duration depends on the tumor site, the total radiotherapy dose and radiotherapy schedule, the use of concurrent chemotherapy and patient-related factors, e.g. age, oral hygiene, alcohol and tobacco use [39; 165; 169]. Oral mucositis results in pain, bleeding and infections, which can lead to dysphagia and nutritional intake impairment [38; 39]. Since it has a significant impact on QoL [5; 29; 40], it is of major importance to evaluate and assess this complication in patients with HNC.

A frequently used evaluation tool is the Toxicity criteria of the Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer (EORTC), which is completed by the radiation oncologist through clinical examination [170]. While this clinician-based assessment is important in establishing a proper management plan for OM and allowing for follow-up, it does not provide information on the functional loss or impact on QoL. To represent treatment-specific functional consequences as well as the impact on QoL directly by the patient, patient-reported outcome measures (PROMs) can be used [38; 171].

Nevertheless, until now, there is no Dutch instrument available to assess patient-reported OM in the HNC population. The Oral Mucositis Weekly Questionnaire-Head and Neck Cancer (OMWQ-HN) however, is an English PROM assessing the impact of OM on patients' well-being and function with shown validity and reliability in HNC patients treated with radiotherapy [37; 39]. Literature indicates that evidence of scalability, reproducibility and construct validity of all language versions of PROMs, used in clinical trials, is needed [172]. Therefore, the aim of

this multicenter, longitudinal study is the cross-cultural adaptation and validation of the Dutch version of the OMWQ-HN (D-OMWQ-HN) in order to provide a valid and reliable tool for assessing patients' perspectives of OM in Dutch-speaking countries.

Methods

This study was conducted at the University Hospitals of Antwerp and Ghent and included two phases: cross-cultural adaptation of the OMWQ-HN and the clinical study with data collection.

Phase 1: cross-cultural adaptation

The original OMWQ-HN is a short and feasible tool to assess OM, specifically developed and validated in HNC patients receiving radiotherapy or chemoradiotherapy. It provides detailed information about patients' mouth and throat pain and soreness and consists of seven items, in which a Likert-type response format is used to answer each item. The time frame to which the questions are addressed is 'the past week'. The first two questions evaluate global health and QoL using a 7-point scale (1: very poor, 7: excellent). The third question investigates the mouth and throat soreness using a 5-point scale (0: no soreness, 4: extreme soreness). If the answer on the third question is 0, the patient is instructed to stop the questionnaire. Otherwise, the patient continues with the remaining four questions. The fourth question, consisting of six items, assesses the impact of the mouth and throat soreness on sleeping, swallowing, drinking, eating, talking and brushing teeth on a 5-point scale (0: not limited, 4: unable to do). The last three questions investigate the degree of mouth and throat pain and soreness on a 11-point scale (0: no pain or soreness, 10: the worst pain or soreness imaginable or possible) [37; 39].

This original version of the OMWQ-HN was translated into the Dutch language according to the cross-cultural adaptation process of translation and back-translation as described in international guidelines [173-175]. Figure 1 shows a flowchart of the cross-cultural adaptation process.

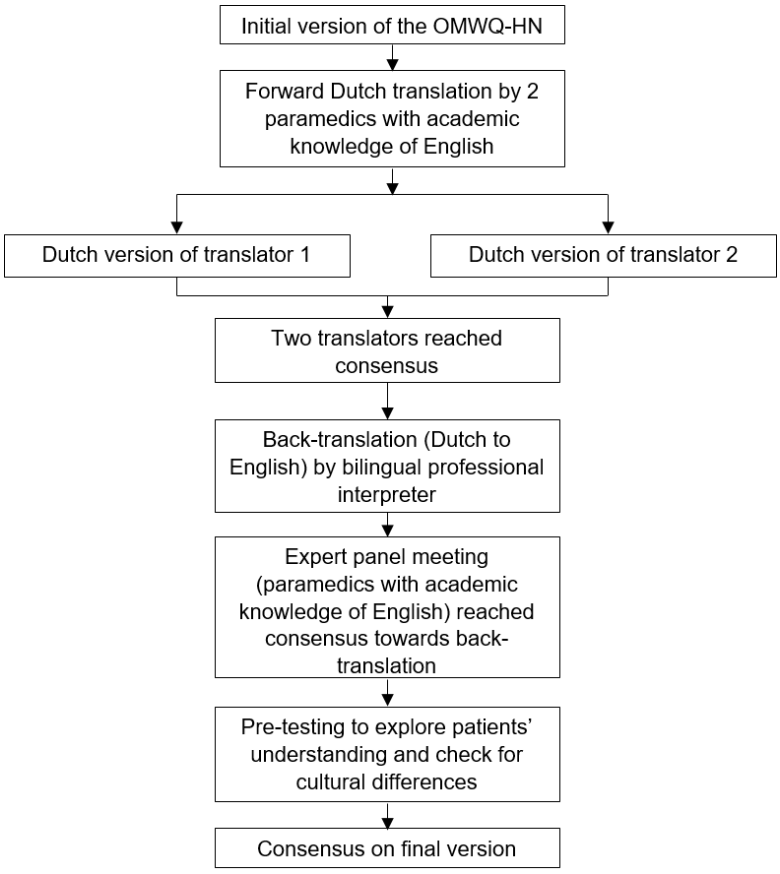

Fig. 1: flowchart of the process of cross-cultural adaptation

Phase 2: clinical study

Subject recruitment

Thirty-five patients with newly diagnosed squamous cell carcinoma of the oral cavity, oropharynx, nasopharynx, hypopharynx or larynx were included in this prospective multicenter study (University Hospitals Ghent and Antwerp). The age >18 years and a treatment with (adjuvant) radiotherapy or concomitant chemoradiotherapy (CCRT) were inclusion criteria. Patients with insufficient cognitive and/or language abilities or patients treated with experimental medication for OM, were excluded. Ethical approval was obtained by the Ethical Committee of the Antwerp University Hospital and the University of Antwerp (Ethisch Comité van het Universitair Ziekenhuis Antwerpen en de Universiteit Antwerpen) (ref. approval no. B300201318159 and B300201837097). Informed consents were collected by the radiation oncologist.

Study design

To assess the psychometric characteristics of the D-OMWQ-HN, all patients were asked to fill in the D-OMWQ-HN, together with the Functional Assessment of Cancer Therapy – Head and Neck (FACT-HN) [176] and the Dutch version of the Swallowing Quality of Life Questionnaire (D-SWAL-QOL) [177-179]. The RTOG/EORTC was completed by the radiation oncologist. All used instruments are fully explained below. The patient questionnaires were administered prior to treatment (baseline) and during weeks 3, 4 and 5 of radiotherapy treatment. The radiation oncologist filled out the RTOG/EORTC at the same time points. During week 4, the D-OMWQ-HN was filled in twice within 24-48 hours for test-retest reliability evaluation. Opioid analgesic use was recorded throughout the study based on patient record. Table 1 shows an overview of all measurements at the different time-points. Patients were asked to fill out the questionnaires while waiting in the hospital waiting rooms or at home. Data collected during week 5 was chosen to assess convergent and discriminant validity since it represents the time-point on which OM will be strongly pronounced and the data quality and collection will still be very good [180].

Table 1: study visits and evaluations

		Study period				
Time-point	Enrollment	*Baseline (between enrollment and start RT)*	*Week 3 of RT*	*Week 4 of RT – version 1*	*Week 4 of RT – version 2*	*Week 5 of RT*
Enrollment:						
Eligibility screen	X					
Informed consent	X					
Assessments:						
Patient, disease and therapy characteristics	X					
D-OMWQ-HN		X	X	X	X	X
FACT-HN		X	X	X		X
D-SWAL-QOL		X	X	X		X
RTOG/EORTC		X	X	X		X
Opioid analgesic use		X	X	X		X

RT, radiotherapy; D-OMWQ-HN, Dutch Oral Mucositis Weekly Questionnaire-Head and Neck Cancer; FACT-HN, Functional Assessment of Cancer Therapy-Head and Neck; D-SWAL-QOL, Dutch Swallowing Quality of Life Questionnaire; RTOG/EORTC, Toxicity criteria of the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer

Instruments

FACT-HN

The Functional Assessment of Cancer Therapy (FACT)-Head and Neck Cancer (-HN) is a multidimensional QoL instrument developed specifically for the oncologic population and consists of the FACT-General (FACT-G) and a HNC-specific subscale [176; 181]. The FACT-G includes 4 subscales, i.e. a physical, functional, emotional and social wellbeing subscale, with in total 28 items. The HN-specific subscale contains of 11 items. A Likert-type response format is used for each item and consists of five levels ranging from 'not at all' to 'very much'. The higher the score, the better the QoL. The FACT-HN has been translated into Dutch and has shown to be a valid and reliable scale [182]. The subscales "physical well-being" and "social well-being" were used to test the convergent and discriminant validity of the D-OMWQ-HN, respectively.

SWAL-QOL

The Swallowing Quality of Life Questionnaire [177-179] is a dysphagia-specific PROM consisting of 44 items, grouped in different subscales: general burden, eating duration, eating desire, symptoms, food selection, communication, fear of eating, social functioning, mental health, sleep, and fatigue. The minimum and maximum scores refer to an extremely impaired QoL and no impairment in QoL, respectively. The subscale fear of eating of the validated Dutch SWAL-QOL (D-SWAL-QOL) was used to test the discriminant validity of the D-OMWQ-HN [158].

RTOG/EORTC: Acute Radiation Morbidity Scoring Criteria

The Toxicity criteria of the Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer (EORTC) [170] is a clinician-rated scale, scored by a radiation oncologist and based on clinical examination. It is an ordinal scale including five levels ranging from 0 (the absence of radiation effects) to 5 (the radiation effects led to death). The RTOG/EORTC consists of different subscales, of which the subscale "mucous membrane" was used to test the convergent and clinical validity of the D-OMWQ-HN.

Statistical analysis

Statistical analyses were performed using SPSS Statistics version 27 (IBM, Armonk, New York).

The Shapiro-Wilk test was used to test the normality of distribution of the D-OMWQ-HN, FACT-HN subscales and D-SWAL-QOL subscales.

By means of factor analysis using Pearson correlation coefficients (r_s) between items of the D-OMWQ-HN, identification and removal of items with a weak correlation was done to maximize internal consistency. Internal consistency was calculated using Cronbach's α coefficients. In order to avoid redundant items, we aimed for a correlation between .7 and .9. Based on these analyses, the final D-OMWQ-HN scale was created and the sum score of the new instrument was used in all subsequent analyses.

Test-retest reliability of the D-OMWQ-HN was measured by means of Intraclass Correlation Coefficients (ICC), using the consecutive week 4 assessments. Convergent and discriminant validity were calculated using Spearman and Pearson correlation coefficients, by correlating D-OMWQ-HN sum scores with the RTOG/EORTC, D-SWAL-QOL and FACT-HN. Confidence intervals were calculated for all scale variables. To demonstrate the sensitivity of the D-OMWQ-HN to detect different levels of impact on QoL (clinical validity), boxplots were made using the RTOG/EORTC scale. The lower bound of the boxplots (first quartile) were used as cut-off values to discriminate between none to light impact, moderate impact or severe impact on QoL.

Linear Mixed effects Models with post-hoc pairwise testing and Bonferroni-Holm correction was used to assess the evolution of the D-OMWQ-HN scores through time. An independent samples T-test was performed to determine the difference in D-OMWQ-HN scores between patients who were using analgesic medication and patients who were not.

The statistical significance level was set at 0.05. For both ICC and Spearman/Pearson correlation, a precision of 0.13 (i.e. half width of the 95% CI) is expected for an anticipated correlation/ICC of 0.80 with a sample size of 35 people.

Results

Participants and drop-outs

Thirty-five participants were recruited for this study, of which six (17%) patients stopped the study earlier. One patient (3%) quitted the study after baseline measurement due to pain caused by radiotherapy. The other five patients (14%) stopped during week four because of weakness due to radiotherapy treatment. RTOG/EORTC data were still collected. Four hundred seventy-five of the 525 (91%) questionnaires were completed by the patients. Figure 2 shows a flowchart of the patients' selection and recruitment procedure. Patient and disease characteristics are presented in table 2.

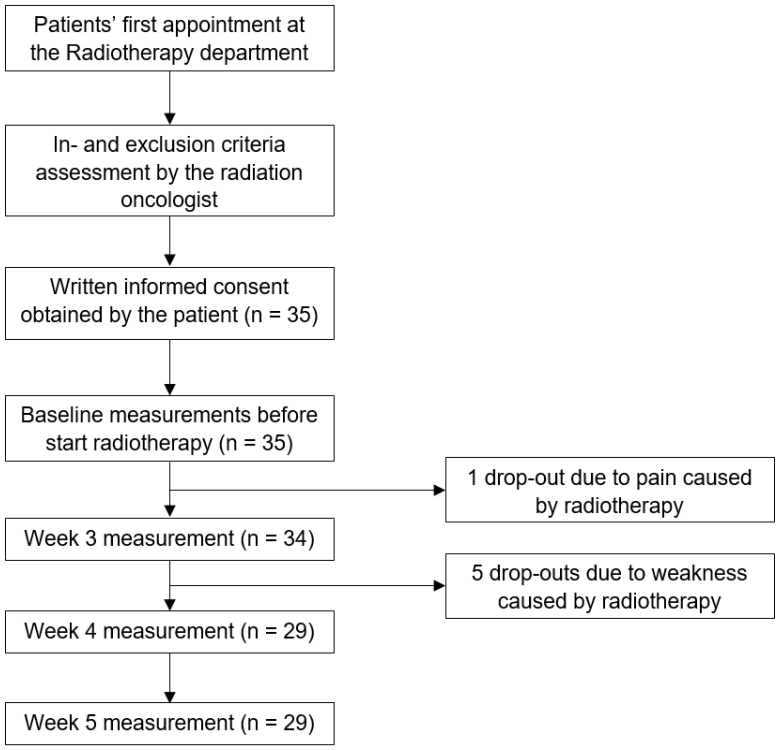

Fig. 2: flowchart of patient recruitment and follow-up

Table 2: patient and disease characteristics

		Patients (n = 35) (%)
Age at diagnose (year)	Mean	65
	Median	67
	Range	49-86
Sex	Male	27 (77)
	Female	8 (23)
Tumor site	Oral cavity	16 (46)
	Oropharynx	4 (11)
	Nasopharynx	1 (3)
	Hypopharynx	4 (11)
	Larynx	10 (29)
Treatment	Primary radiotherapy	12 (34)
	Surgery + adjuvant (chemo)radiotherapy	9 (26)
	Concomitant chemoradiotherapy	14 (40)

Factor analysis

Factor analysis showed that the item concerning brushing teeth (4F) had a low (< .5) item-total correlation relative to the other items (table 3) [37].

Table 3: results of factor analysis based on Pearson correlation coefficient

	D-OMWQ-HN		
	r_s	*p*	95% CI
Item 1	.516	< .001	[0.191 - 0.739]
Item 2	.518	< .001	[0.194 - 0.740]
Item 3	.845	< .001	[0.697 - 0.924]
Item 4A	.586	< .001	[0.286 - 0.781]
Item 4B	.791	< .001	[0.602 - 0.896]
Item 4C	.758	< .001	[0.547 - 0.878]
Item 4D	.755	< .001	[0.542 - 0.877]
Item 4E	.593	< .001	[0.296 - 0.786]
Item 4F	.466	< .001	[0.127 - 0.708]
Item 5	.870	< .001	[0.742 - 0.937]
Item 6	.792	< .001	[0.604 - 0.897]
Item 7	.841	< .001	[0.690 - 0.922]

r_s, Pearson correlation coefficient; p, significance level; CI, confidence interval

Reliability

By deleting items 1 and 2, as proposed by Epstein et al., internal consistency increased with .1, resulting in a high final consistency during week 5 (α = .784), pointing out a very good reliability [37].

Test-retest reliability of the D-OMWQ-HN was very strong (ICC = .953, $p < .001$).

Based on the results of factor analysis and reliability, item 1 (overall health), item 2 (overall QoL) and item 4F (limitations in brushing teeth) were excluded, resulting in the final scale consisting of 9 questions (Appendix 1).

The total D-OMWQ-HN-score was calculated as the sum of all items. This score was used in all further analyses and is referred to as the D-OMWQ-HN score.

Validity

Convergent validity

To assess convergent validity, the subscale "mucous membrane" of the RTOG/EORTC and the subscale "physical well-being" of the FACT-HN were used. Spearman correlation between the D-OMWQ-HN score and RTOG/EORTC was moderate, while Pearson correlation between D-OMWQ-HN score and subscale "physical well-being" was high during week 5 (Table 4).

Discriminant validity

To assess discriminant validity, the subscale "social well-being" of the FACT-HN and the subscale "fear of eating" of the D-SWAL-QOL were used. Poor correlations were observed during week 5 between D-OMWQ-HN scores and both subscales (Table 4).

Table 4: correlations (r_s) between D-OMWQ-HN and RTOG/EORTC, FACT-HN and D-SWAL-QOL during week 5

		D-OMWQ-HN	
	r_s	*p*	95% CI
RTOG/EORTC mucous membrane	.471	< .001	-
Physical well-being (FACT-HN)	.739	< .001	[0.516 - 0.868]
Social well-being (FACT-HN)	.071	.719	[-0.297 - 0.421]
Fear of eating (D-SWAL-QOL)	.273	.145	[-0.097 - 0.577]

r_s, Pearson/Spearman correlation coefficient; p, significance level; CI, confidence interval

Clinical validity

To demonstrate the sensitivity of the D-OMWQ-HN to detect different levels of OM impact, boxplots were made based on the results of the RTOG/EORTC. Fig. 3 shows that worse (i.e. higher) scores on RTOG/EORTC correlate with worse D-OMWQ-HN scores. None of the patients scored grade 4 on RTOG/EORTC. Based on the D-OMWQ-HN-values, corresponding with the first quartiles on the RTOG-subgroups, cut-off values can be determined discriminating between none to light impact (D-OMWH-HN < 21) moderate impact (D-OMWQ-HN < 27) and severe impact (D-OMWQ-HN ≥ 27) of OM on QoL.

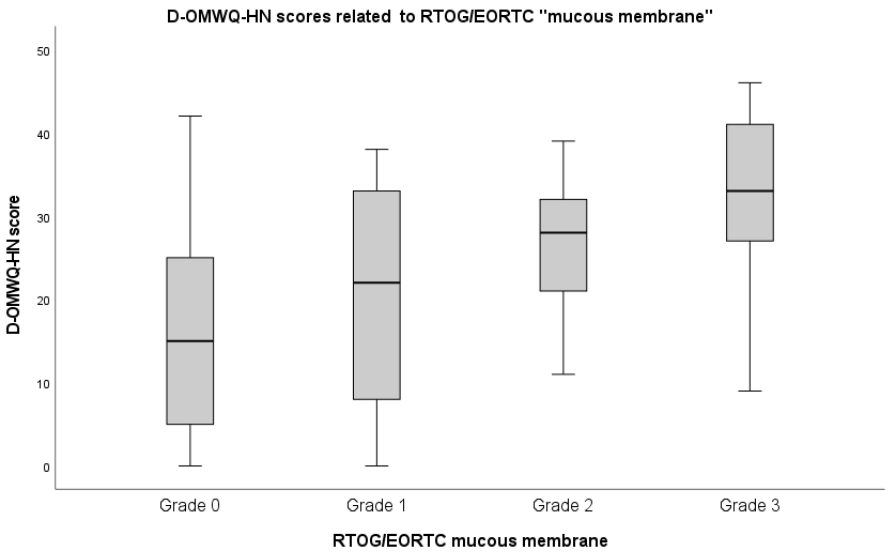

Fig. 3: D-OMWQ-HN score related to RTOG/EORTC "mucous membrane" subscale

Evolution of D-OMWQ-HN scores through time

Fig. 4 shows that D-OMWQ-HN scores deteriorate during radiotherapy treatment. Linear Mixed effects Models showed significant differences in D-OMWQ-HN scores during treatment ($F_{3\text{-}125}$ = 14.719, p < .001). Post hoc analyses, adjusted by means of Bonferroni correction, showed significant effects between all weeks, except between week 4 and 5 (Table 5).

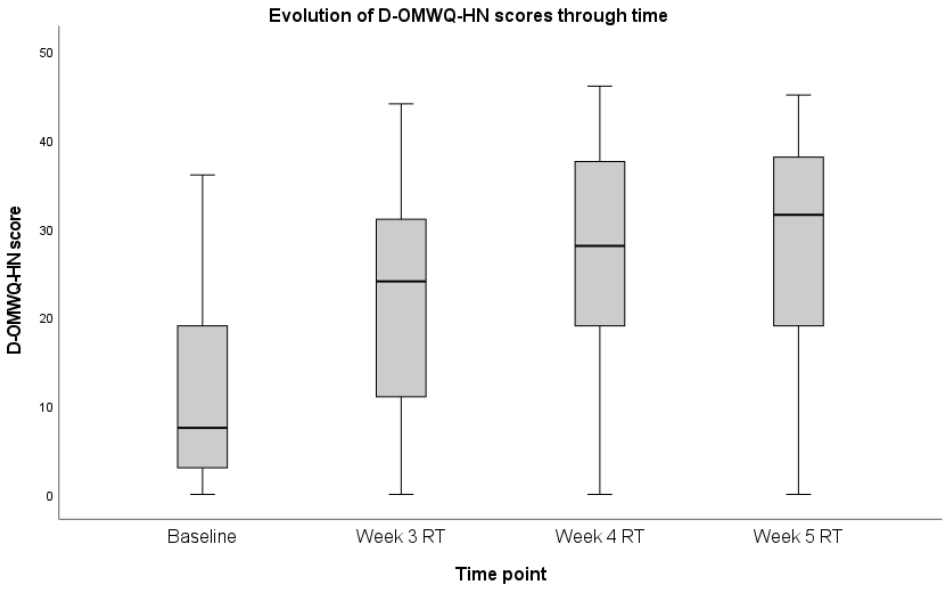

Fig. 4: evolution of D-OMWQ-HN scores during radiotherapy treatment

Table 5: Post hoc analyses with Bonferroni correction for the evolution of D-OMWQ-HN scores through time

		D-OMWQ-HN	
		p	**95% CI**
Baseline	*Week 3*	< .001	[-15.380 – -8.029]
	Week 4	< .001	[-20.167 – -12.742]
	Week 5	< .001	[-22.372 – -14.787]
Week 3	*Week 4*	.026	[-8.474 – -1.026]
	Week 5	.002	[-10.679 – -3.072]
Week 4	*Week 5*	.275	[-5.966 – 1.716]

p, significance level; CI, confidence interval

Use of analgesic medication

Independent samples T-test showed that patients who are using analgesic medication show significantly worse D-OMWQ-HN scores than patients who are not (t(127) = -3.576, $p < .001$).

Discussion

In general, the implementation of PROMs in both clinical practice and research is increasing [183; 184]. They are used to assist clinicians to select the best treatment, to enrich the understanding of patients' experiences and for assessing the quality of health care. In clinical trials, they are increasingly considered as valuable instruments to collect patient-centered data, since they provide unique information about the patients' perspective towards a medical condition and its treatment [183; 184]. Translation and validation of all new language versions of PROMs are therefore needed [172]. Since OM is one of the most common complications in HNC patients during radiotherapy treatment, with a major impact on QoL, we conducted this study to develop the Dutch version of the OMWQ-HN. Our study showed the impact of OM on the patient's well-being and demonstrated again the importance of assessing patient-reported outcomes to learn about their experiences during a burdensome period of RT treatment. The results of this study indicate that the D-OMWQ-HN is a reliable and valid PROM to measure the impact of OM in patients treated with (adjuvant) (chemo)radiotherapy for HNC.

By performing factor analysis and calculating internal consistency, items 1, 2 and 4F of the original D-OMWQ-HN were removed, resulting in the final scale with high internal consistency, including 9 questions. These results are consistent with the original study of Epstein et al. [37]. The low correlations of items 1 (overall health) and item

2 (QoL) with the questions related to OM, can be explained by the fact that overall health and QoL can be influenced by other factors, e.g. psychosocial factors [185; 186]. It is also expected that changes in specific symptoms (e.g. OM) not always reflect changes in overall health or QoL [37]. Item 4F (concerning brushing teeth) was also poorly correlated with the other items. The reason for this result is probably due to the high number of missing data on this question. There was no control for patients having dental prosthesis or for patients being edentate.

Convergent validity was assessed by using the subscale "mucous membrane" of the RTOG/EORTC and the subscale "physical well-being" of the FACT-HN. In general, convergent validity shows that two measures, that are supposed to measure the same construct, are in fact related. Correlation was assumed on these two subscales since, firstly, "mucous membrane" assesses the severity of damage to the oral mucosa clinician-based, and secondly, "physical well-being" contains questions related to pain and soreness due to cancer treatment [170; 176; 187-189]. Coefficients were moderate to high, suggesting that the D-OMWQ-HN measures the same construct as the subscales used. However, the correlation coefficients with the RTOG were moderate, indicating that the instruments are not redundant. To test discriminant validity, it was assumed that the D-OMWQ-HN would not correlate with "fear of eating" (subscale of D-SWAL-QOL) and "social well-being" (subscale of FACT-HN) [176-179; 188]. In general, discriminant validity shows a lack of correlation between two measures that should theoretically be unrelated. Based on the shown low correlations between the D-OMWQ-HN and "fear of eating" and "social well-being" respectively, discriminant validity was demonstrated.

The D-OMWQ-HN can successfully detect differences in OM impact (based on RTOG/EORTC comparison) and cut-off scores to define these different impact levels were determined. We hypothesize that by using these cut-offs, patients could be better counseled and treated with correctly chosen and dosed analgesics. Moreover, in this study, patients taking analgesics scored worse on the D-OMWQ-HN, demonstrating that despite their use, the impact of OM still remains high. It is however possible that patients using analgesics are more aware of the OM and consequences on daily (quality of) life.

A significant deterioration in D-OMWQ-HN scores during radiotherapy treatment was found, showing its sensitivity to detect changes through time. Scores were worst during week 5, which strengthens the choice to assess validity based on these results. Our findings are consistent with literature, describing the occurrence of mucosal erythema in the first week of daily fractionated RT programs, with a peak of patchy/confluent mucositis during the fourth to fifth week [10; 180].

The high rate of compliance to fill in the questionnaire demonstrates the feasibility of this new instrument. The limited number of questions in the D-OMWQ-HN contributes to this success, which is in concordance with previous studies concluding that PROMs consisting of >30 questions, impose higher burden on the patient [190].

This study is however not without limitations. To detect differences in the impact of OM, we made conclusions based on RTOG/EORTC scale. However, in our study, there were no patients who were given a grade 4 score on this instrument, which raises questions about the practicality of the levels of impact. Future research with a larger study population should examine whether our impact levels are valid.

This validation study is of major importance since OM is one of the most impacting and dose-limiting toxicities for HNC patients during radiotherapy and Dutch validated PROMs assessing the impact of OM are lacking. The D-OMWQ-HN gives detailed information about patients' mouth and throat pain and soreness and its functional limitations. It can be used to compare effects in mucositis interventions during radiotherapy treatment, but also in clinical practice to assess patients' experiences [37]. Since it is a short questionnaire, feasible to be completed without the supervision of a health-care provider, the questionnaire can be used to optimize consultations with the radiation oncologist. The D-OMWQ-HN can also be a useful tool to gain insight in the prevalence and incidence of OM in trials assessing new treatment techniques for patients with HNC. By using and analyzing the D-OMWQ-HN, caregivers can provide more patient-centered clinical care.

In summary, it can be concluded that the D-OMWQ-HN is a valid, reliable and feasible tool to assess patient-reported OM in patients with HNC treated with (adjuvant) (chemo)radiotherapy. The instrument allows the impact of OM on a patient's QoL to be measured in a standardized way.

Chapter 7

Increasing adherence to prophylactic swallowing exercises during head and neck radiotherapy: the multicenter, randomized controlled PRESTO-trial

This chapter has been published in

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Chapter 7: Increasing adherence to prophylactic swallowing exercises during head and neck radiotherapy: the multicenter, randomized controlled PRESTO-trial

Abstract

Background Prophylactic swallowing exercises (PSE) during radiotherapy can significantly reduce dysphagia after radiotherapy in head and neck cancer (HNC). However, its positive effects are hampered by low adherence rates during the burdensome therapy period. Hence, the main goal of this multicenter randomized controlled trial (RCT) was to investigate the effect of 3 different service-delivery modes on actual patients' adherence.

Methods A total of 148 oropharyngeal cancer patients treated with primary (chemo)radiotherapy were randomly assigned to a 4 weeks PSE program, either diary-supported (paper group; n=49), app-supported (app group; n=49) or therapist-supported (therapist group; n=50). Participants practiced 5 days/week, daily alternating tongue strengthening exercises with chin tuck against resistance exercises. Adherence was measured as the percentage of completed exercise repetitions per week (%reps). Statistical analysis was performed by means of SPSSv27, using Linear Mixed-effects Models with post-hoc pairwise testing and Bonferroni-Holm correction.

Results Adherence and evolution of adherence over time was significantly different between the three groups ($p < .001$). Adherence rates decreased in all three groups during the 4 training weeks ($p < .001$). During all 4 weeks, the therapist group achieved the highest adherence rates, whilst the app group showed the lowest adherence rates.

Conclusions PSE adherence decreased during the first 4 radiotherapy weeks regardless of group, but with a significant difference between groups. The therapist group achieved the highest adherence rates with a rather limited decline, therefore, increasing the face-to-face contact with a speech-language therapist can overcome the well-known problem of low adherence to PSE in this population.

Background

Prophylactic swallowing exercises (PSE) in patients with head and neck cancer (HNC) undergoing radiotherapy or concomitant chemoradiotherapy (RT/CRT) have a significant positive effect on muscle condition, swallowing function and quality of life (QoL) [2; 8; 9; 55; 63; 67]. Since dysphagia can lead to malnutrition, aspiration and related co-morbidities in HNC patients, prevention of this common side-effect is essential to increase QoL and long-term survival and thus to limit the load on our healthcare resources [2; 8; 9; 86; 191; 192]. Especially, since the number of surviving patients is increasing, due to improvements in diagnostics, treatment modalities such as concomitant CRT, and the increase of human papillomavirus (HPV)-related oropharyngeal cancer (OPC) patients, prevention of late sequelae becomes paramount [59].

Although PSE is known to significantly reduce dysphagia in HNC patients treated with RT/CRT, adherence rates are generally low (13%) to moderate (71%) [76; 79; 192]. This compromises the favorable effects the exercises have. Previous research has already shown that being adherent to PSE during RT/CRT is essential to benefit from the positive effects on swallowing function [66; 193]. In general, adherence can be improved by the use of continuous supervision, feedback after successful exercise performance and a close relationship between the patient and therapist [80; 83]. This indicates that the way the exercises are delivered, the service-delivery mode, can influence the degree of adherence [82-84]. Although little studied in HNC patients, this service-delivery mode might also impact on adherence to PSE in this population [11; 85].

Most commonly reported service-delivery modes for PSE are diary-supported home practice, app-supported home practice and speech and language pathologist (SLP)-supported practice [8; 9; 11; 86; 194]. The first option, diary-supported PSE, involves little additional cost and gives the patients the opportunity to practice whenever they want. Keeping a diary allows the therapist to monitor the exercises, thereby helping to increase adherence [85]. In app-supported PSE, the second option, telehealth applications are used to guide patients through home practice, without SLP-supervision of the therapy sessions. These are considered to be possible tools to improve traditional health care with better exercise adherence rates [152; 195]. Previous research showed that telepractice models to deliver speech-language therapy interventions are feasible in HNC patients and that they would be helpful to implement intensive rehabilitation in routine practice [11; 86; 195]. The third option, therapist-supported PSE, has the advantage of having continuous supervision and motivational support by an SLP, which has already been shown to improve adherence [85; 196].

Since the need for the development of an effective adherence improving PSE-program is crucial and internationally recognized [79; 86], the aim of this multicenter randomized controlled trial (RCT) was to investigate the effect of specific adherence improving measures on patients' actual adherence to PSE. Adherence was examined across the three before mentioned service-delivery modes: (1) diary-supported PSE, (2) app-supported PSE and (3) therapist-supported PSE.

Materials and methods

Study design and participants

The PRophylactic Swallowing Exercise Therapy program for patients with Oropharyngeal cancer (PRESTO) was a multicenter, open-label randomized controlled trial. Patients were enrolled at four Belgian hospitals (University Hospitals of Antwerp, Ghent and Leuven and General Hospital Sint-Jan Bruges).

Patients with a stage III or IVA-B (TNM7) newly diagnosed squamous cell carcinoma of the oropharynx were prospectively recruited for this study. Candidates for enrollment were both men and woman older than 18 years, with no cognitive or language deficits that might interfere with the correct implementation of the swallowing therapy protocol. Patients were treated with 6-7 weeks fractionated RT/CRT with or without induction chemotherapy. Exclusion criteria were the presence of a recurrent carcinoma or metastasis from a non-HNC carcinoma and previous RT/CRT or surgery in the head-neck region with possible impact on swallowing function. Written informed consent was obtained from all participants.

The minimization program QMinim was used to randomly assign all participants with a 1:1:1 allocation to one of the three exercise groups: diary-supported PSE (paper group), app-supported PSE (app group) and therapist-supported PSE (therapist group). The minimization factors were age (20-60 vs. ≥60 years old), treating center, presence of baseline dysphagia and treatment (radiotherapy or concomitant chemoradiotherapy). The three groups differed in degree and kind of adherence-improving measures. All patients performed the same PSE program 5 times a week during the first 4 weeks of RT/CRT. Limiting the therapy program to the first 4 weeks of RT/CRT was a general measure to maximize adherence since acute toxicity typically peaks during week 5 of radiotherapy treatment [10; 180]. The PSE comprised 2 evidence-based exercises, alternating daily and targeting the main muscle groups involved in swallowing. First, tongue strengthening exercises (TSE) were done since tongue strength is the main bolus-driving force. Furthermore, reduced tongue strength can cause oral and pharyngeal residue and aspiration [47]. The TSE were performed by using the Iowa Oral Performance Instrument (IOPI, model 3.2, IOPI Medical LLC, Woodinville, WA, USA) (Figure 1) and consisted of 120 tongue presses per

session, divided into 12 sets of 10 repetitions. Patients were instructed to pause for 30 seconds between every set. Second, chin-tuck against resistance (CTAR) exercises were used since they have a significant impact on the suprahyoid muscles [144]. The exercises were done by using the Swallowing Exercise Aid (SEA) [144] (Figure 2) and one session consisted of 30 sets of 5 repetitions for a total of 150 chin-tucks per day. Fifteen seconds of rest was provided between sets. The fifth repetition was a combination of a chin-tuck with an effortful swallow since this exercise has been shown to improve tongue-base posterior motion and tongue-base pharyngeal wall pressures [145]. Patients practiced at 60-80% of their 1repetition maximum (1RM), which was recalculated every week [150]. We practiced following the overload principle and took into account a high intensity [71].

Fig. 1 Iowa Oral Performance Instrument (model 3.2, IOPI Medical LLC, Woodinville, WA, USA)

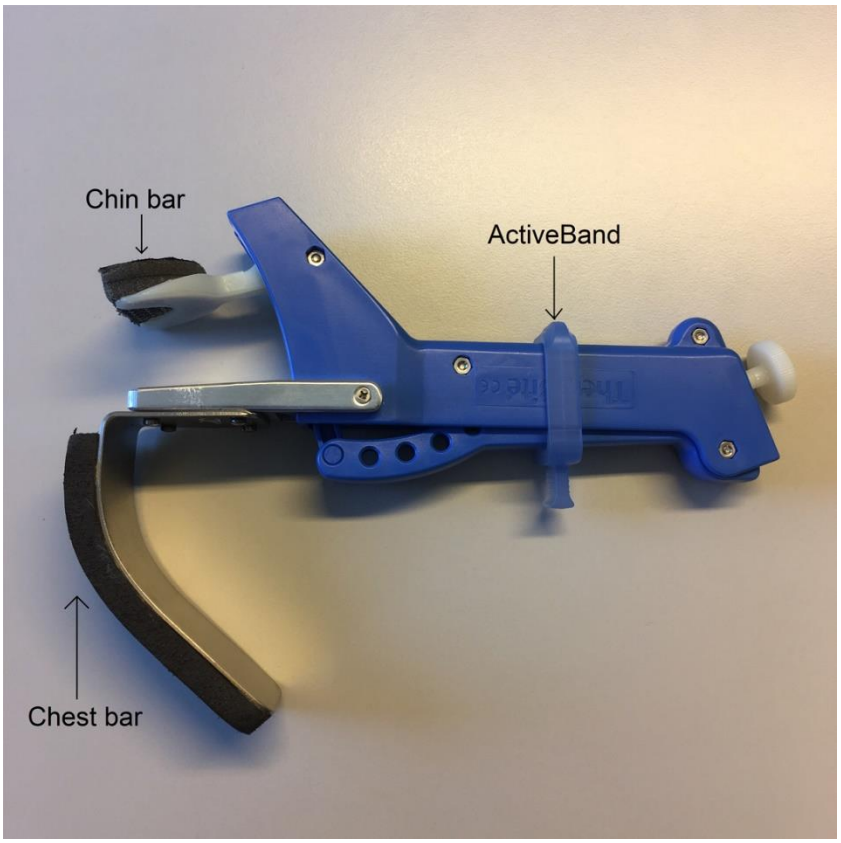

Fig. 2 Swallowing Exercise Aid (Antoni Van Leeuwenhoek, Netherlands Cancer Institute)

Adherence

The degree of adherence was expressed as the percentage of completed repetitions per week (%reps) and by means of 4 different categories, defined by Wall et al., including negligible practice (<25%reps), low practice (25-50%reps), moderate practice (50-75%) and high practice (>75%) [11]. At the end of the session, all patients, regardless of their group, were questioned about the degree of difficulty they had in completing the task, about the factors contributing to this difficulty and if they had any concerns or suggestions.

Paper group

The paper group performed the first exercise session under supervision of the SLP. After this first session, the IOPI and SEA were given home, patients received a logbook with written instructions and they continued practicing at home. They were asked to register in their logbook how many exercise repetitions they performed each day and whether these repetitions were successful or not. Adherence was then calculated based on the patients' record.

Once a week, an appointment with the SLP was scheduled to recalculate the target level, based on their new 1RM.

App group

Similar to the paper group, the app group performed the first exercise session together with the SLP. During this first session, participants were coached in the use of the tablet and app. Both the tablet and exercise devices were then given home so that further practice could be done at home. The app allowed registering all repetitions and whether they were successful or not. Each week, an appointment with the SLP was scheduled to recalculate the target level and to read data from the tablet. Adherence was calculated based on this data.

The application was developed in collaboration with the 3D animation, app and game studio Cyborn, Antwerp, Belgium (www.cyborn.be). It was provided to patients on a SAMSUNG GALAXY TAB A6 and practicing at home didn't require internet connection. Every week, the SLP connected the tablet with Wi-Fi to enable synchronization and data upload to the server.

The app consisted of instructional videos and images for both exercises. Patients could watch them as many times as needed to fully understand the exercise. The app uses gamification, i.e. using game elements in a non-game environment, with the aim of making a difficult task easier and more pleasant [198]. By means of gamification, it was expected that the app would help, support and motivate patients during practice. The aim of the game was to help a squid to make her underwater world more beautiful. Every time the patient practiced, he/she could win plants, flowers, stones and fish to brighten up the squids' coral reef. Figure 3 shows screenshots of the application. The number of exercises and repetitions the patients completed, were saved.

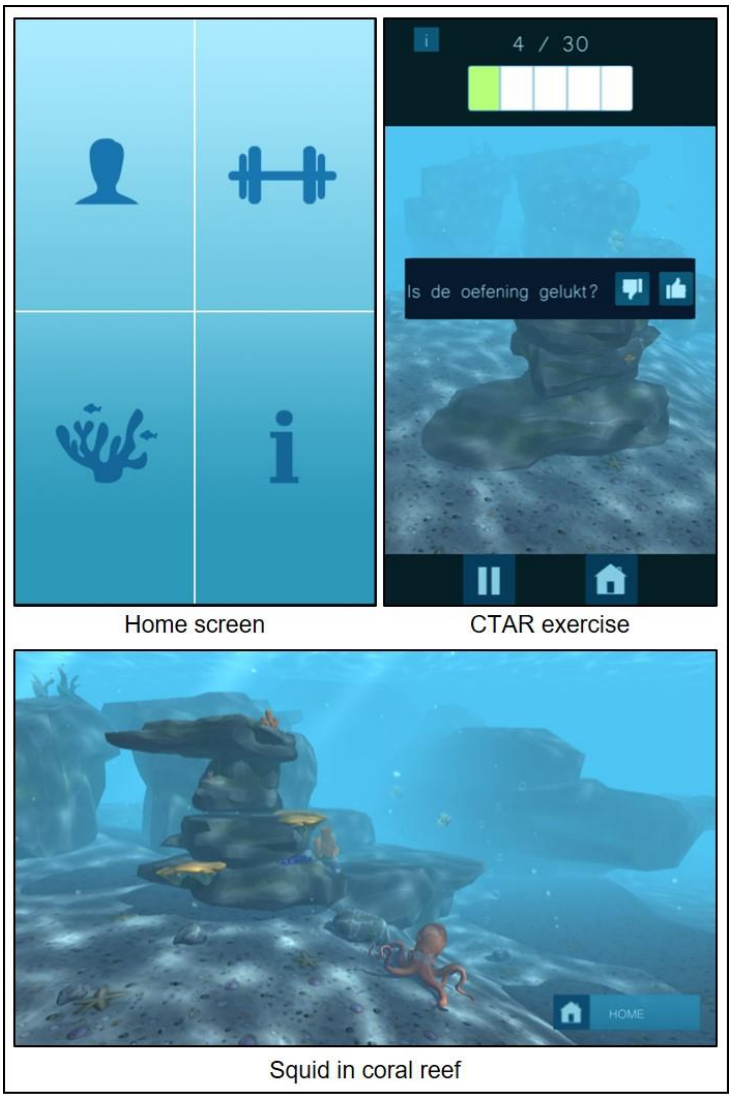

Fig. 3 The application

Every week, patients in the app group were questioned about their experiences with the tablet and application using visual analogue scales (VAS). These scales were added in a later phase of the study, meaning that only a subset of patients systematically completed these questions. The VAS were 100mm lines on which the patients were asked to place a vertical mark to indicate to what extent they agreed with the statement. The distance to the vertical mark was then measured to create a score. Table 1 shows an overview of the all scales concerning the tablet and app.

Table 1: overview of VAS concerning the tablet and app

User-friendliness		
Not user-friendly	———	Very user-friendly
Starting and opening of the app		
Difficult	———	Easy

Clarity of the explanation		
Unclear	———	Very clear
Usability of the explanation		
Unusable	———	Very useful
Layout of the app		
Unattractive	———	Attractive
Added value of the game element		
No added value	———	Definitely added value
Adequacy of the game element		
Not adequate	———	Very adequate

Therapist group

The patients in the therapist group were given face-to-face therapy for 5 days/week. Each session, clear and repeated instructions were given and patients received continuous feedback on their performance by the SLP. The therapist kept a logbook and registered the number of exercise repetitions the patients performed each day, and whether these repetitions were successful or not. Adherence was calculated based on therapist data.

The full study protocol has been published previously [197].

Statistical analysis

Sample size calculation.

The sample size calculation was performed for the primary outcome, namely MASA-C, using GLIMMPSE online software for power calculation in linear mixed effects models. No power calculation was done for the outcome adherence. The targeted total sample size, taking into account 20% dropouts, was 150; i.e. 50 patients per group. More details on the sample size calculation are presented in the protocol publication [197].

Data analysis.

Descriptive statistics were used to summarize patient characteristics per treatment group. A linear mixed-effects model with group, time and group by time interaction as fixed effects was used to study the evolution of adherence in the three groups. A random intercept per subject was added to account for the correlation between observations coming from the same individual. Time was considered categorical to be able to capture a non-linear evolution over time. Post-hoc pairwise

testing with Bonferroni-Holm correction for multiple testing was performed. As the adherence rates were not normally distributed, with a peak at 0% and 100%, an additional sensitivity analysis using ordinal logistic generalized estimating equations (GEE) with the 4 categories defined by Wall et al. (high, moderate, low, negligible practice) was performed.

We hypothesized that there would be a significant difference in adherence between the three groups, with the highest levels of adherence found in the therapist group, followed by the app group and that the lowest adherence rates would be found in the paper group. Attitudes towards exercises were analyzed by means of descriptive statistics. A linear mixed-effects model was also used to examine the effect of age and patients' experiences towards mobile phones and apps on adherence in the app group.

Data was assumed to be missing at random and this missingness was ignored in the analyses. In the linear mixed effects model all information on the available time points is incorporated. Since only 11.4% of data was missing, we did not perform a sensitivity analysis using multiple imputation, as described in our statistical analysis plan [197].

A *p*-value of less than 0.05 was considered statistically significant. All analyses were conducted using SPSS Statistics version 27 (IBM, Chicago, IL, USA). Statistical analysis was performed under the supervision of a biostatistician.

Results

Participants

One hundred and fifty patients were recruited for this study. In one patient, baseline measurements were never taken due to an acute life-threatening hospitalization. Another patient was excluded due to a change in the study protocol, namely by adding the exclusion criteria of having a tracheotomy influencing the execution of the CTAR exercise. This leaves us with a total cohort of 148 patients. Patients, disease and treatment characteristics of the whole cohort and separate groups can be found in table 2. One patient had multiple primary tumors, here the larger T-stage was taken into account in the calculations.

Table 2: patients, disease and treatment characteristics

	Total cohort n = 148 (%)	**Paper group n = 49 (%)**	**App group n = 49 (%)**	**Therapist group n = 50 (%)**
Age	M = 63 SD = 8.5 Range = 41-86	M = 63 SD = 9.5 Range = 41-86	M = 63 SD = 7.9 Range = 41-83	M = 63 SD = 8.2 Range = 45-80
Gender				
Female	35 (24)	14 (29)	11 (22)	10 (20)
Male	113 (76)	35 (71)	38 (78)	40 (80)
T classification				
1-2	75 (51)	25 (51)	22 (45)	28 (56)
3-4	73 (49)	24 (49)	27 (55)	22 (44)
N classification				
0	7 (5)	3 (6)	3 (6)	1 (2)
1	23 (15)	7 (14)	7 (14)	9 (18)
2-3	118 (80)	39 (80)	39 (80)	40 (80)
Treatment				
RT	21 (14)	6 (12)	8 (16)	7 (14)
CRT	102 (69)	37 (76)	32 (65)	33 (66)
CRT with induction CT	25 (17)	6 (12)	9 (19)	10 (20)
HPV status				
Positive	76 (51)	24 (49)	23 (47)	29 (58)
Negative	72 (49)	25 (51)	26 (53)	21 (42)

M mean, SD standard deviation, RT radiotherapy, CRT chemoradiotherapy, CT chemotherapy

Patients who immediately dropped out after baseline measures (paper group: n = 1, app group: n = 3, therapist group: n = 1) were not included in the adherence analyses, giving a final number of 48 patients in the paper group, 46 in the app group, and 49 in the therapist group. Table 3 shows an overview of all drop-outs with the timing of drop-out and reason for drop-out. During the exercise weeks, there were 9 drop-outs in the paper group, 8 drop-outs in the app group and 4 drop-outs in the therapist group. As shown in table 3, a total of 18 patients refused further participation in the study. The most common reasons were pain, general weakness and the additional burden the exercises put during the RT/CRT. One patient refused further participation because of disbelief in the exercises.

Table 3: overview of drop-outs

	Timing						Reason
	Before start*	During week 1	During week 2	During week 3	During week 4	After week 4	
Paper group (n = 11)	1	5	2	-	2	1	• Hospitalization with impossibility of continuing exercises (n=2) • Refuse to further participation (n=8) • Died (n=1)
App group (n = 13)	3	3	3	2	-	2	• Acute hospitalization with impossibility of continuing exercises (n=1) • Progressive disease (n=1) • Refuse to further participation (n=8) • Died (n=3)
Therapist group (n = 6)	1	1	2	1	-	1	• Acute hospitalization with impossibility of continuing exercises (n=1) • Refuse to further participation (n=2) • COVID-19 infection for which applicable rules required stop of study contacts (n=2) • Submental swelling (n=1)

**excluded from the statistical analysis*

Adherence

Linear mixed-effects models showed significant effects of group ($F_{(2, 119)} = 20.194$, $p < .001$), time ($F_{(3, 342)} = 43.988$, $p < .001$) and group by time interaction ($F_{(6, 342)} = 4.546$, $p < .001$). These effects were confirmed by the additional GEE analysis. Adherence rates decreased in all 3 groups during the 4 training weeks, but with significant differences between groups. The highest decline was found in the app group and the smallest decline in the therapist group. During all 4 weeks, the therapist group achieved the highest adherence rates (figure 4). Between week 1 and 4, adherence rates decreased significantly in the paper group from 77%reps to 55%reps; from 72%reps to 27%reps in the app group and from 92%reps to 73%reps in the therapist group. Post hoc analyses, adjusted by means of Bonferroni-Holm correction, were performed and are shown in table 4. Adherence rates during week 1 and 2 were already significantly lower in the app group compared to the therapist group and during week 2 the paper group reached significantly higher adherence rates than the app group. During week 3 and 4, there was a significant difference between each of the three groups: adherence was significantly higher in the paper group compared to the app group and patients in the therapist group achieved significantly higher adherence rates than patients in the other 2 groups.

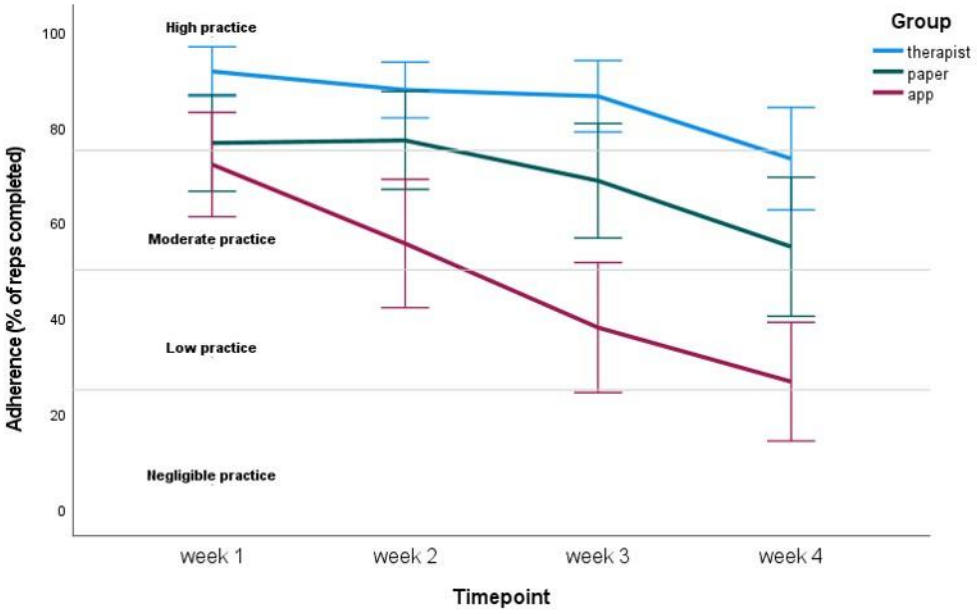

Fig. 4 Adherence rates through time by service-delivery mode. Levels of adherence by Wall et al. (2016) applied

Table 4: post-hoc comparisons between therapy groups based on linear mixed effects model for %reps with Bonferroni Holm correction for multiple testing

	Paper group vs. app group			Paper group vs. therapist group			App group vs. therapist group		
	p	Difference (M%)	95% CI	*p*	Difference (M%)	95% CI	*p*	Difference (M%)	95% CI
W1	.539	4.51	[-9.93-18.93]	.099	14.95	[-28.68- -1.22]	.035	19.46	[-33.53- -5.37]
W2	.035	21.55	[5.46-35.69]	.112	10.56	[-28.20-.37]	<.001	32.11	[-49.11- -19.88]
W3	.002	30.68	[13.98-44.32]	.025	17.67	[-35.47- -6.70]	<.001	48.35	[-64.89- -35.58]
W4	.006	28.18	[11.27-41.99]	.025	18.40	[-36.00- -7.11]	<.001	43.58	[-62.96- -33.40]

W1, week 1; W2, week2; W3, week 3; W4, week 4; M%, mean percentage; CI, confidence interval

Levels of adherence

Wall and colleagues [11] defined 4 levels of adherence to PSE, including negligible practice (<25%reps), low practice (25-50%reps), moderate practice (50-75%) and high practice (>75%). In Figure 2, we applied those levels of adherence on current results. The adherence in the therapist group can be labeled as high during the first 3 weeks and moderate during week 4 (73%). The paper group reached high adherence rates during week 1 and 2 and moderate rates during week 3 and 4, whereas the app group had moderate (week 1 and 2) to low (week 3 and 4) adherence rates.

Influence of age and digital experience in the app group

When dividing the app group into two age groups, <60 years old and >60 years old, no significant differences were found in adherence rates ($F_{(1, 135)} = 1.712$, $p < .193$). Moreover, there was no impact of the degree of experience the patients had with tablets/mobile apps on patients' adherence ($F_{(2, 135)} = .049$, $p = .952$).

In 13 of the 46 patients in the app group, the attitudes towards the tablet and app were systematically questioned. Table 5 gives an overview of the results of the visual analogue scales. Overall, the tablet and app were judged to be user-friendly, the app startup was found easy and the app was found to be very clear and useful. However, the added value of the game element and its adequacy concerning age, gender, etc. were scored less strong.

Table 5: results of VAS concerning attitudes and experiences towards tablet/app (n = 13)

	Usability tablet	Opening + starting app	Transparency explanations and videos	Usability explanations and videos	Lay-out app	Added value game element	Adequacy of game
M (SD)	85 (13.7)	93 (10.0)	92 (11.8)	90 (13.2)	86 (15.1)	59 (36.4)	57 (35.5)

Discussion

This multicenter RCT is only the second to investigate the effect of service-delivery mode on adherence to PSE in patients with oropharyngeal cancer. We found a significant impact of service-delivery mode (therapist, paper, app), time (1-4 weeks of RT) and the interaction of both on adherence.

During the 4 training weeks, adherence rates decreased significantly, which is consistent with previous studies [10; 11; 78; 85]. Messing and colleagues showed that adherence to PSE decreases rapidly during RT and drops to very low levels by the end of the treatment [10]. This remarkable decrease reflects the effect of RT-induced acute toxicity, which, as often described in literature, kicks in the second or third week of radiotherapy, peaks during the fifth week and lasts until the end or even after treatment [10; 85].

Although overall adherence rates in PRESTO decrease, they were found to be higher than the reported rates by Wall et al. [11]. In addition, the adherence rates in our paper-group were also higher than the rates in the study of Messing et al. [10]. Possible reasons for this discrepancies are differences in therapy content as well as organizational issues. Firstly, both Messing and Wall used a battery of exercises, while current study only consisted of two different types of exercises, which in addition, alternated daily [10; 11]. Previous research in home-based physical therapy showed that higher adherence rates

can be achieved when limiting the prescribed exercises to only two different types [199]. This finding can also be applied to our results. Next to that, the treatment period in current study was limited to the first 4 weeks of RT/CRT, taking into account the well-known problem of peaking acute toxicities during week 5 [10; 180]. The idea was to maximally strengthen the patients' swallowing system, before the patients suffer severely from the acute toxicities. We hypothesized that it might be mentally easier for the patients when they know the PSE will only last for the first four weeks and not until the end of the RT/CRT period, which might seem hardly reachable at the beginning. Note that due to differences in adherence definitions, caution is warranted when comparing different studies [76].

Current results show that adherence rates depend on service-delivery mode, with the highest adherence rates found in the therapist group. This highlights the positive effect of a combination of continuous supervision, feedback on performance and a close relationship between patient and therapist. These findings are both in line with results found within physical therapy research and with previous findings towards adherence rates to PSE in HNC patients [11; 82-85]; Hajdú et al. suggested that frequent supervision has a decisive effect on adherence [85]. Compared to the therapist group, lower adherence rates were found in both the app and paper group and during week 3 and 4, the adherence in the app group was significantly lower than the adherence in the paper group. Contradictory results were found by Wall et al., as they showed a trend towards higher adherence in the app-supported group compared to the home practice group [11]. In addition, also the study of Starmer and colleagues, working with an application as an adjunct to standard therapy, showed discrepancies with our results [152]. The lower adherence rates found in the app group compared to the paper group might be explained by the not so much appreciated game element in the app. Some patients indicated that it was too childish, others stated that they did not pay much attention to it. Another explanation might be the impractical way of performing exercises with the tablet, leading to little motivation; since the tablet was not directly linked to the exercise devices, patients had to enter the performed exercises themselves during practice.

In addition to the higher adherence rates found in the therapist group, there were clearly less dropouts in this group, supporting the idea of higher motivation.

Our study is however not without limitations. First of all, adherence data in both the paper and app group rely solely on participant information, which could possibly create a bias. During the study, we understood that some patients don't want to disappoint the SLP by admitting they didn't practice (enough). This may have led to a false record of adherence and thus

a presumably slightly lower adherence than reported above. Second, only 13 of the 46 patients in the app group were questioned about their experiences with the app, making it difficult to build any firm conclusions based on this data.

Since our results suggest higher adherence rates to PSE in patients continuously supported by the therapist, it might be interesting to find out if these results can also be achieved when practicing more than 4 weeks. However, no clear guidelines exist in when the exercises should start and how long they should last in time. In this study, we practiced only the first 4 weeks since literature shows that feasibility of completing PSE decreases during the last treatment weeks and the aim of this RCT was to optimize adherence rates [9; 75]. Nonetheless, the question arises if practicing the 4 four weeks is enough to achieve benefits on swallowing function, muscle strength and QoL. Future research should focus on the effects of differences in timing and duration of PSE and of course, if therapist supervision could lead to high (or acceptable) adherence rates during the last weeks of RT/CRT.

In this study, the paper group achieves high adherence rates during the first two weeks of RT/CRT, without a significant difference compared to the therapist group, and moderate rates during week 3 to 4. Based on these results, a possible solution to improve adherence might be an increase in supervised sessions towards the end of exercise weeks, as our findings suggest that stimulation and motivation by an SLP is most needed in the last exercise weeks. A combination of home practice the first two weeks with face-to-face exercises afterwards is subject for further research. In addition, future research should also focus on whether practicing from home, but with daily therapist interaction via an app, would achieve the same results as practicing with an SLP in real life.

The next steps within the PRESTO study are to examine the effects of increased adherence on muscle strength, swallowing function and QoL, possible confounding factors and the cost-effectiveness.

In conclusion, our randomized controlled trial found significant differences in adherence rates to PSE based on service-delivery mode in HNC patients undergoing RT/CRT. Highest rates were found in the therapist group while adherence was moderate to low in the paper and app group respectively. Based on these findings, we can conclude that increasing the face-to-face contact with a SLP can be the solution to the well-known problem of low adherence to PSE in this patient population.

Chapter 8

Prophylactic swallowing therapy during head and neck cancer radiotherapy: effect of service-delivery mode and overall adherence level on swallowing function and muscle strength – the PRESTO trial

This chapter has been submitted in

Baudelet M., Van den Steen L., Duprez F., Goeleven A., Nuyts S., Nevens D., Vandenbruaene C., Massonet H., Vergauwen A., Vauterin T., Verstraete H., Wouters K., Vanderveken O., De Bodt M., Van Nuffelen G. Prophylactic swallowing therapy during head and neck cancer radiotherapy: effect of service-delivery model and overall adherence level on swallowing function and muscle strength. The PRESTO trial. *Dysphagia*.

Chapter 8: Prophylactic swallowing therapy during head and neck cancer radiotherapy: effect of service-delivery mode and overall adherence level on swallowing function and muscle strength – the PRESTO trial

Abstract

Background. Prophylactic swallowing exercises (PSE) during head-and-neck cancer (HNC) (chemo)radiotherapy (CRT) have a positive effect on swallowing function and muscle strength. Adherence rates to PSE are however moderate to low, undermining these effects. Since the service-delivery mode (SDM), the way the exercises are offered, can influence adherence, the aim of the PRESTO-trial was to investigate the effect of SDM on swallowing function and muscle strength during and post-CRT. In addition, the effect of overall adherence (OA), independent of SDM, was also investigated.

Materials and methods. A total of 148 HNC patients, treated with CRT, were randomly assigned to one of the 3 SDM's (paper-supported, app-supported or therapist-supported PSE) and performed a 4-week PSE program. OA was calculated based on the percentage of completed exercises. Patients were divided into OA levels: the OA75+ and OA75- group performed respectively ≥75% and <75% of the exercises. Swallowing function based on Mann Assessment of Swallowing Ability – Cancer (MASA-C), tongue and suprahyoid muscle strength during and up to 3 months after CRT were compared between the SDM's and OA levels. Linear Mixed-effects Models with post-hoc pairwise testing and Bonferroni-Holm correction was used.

Results. No significant differences were found between the three SDM's. Significant time effects were found: MASA-C scores decreased and muscle strength increased significantly during CRT. By the end of CRT, the OA75+ showed significantly better swallowing function compared to OA75-. Muscle strength gain was significantly higher in the OA75+ group.

Conclusion. SDM had no impact on swallowing function and muscle strength, however, significant effects were shown for OA level. Performing a high level of exercise repetitions is essential to benefit from PSE.

Background

During the last decade, the use of prophylactic swallowing exercises (PSE) in patients treated with radiotherapy or concomitant chemoradiotherapy (RT/CRT) for head and neck cancer (HNC) is gaining more interest[1; 2; 8; 9]. The rationale behind these prophylactic strategies is prevention of weakness and disuse atrophy of the swallowing musculature[2; 200]. Previous research showed that prophylactic swallowing therapy can lead to less muscle atrophy and an improved dysphagia-related QoL with less aspiration, less feeding tube dependency and less hospitalization post-treatment[1; 8; 66; 67]. Adherence rates to PSE are however moderate to low (71-13%) and typically decline during RT/CRT[10; 78]. This threatens the positive effect the exercises have: Duarte et al. showed that the swallowing function in patients who were adherent to PSE exercises was better preserved at the end of RT/CRT than in patients who were not adherent to the exercises[66]. Moreover, Peng et al. observed no significant differences between pre- and post-treatment swallowing function in patients who adhered to the PSE exercises, whereas patients who did not adhere to them showed a tendency toward worse swallowing function[193].

Previous research indicated already that the way the exercises are given, the service-delivery mode, has a significant effect on patients' adherence[11; 85]. Most commonly reported service-delivery modes for PSE are diary-supported home practice, app-supported home practice and speech-language pathologist (SLP)-supported practice[8; 9; 11; 86; 194]. Wall and colleagues compared adherence rates in those three groups and found during week 1-3 of RT/CRT significant higher rates in patients performing SLP-supported PSE compared to patients practicing at home, without supervision. They also showed a trend towards higher adherence rates in the app-supported group compared to the home practice group[11]. Based on these findings, the question arises whether service-delivery mode of PSE can also impact on swallowing function and muscle strength during and post-RT/CRT.

Therefore, the aim of the PRESTO trial was to investigate the effect of three different service-delivery modes for executing an intensive PSE program on the swallowing function and muscle strength in HNC patients. In addition, the effect of overall adherence (OA), based on the total percentage of completed exercises, was assessed.

Methods

Study design and participants

The PRophylactic Swallowing Exercise Therapy program for patients with Oropharyngeal cancer (PRESTO) trial is a multicenter, prospective randomized controlled trial (RCT). Patients with stage III or IVA-B (TNM7) newly diagnosed squamous cell carcinoma of the oropharynx were recruited at four Belgian hospitals (University Hospitals of Antwerp/Iridium Network, Ghent, Leuven and General Hospital Sint-Jan Bruges). Potential candidates were both men and women, >18 years old, showing no cognitive or language deficits. Patients were treated with 6-7 weeks fractionated RT/CRT with or without induction chemotherapy. Exclusion criteria were the presence of a recurrent carcinoma or metastasis from a non-HNC carcinoma and previous RT/CRT or surgery in the head-neck region with possible impact on swallowing function.

All subjects who gave written informed consent to participate in the study, were randomly assigned to one of the following service-delivery modes: paper-supported PSE (paper group), app-supported PSE (app group) or therapist-supported PSE (therapist group), and this by means of the minimization program QMinim.

All participants, irrespective of their assigned group, performed a 4-week PSE-program for five days a week. Since acute toxicity becomes excessively pronounced from the fifth week of radiotherapy treatment, affecting patients' adherence, the duration of the program was limited to the first four weeks of RT/CRT[10; 85], whereas previous studies applied PSE during the complete RT period[8; 193]. The PSE-program consisted of two evidence-based exercises, alternating daily and targeting the main muscle groups involved in swallowing. First, tongue strengthening exercises were performed by using the Iowa Oral Performance Instrument (IOPI, model 3.2, IOPI Medical LLC, Woodinville, WA, USA) and consisted of 120 tongue presses per session, divided into twelve sets of ten repetitions. Second, chin tuck against resistance exercises were done by using the Swallowing Exercise Aid[144] and one session consisted of 150 chin-tucks, divided into 30 sets of five repetitions. The fifth repetition was a combination of a chin-tuck with an effortful swallow. Patients practiced at 60-80% of their 1repetition maximum (1RM), depending on the exercise, which was recalculated every week[150].

Service-delivery mode

The three service-delivery mode groups differed in degree and kind of adherence-improving measures. The first group, the paper-group, received a logbook and written instructions to practice at home. They were asked to register how many

exercises they performed and if they experienced any difficulties. The second group, the app-group, practiced at home using an application, which included instructional videos for the patients to re-watch as many times as needed. Repeated instructions were given through the app and gamification was used to make the difficult task more pleasant. The patients registered via the app how many exercise repetitions they did and if any difficulties arose. More detailed information on the development and content of the application was published previously[201]. In both groups, the first session was completed under supervision of the SLP and every week an appointment was scheduled to recalculate the target value. The third group, the therapist-group, was given face-to-face therapy for five days/week. Each session, clear and repeated instructions were given and patients received continuous feedback on their performance. The SLP kept a logbook and registered how many exercises the patients did.

Primary outcome: swallowing function

The primary outcome of this RCT was the swallowing function, based on the Mann Assessment of Swallowing Ability – Cancer (MASA-C)[155]. The MASA-C is a reliable and valid swallowing assessment tool that is sensitive to detect differences in swallowing performance in HNC patients with and without dysphagia. In this study, it was conducted with three different bolus types: 10 ml of thin liquid (IDDSI [international dysphagia diet standardization initiative[202]] 0), 10 ml of thickened water (IDDSI 3) and one bite of a cake (IDDSI 6). The maximum score is 200, referring to normal swallowing, scores beneath 186 refer to dysphagia. When patients refused to eat the thickened water or cake due to any reason, and thus making it impossible to correctly evaluate their swallowing act, the lowest score on this subtest of items (swallowing act) was given.

Secondary outcome: muscle strength

Tongue and suprahyoid muscles strength were secondary outcome measures. The IOPI Pro, model 3.1 (IOPI Medical LLC, Woodinville, WA, USA) was used to measure maximal anterior and posterior tongue strength and tongue strength during a dry swallow. The location to measure anterior maximal isometric pressure (MIP_a) was determined by placing the proximal end of the bulb immediately behind the upper teeth at the midline of the palate. The location for the posterior MIP (MIP_p) was defined by placing the main part of the bulb at the level of the transition from the hard to the soft palate. Patients are asked to push the bulb as hard as possible against the palate while the exerted pressure in kilopascal (kPa) is shown on the LCD screen of the IOPI. The highest value of three trials was considered the MIP. To obtain the tongue strength during swallowing (Pswal), participants were asked to execute an effortful saliva swallow with the tongue bulb in the

same positions as MIP_a and MIP_p for respectively $Pswal_a$ and $Pswal_p$. Again, the highest value of three trials was considered to be the Pswal and used for analysis. The maximal strength of the suprahyoid muscles (MIP_{shm}) was measured by means of a dynamometer (Microfet™, Biometrics, Almere, The Netherlands)[151]. Participants were asked to place their chin on the chin bar, keep their mouth and teeth closed and press their chin down as hard as possible while the patients' head is stabilized by a fixed belt. The exerted pressure is shown in Newton (N) and the highest value of three trials is considered the maximal isometric chin-tuck strength.

The evaluation of swallowing function based on MASA-C as well as the measurements of muscle strength were done by the SLP at baseline, every week during the four weeks of PSE, at the end of RT/CRT and 1 and 3 months after RT/CRT. When a patient was treated with induction chemotherapy, the baseline measurement was performed immediately before the start of radiotherapy.

The full protocol has been described and published previously[197].

Overall adherence

As an additional analysis, the effect of overall adherence (OA), irrespective of service-delivery mode, on swallowing function and muscle strength was also investigated. Participant's OA was computed by summing all repetitions during the 4 training weeks, dividing this by the maximum number of repetitions (i.e. 2700 reps) and multiplying it by 100. Based on their OA, the PRESTO-participants were regrouped in 4 OA levels: OA75+, performing ≥75% of the prescribed exercises, i.e. high practice, OA50-75, performing 50-75% of the prescribed repetitions, i.e. moderate practice, OA25-50, performing 25-50% of the exercises, i.e. low practice, and OA25-, performing <25% of the exercises, i.e. negligible practice[11].

Statistical analysis

Sample size calculation.

The sample size calculation was performed using GLIMMPSE online software for power calculation in linear mixed effects models. The targeted total sample size, taking into account 20% dropouts, was 150 (n= 50/group, depending on minimization). More details on sample size calculation are presented in the protocol publication[197].

Data analysis.

Descriptive statistics were used to summarize patient characteristics per service-delivery mode group and per OA level.

For MASA-C, a linear mixed effects model with group, time and group by time interaction as fixed effects was used. In addition, the same model was corrected for OA level as fixed effect. The interaction effect of group by time was removed out of the model when no significant results were observed. The final model included group, time, adherence level and adherence level by time interaction as fixed effects. In case significant time effects were found, post-hoc pairwise testing with Bonferroni-Holm correction for multiple testing was performed for the results between baseline and the end of RT/CRT, baseline and three months post RT/CRT and between end of RT/CRT and three months post RT/CRT. When significant group/OA level effects were found, post-hoc pairwise testing with Bonferroni-Holm correction for multiple testing was performed for the results at baseline, end of RT/CRT and three months post RT/CRT.

For muscle strength, the percentage of strength gain or loss compared to baseline was systematically calculated. A linear mixed effects model with group, time and group by time interaction as fixed effects was used. Again, in addition, the model was corrected for OA level as fixed effect and when no significant group by time interaction effects were found, this was removed from the model. The final model included group, time, adherence level and adherence level by time interaction as fixed effects. In case significant time effects were found, post-hoc pairwise testing with Bonferroni-Holm correction for multiple testing was performed for the results between baseline and week 1 of RT/CRT, baseline and the end of RT/CRT, baseline and three months post RT/CRT and between end of RT/CRT and three months post RT/CRT. When significant group/OA level effects were found, post-hoc pairwise testing with Bonferroni-Holm correction for multiple testing was performed for the results at the end of RT/CRT and 3 months post RT/CRT.

We hypothesized improved swallowing function and muscle strength in (1) patients in the therapist group when comparing the 3 service-delivery modes and (2) patients in the OA75+ group compared to the other OA levels.

Data was assumed to be missing at random. In the linear mixed effects model all information on the available time points is incorporated. Since for MASA-C IDDSI 0 only 11.6% of data was missing, we did not perform a sensitivity analysis using multiple imputation, as described in our statistical analysis plan.

Patients who dropped out during the PSE weeks due to medical circumstances or patients who lost (parts of) there logbook, were not included in the OA analyses. The number of exercises performed during that/those specific week(s) must be considered as missing instead of zero. These missing values made it impossible to assign these participants to an OA level.

Since >20% of the patients had missing values for adherence, a sensitivity analysis was performed. In this sensitivity analysis, patients with missing data were assigned into an OA level based on the available adherence data and the knowledge that the adherence rates won't increase over time during RT/CRT [10; 78; 201].

A *p* value of <0.05 was considered statistically significant. All analyses were conducted using SPSS Statistics version 27 (IBM, Chicago, IL, USA).

Results

Participants

One hundred and fifty patients were recruited for this study. Two patients were excluded from this cohort. The first patient was excluded due to a change in the study protocol, namely by adding the exclusion criteria of having a tracheotomy influencing the execution of the CTAR exercise. The second patient was hospitalized due to an acute life-threatening disease before baseline measures were conducted and could therefore not participate in the study. Finally, a cohort of 148 patients was maintained for further analysis. Patient, disease and treatment characteristics of the whole cohort and separate service-delivery mode groups can be found in table 1. Figure 1 shows a flowchart of the patients' inclusion, dropouts and follow-up.

There were 26 dropouts before or during PSE (i.e. before or during the first four weeks of RT/CRT), exercise data on tablets was not correctly saved in four patients and another three patients lost their exercise logbook. This resulted in these 33 patients not being able to be assigned into an OA level, leading to the inclusion of 115/148 (78%) patients into these different categories.

Since the number of patients per OA level was too small to allow for comparison between the 4 groups, the choice was made to combine groups: OA75+ vs. OA75- (consisting of OA25-, OA25-50 and OA50-75). Additionally, reducing the number of OA levels as described, resulted in a better model fit and Akaike's Information Criteria (AIC) compared to the models for the four separate OA levels.

Table 2 shows the number of patients per OA level by service-delivery mode and table 3 shows patient, disease and treatment characteristics of the OA75+ and OA75-.

Table 1: patient, disease and treatment characteristics

	Total cohort n = 148 (%)	Paper group n = 49 (%)	App group n = 49 (%)	Therapist group n = 50 (%)
Age	M = 63 SD = 8.5 Range = 41-86	M = 63 SD = 9.5 Range = 41-86	M = 63 SD = 7.9 Range = 41-83	M = 63 SD = 8.2 Range = 45-80
Gender				
Female	35 (24)	14 (29)	11 (22)	10 (20)
Male	113 (76)	35 (71)	38 (78)	40 (80)
T classification				
1-2	75 (51)	25 (51)	22 (45)	28 (56)
3-4	73 (49)	24 (49)	27 (55)	22 (44)
N classification				
0	7 (5)	3 (6)	3 (6)	1 (2)
1	23 (15)	7 (14)	7 (14)	9 (18)
2-3	118 (80)	39 (80)	39 (80)	40 (80)
Treatment				
RT	21 (14)	6 (12)	8 (16)	7 (14)
CRT	102 (69)	37 (76)	32 (65)	33 (66)
CRT with induction CT	25 (17)	6 (12)	9 (19)	10 (20)
HPV status				
Positive	76 (51)	24 (49)	23 (47)	29 (58)
Negative	72 (49)	25 (51)	26 (53)	21 (42)
Dysphagia at baseline, based on MASA-C				
No				
Yes	119 (80)	39 (80)	38 (78)	42 (84)
	29 (20)	10 (20)	11 (22)	8 (16)
Treating center				
UZ Antwerpen/Iridium Network	32 (22)	11 (22)	10 (20)	11 (22)
UZ Gent	57 (38)	19 (39)	19 (39)	19 (38)
UZ Leuven	41 (28)	12 (25)	14 (29)	15 (30)
AZ Sint-Jan Brugge	18 (12)	7 (14)	6 (12)	5 (10)

M mean, SD standard deviation, RT radiotherapy, CRT chemoradiotherapy, CT chemotherapy, MASA-C Mann Assessment of Swallowing Ability – Cancer

Table 2: number of patients per OA level by service-delivery mode

	Paper-group (n = 36)	App-group (n = 34)	Therapist-group (n = 45)	Total (n = 115)
OA25-	3 (8.3%)	10 (29.4%)	0 (0%)	13
OA25-50	4 (11.1%)	4 (11.8%)	1 (2.2%)	9
OA50-75	8 (22.2%)	12 (35.3%)	11 (24.4%)	31
OA75+	21 (58.3%)	8 (23.5%)	33 (73.3%)	62
OA75-	15 (41.7%)	26 (76.5%)	12 (26.7%)	53
OA75+	21 (58.3%)	8 (23.5%)	33 (73.3%)	62

Table 3: patient, disease and treatment characteristics of the OA75+ and OA75- group

	OA75+ n = 62	OA75- n = 53
Age	M = 64 SD = 8.6 Range = 41-80	M = 62 SD = 8.0 Range = 50-83
Gender		
Female	9 (15)	17 (32)
Male	53 (85)	36 (68)
T classification		
1-2	33 (53)	27 (51)
3-4	29 (47)	26 (49)
N classification		
0	1 (2)	4 (8)
1	12 (19)	5 (9)
2-3	49 (79)	44 (83)
Treatment		
RT	10 (16)	6 (11)
CRT	40 (65)	40 (76)
CRT with induction CT	12 (19)	7 (13)
HPV status		
Positive	35 (56)	27 (51)
Negative	27 (44)	26 (49)
Dysphagia at baseline, based on MASA-C		
No	49 (79)	43 (81)
Yes	13 (21)	10 (19)
Treating center		
UZ Antwerpen/Iridium Netwerk	11 (18)	11 (21)
UZ Gent	26 (42)	23 (43)
UZ Leuven	16 (26)	12 (23)
AZ Sint-Jan Brugge	9 (14)	7 (13)

M mean, SD standard deviation, RT radiotherapy, CRT chemoradiotherapy, CT chemotherapy, MASA-C Mann Assessment of Swallowing Ability

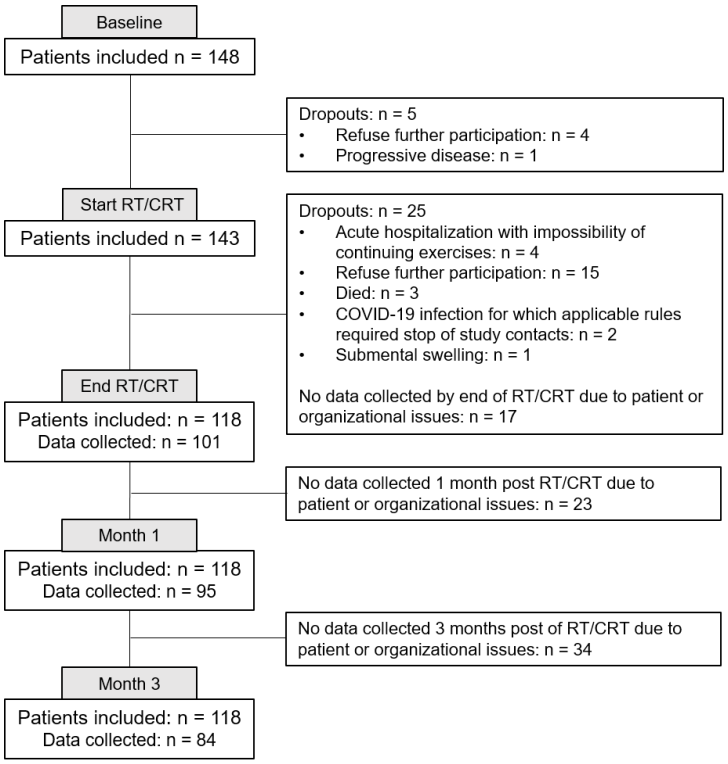

Figure 1: flowchart patient inclusion, dropouts and follow-up

Swallowing function based on MASA-C

Figure 2 shows the evolution of MASA-C IDDSI 0, 3 and 6 scores over time per adherence group.

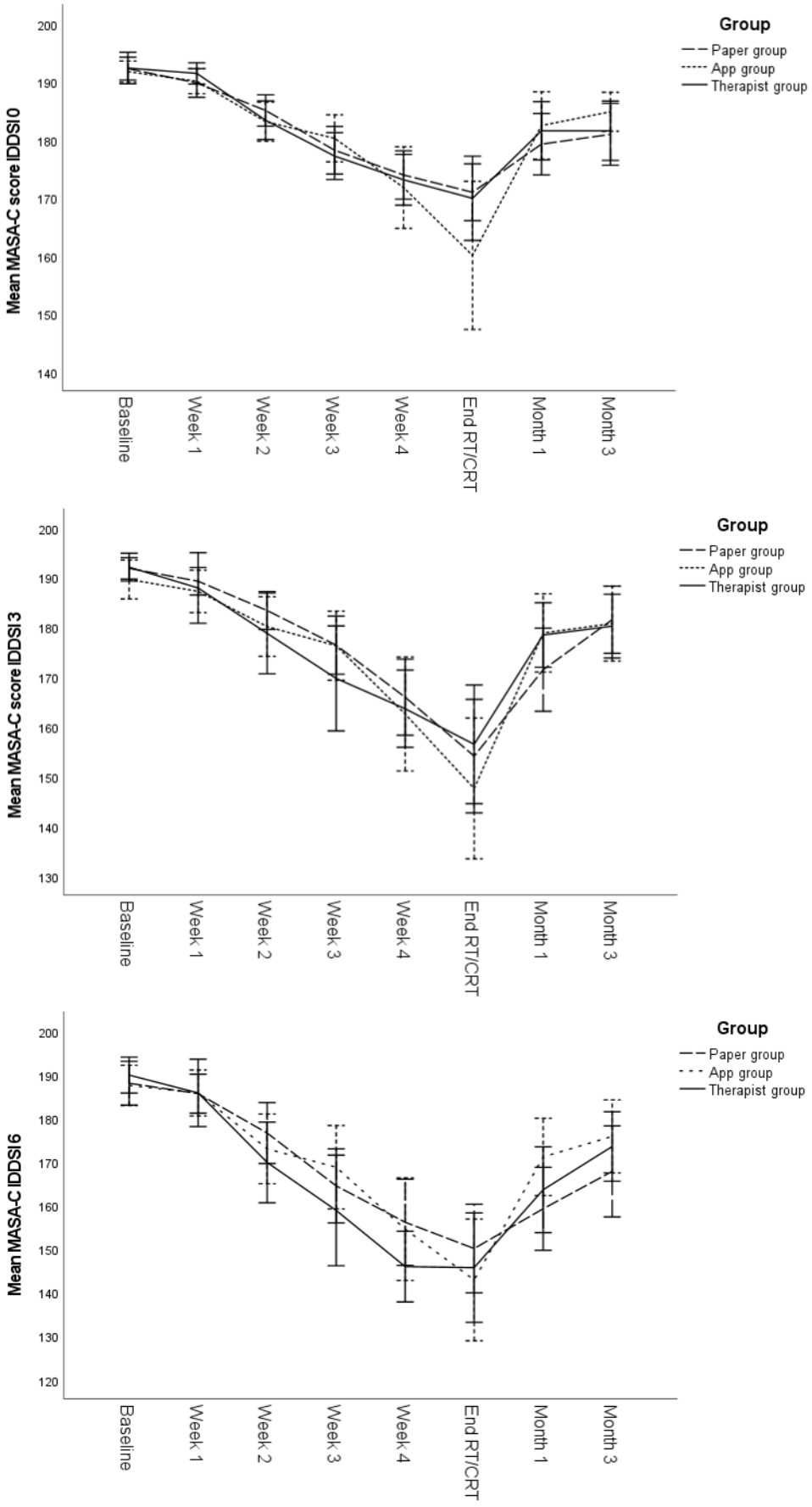

Figure 2: evolution of MASA-C IDDSI 0, 3 and 6 scores over time, error bars 95% CI

Linear mixed effects model with time, group and group by time interaction shows a significant interaction-effect on IDDSI 0 ($F_{14\text{-}695} = 1.859$, $p = .028$). When correcting this model for adherence, with adherence as a categorical variable (OA75+ vs. OA75-), this interaction-effect is no longer observed, from which we infer that adherence, rather than group, affects swallowing function. Since group by time interaction is no longer significant, this variable was removed in our model.

In the linear mixed effects model with group, time, adherence and adherence by time interaction, significant time effects are observed for IDDSI 0 ($F_{7\text{-}637} = 88.187$, $p < .001$) , IDDSI 3 (F[7-584] = 56.368, $p < .001$) and IDDSI 6 ($F_{7\text{-}567} = 71.811$, $p < .001$), significant effects of adherence are also observed for IDDSI 0 ($F_{1\text{-}112} = 5.395$, $p = .022$), IDDSI 3 ($F_{1\text{-}112} = 7.566$, $p = .007$) and IDDSI 6 ($F_{1\text{-}110} = 4.215$, $p = .042$). Adherence by time interaction is significant for IDDSI 0 ($F_{7\text{-}637} = 2.171$, $p = .035$) and IDDSI 3 ($F_{7\text{-}584} = 2.875$, $p = .006$), however not for IDDSI 6 ($F_{7\text{-}567} = 1.237$, $p = .280$).

Post hoc analyses with Bonferroni-Holm correction show significant decreases in MASA-C scores between baseline and the end of RT/CRT and between baseline and three months post RT/CRT. Significant increases between the end of RT/CRT and three months post RT/CRT were observed. These results apply for all three consistencies and both groups. Results are shown in table 4.

Table 4: results of post hoc tests with Bonferroni-Holm correction for the evolution of MASA-C scores through time, depending on group

		MASA-C IDDSI 0		**MASA-C IDDSI 3**		**MASA-C IDDSI 6**	
Difference in time-point							
OA75+		Estimate* (95%CI)	*p*	Estimate (95%CI)	*p*	Estimate (95%CI)	*p*
Baseline	**End RT/CRT**	-21.11 [-24.33- -17.89]	*<.001*	-32.19 [-38.49- -25.89]	*<.001*	-40.81 [-47.70- -33.91]	*<.001*
	3 months	-11.74 [-15.16- -8.33]	*<.001*	-11.32 [-17.78- -4.87]	*<.001*	-17.04 [-24.05- -10.04]	*<.001*
End RT/CRT	**3 months**	9.37 [5.78-12.95]	*<.001*	20.87 [14.01-27.73]	*<.001*	23.76 [16.24-31.29]	*<.001*
OA75-		**Estimate (95%CI)**	***p***	**Estimate (95%CI)**	***p***	**Estimate (95%CI)**	***p***
Baseline	**End RT/CRT**	-28.41 [-32.17- -24.65]	*<.001*	-46.27 [-53.44- -39.09]	*<.001*	-46.24 [-53.90- -38.58]	*<.001*
	3 months	-10.52 [-14.36- -6.67]	*<.001*	-14.01 [-21.09- -6.39]	*<.001*	-22.94 [-30.60- -15.28]	*<.001*
End RT/CRT	**3 months**	17.89 [13.60-22.19]	*<.001*	32.26 [24.29-40.23]	*<.001*	23.30 [14.66-31.95]	*<.001*

*Negative estimates indicate decreases

Post hoc analyses with Bonferroni-Holm correction show significant differences in MASA-C scores between adherence groups (OA75+ and OA75-) for IDDSI 0 and IDDSI 3 at the end of RT/CRT ($p < .001$). No significant differences were found for IDDSI 6. Figure 3 shows MASA-C scores through time by OA75 level with significant post hoc results indicated by means of a rectangle.

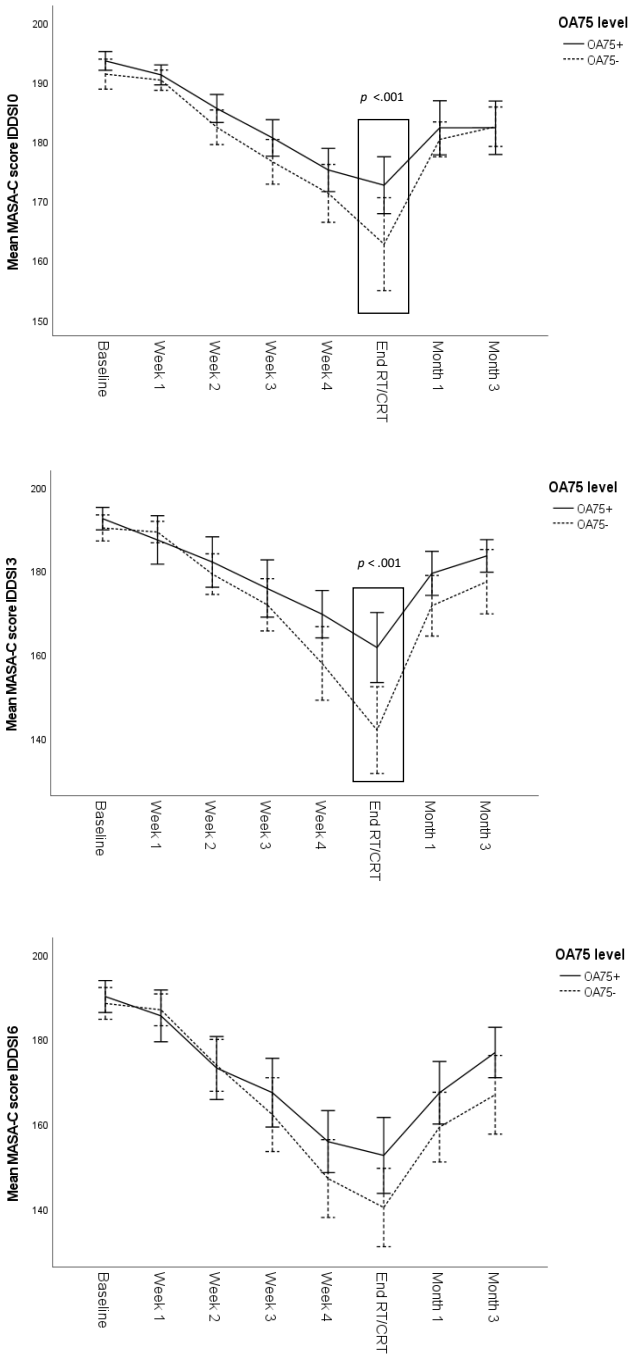

Figure 3: MASA-C scores through time by OA75 level, error bars: 95% CI

Muscle strength

Linear mixed effects model with time, group and group by time interaction shows a significant interaction-effect on percentage of MIP_{shm} gain ($F_{14\text{-}627} = 5.258$, $p = .038$). When correcting this model for adherence, with adherence as an ordinal variable (OA75+ vs. OA75-), this interaction-effect is no longer observed, from which we infer that adherence, rather than

group, affects muscle strength. Since group by time interaction is no longer significant, this variable was removed in our model.

In the linear mixed effects model with group, time, adherence and adherence by time interaction, significant time effects are observed for MIP_a ($F_{7\text{-}604} = 4.794$, $p < .001$), MIP_p ($F_{7\text{-}575} = 3.487$, $p = .001$), $Pswal_a$ ($F_{7\text{-}569} = 2.858$, $p = .006$), $Pswal_p$ ($F_{7\text{-}528} = 5.603$, $p < .001$) and MIP_{shm} ($F_{7\text{-}575} = 4.362$, $p < .001$) with an increase in percentage of muscle strength gain for all measurements.

Significant effects of adherence are observed for MIP_a ($F_{1\text{-}113} = 10.909$, $p = .001$) and MIP_p ($F_{1\text{-}112} = 8.992$, $p = .003$) and adherence by time interaction is significant for MIP_a ($F_{7\text{-}603} = 5.509$, $p < .001$) and MIP_p ($F_{7\text{-}575} = 2.221$, $p = .009$).

Post hoc analyses with Bonferroni-Holm correction for time are shown in table 5; figure 4 shows the percentages of muscle strength gain through time by OA75 levels with significant post hoc results.

Table 5: results of post hoc tests with Bonferroni-Holm correction for the evolution of muscle strength gain through time, depending on group

		MIPa		MIPp		Pswala		Pswalp		MIPshm	
Difference in time-point											
OA75+		Estimate (95%CI)	*p*	Estimate (95%CI)	*p*	Estimate (95%CI)	*p*	Estimate (95%CI)	*p*	Estimate (95%CI)	*p*
Baseline	**Week 1**	11.15 [5.95-16.34]	*<.001*	8.04 [1.60-14.47]	.087	22.34 [7.16-37.52]	*.028*	22.49 [6.13-38.86]	*.029*	8.44 [2.06-14.82]	.067
	End RT/ CRT	10.08 [4.21-15.94]	*<.001*	5.05 [-2.40-12.49]	.734	19.35 [2.10-36.61]	.168	30.75 [10.78-50.72]	*.013*	1.52 [-5.93-8.97]	1
	3 months	20.75 [14.84-26.67]	*<.001*	19.69 [12.31-27.08]	*<.001*	33.36 [15.96-50.76]	*.001*	42.08 [23.23-60.92]	*<.001*	9.04 [1.71-16.36]	.094
End RT/CRT	**3 months**	10.68 [4.22-17.14]	*.006*	14.65 [6.44-22.85]	*.003*	14.01 [-5.12-33 13]	.532	11.33 [-10.64-33.30]	.623	7.52 [-.70-15.73]	.364
OA75-		**MIPa**		**MIPp**		**Pswala**		**Pswalp**		**MIPshm**	
Difference in time-point											
		Estimate (95%CI)	*p*	Estimate (95%CI)	*p*	Estimate (95%CI)	*p*	Estimate (95%CI)	*p*	Estimate (95%CI)	*p*
Baseline	**Week 1**	7.23 [1.46-13.01]	.057	5.93 [-1.47-13.34]	.581	13.34 [-4.19-30.87]	*.532*	32.92 [13.70-52.14]	*.005*	13.44 [6.21-20.66]	.002
	End RT/ CRT	-1.52 [-9.27-6.22]	1	-4.25 [-14.72-6.22]	.850	-.12 [-24.82-24.58]	.992	-1.52 [-31.21-28.17]	.920	-2.34 [-12.98-8.30]	1
	3 months	1.06 [-6.00-8.12]	1	2.42 [-6.50-11.33]	.850	21.13 [-.23-42.49]	.262	43.63 [19.85-67.42]	*.002*	-1.30 [-10.14-7.55]	1
End RT/CRT	**3 months**	2.56 [-6.17-11.34]	1	6.67 [-5.04-18.38]	.792	21.25 [-6.49-48.99]	.532	45.15 [12.16-78.15]	*.029*	1.05 [-10.70-12.79]	1

MIP_a Anterior Maximal Isometric Pressure, MIP_p Posterior Maximal Isometric Pressure, $Pswal_a$ Anterior tongue strength during swallowing, $Pswal_p$ Posterior tongue strength during swallowing, MIP_{shm} maximal strength of the suprahyoid muscles

*Negative estimates indicate decreases

Post hoc analyses with Bonferroni-Holm correction show significant differences in percentage of MIP_a gain between adherence groups (OA75+ and OA75-) at the end of RT/CRT ($p = .029$) and at three months post RT/CRT ($p < .001$). For MIP_p,

significant differences between adherence groups were observed at three months post RT/CRT (p = .007). Figure 4 shows these significant post hoc results by means of a rectangle.

The sensitivity analysis for the missing adherence levels confirmed our results.

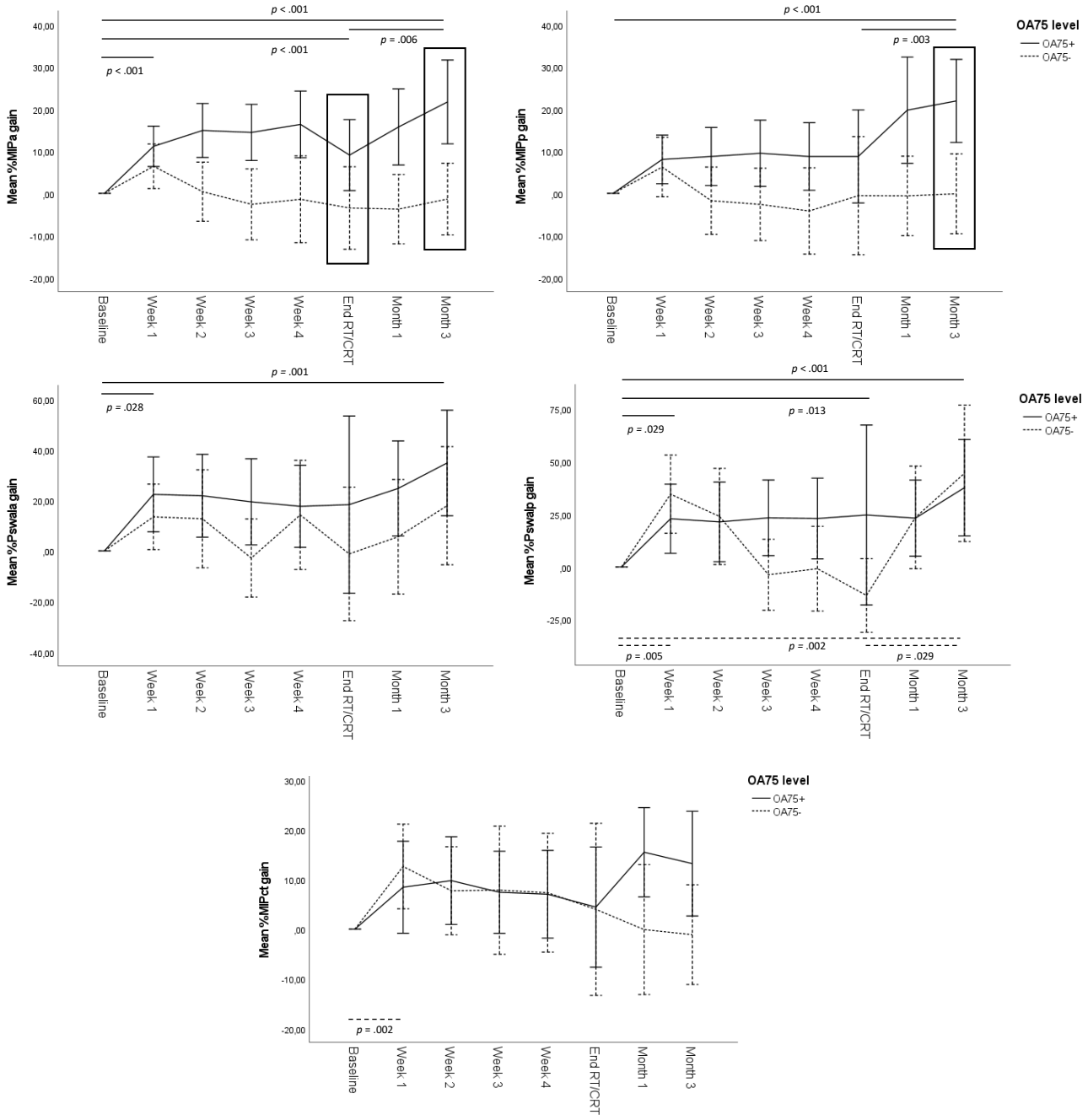

Figure 4: percentages muscle strength gain through time by OA75 levels with significant post hoc results after Bonferroni-Holm correction, error bars: 95% CI.

Discussion

This multicenter randomized controlled trial investigated the effect of service-delivery mode (paper-, app- and therapist-supported) of PSE in HNC patients on swallowing function and muscle strength during and after RT/CRT treatment. No significant effects of service-delivery mode were found. This is consistent with the study by Wall et al., in which no significant effects of service-delivery mode were observed for all swallowing and nutrition-related outcomes[203]. Additionally in our study, participants were divided according to their overall adherence level, independently of their assigned service-delivery mode. Results showed significantly better swallowing function and muscle strength gain in patients practicing ≥75% (OA75+) of the prescribed exercises compared to patients practicing <75% (OA75-).

To our knowledge, there are no other studies that investigated the effect of PSE on instrumentally measured muscle strength during and after RT/CRT. Carroll and colleagues suggested, however, that in patients who performed PSE during RT/CRT, tongue base muscle mass may be better preserved than in patients who did not, due to less atrophy[63]. Furthermore, the randomized controlled trial of Carnaby-Mann et al. observed less structural deterioration in muscle composition in patients performing PSE[8]. Both findings are in line with the overall positive effect of PSE on muscle strength in the PRESTO-trial.

It is however remarkable that our patients were able to increase their tongue and suprahyoid muscles strength, despite the acute toxicities. To our knowledge, this is the first study demonstrating an actual and significant increase in muscle strength during RT/CRT by means of strengthening exercises. Hereby, it is important to notice that the degree of adherence matters: tongue strength increases significantly in the OA75+ group compared to the OA75- group, where the strength is more likely to remain stable or decrease during RT/CRT. A high intensity of exercise, translated in PRESTO as five days a week combined with a high number of repetitions per session, and the use of devices that provide biofeedback is key to show positive effects on muscle strength. The importance of the principles of motor learning and strength training is clearly illustrated here[150].

Despite the shown reliability of all strength measures used[151; 204], remarkable increases were demonstrated for all muscle strength measures between baseline and week 1 of RT/CRT. To improve the precision of the assessment and to exclude learning curve effects, both Adams et al. and Kraaijenga et al. suggest the use of a familiarization session before

baseline measurements[151; 204]. Current study didn't use a familiarization session before the effective strength measurements. Although, since the large increases in strength, familiarization with the devices cannot be the only explanation of this remarkable phenomenon. A probable explanation for this rapid and significant improvement may be found in the physiology of strength training. During the initial phase of strength training, adaptations occur in the way the nervous system activates the muscles. When an individual starts performing strength training, a learning process occurs that allows for the correct recruitment and firing rate of the relevant motor units, as well as de-activation of antagonistic muscles. This also occurs in tongue muscles: learning improves performance and induces plasticity in corticomotor pathways[205]. Changes in the coordination of motor unit recruitment occur as well as changes in the learning how to improve this recruitment and thus improve muscle activation during a specific strength task. In this way, the learning effect causes an increase in strength, without necessarily achieving an increase in muscle mass. In a later phase of strength training, structural changes in the muscles themselves will occur: growth in muscle size and changes in muscle composition follow the improvement in strength[150; 206; 207].

After week 1, the OA75+ group was able to maintain the strength improvement during and until the end of RT/CRT. This plateau effect was not present in the OA75- group. Van den Steen et al. evaluated the feasibility of tongue strength measures during RT/CRT in HNC patients, not performing PSE. Consistent with our results in the OA75- group, a decrease in MIP_a and MIP_p was observed[58].

After RT/CRT, no detraining effects were found for any of the five strength measurements. Moreover, between the end of RT/CRT and three months post RT/CRT, a significant increase was found for both anterior and posterior tongue strength in the OA75+ group. Possible explanations for this continuous increase could be the decrease in acute toxicity (mucositis, pain) or an improvement in oral intake. However, since the increase in tongue strength after RT/CRT was not found in the OA75- group, it can be suggested that an effective improvement in muscle strength in the OA75+ group occurred.

Despite the increase in muscle strength and its transference to swallowing strength, a significant decrease in swallowing function during RT/CRT was still observed. Between baseline and the end of RT/CRT, a strong deterioration was seen, followed by a recovery, however not to baseline levels. These results are consistent with other studies in which intensive preventive swallowing therapy is applied[8-10; 67; 203]. van der Molen et al., for example, described a significant decrease

in oral intake during RT/CRT in patients performing PSE. However, previous research also showed that patients performing PSE showed beneficial effects on post-treatment swallowing function compared to control groups, not performing PSE[1; 8; 63]. The current study did not include a control group, but the results show that higher adherence to PSE results in less deterioration of the swallowing function. This is in line with the results of previous research[66; 193]. Duarte et al.[66], for example, evaluated patients receiving PSE during RT/CRT and showed that swallowing function was better preserved at the end of RT/CRT in patients adherent to PSE.

Based on previous analyses on PRESTO results, we know that there are significant differences in adherence among the three service-delivery modes: high adherence rates were found in the therapist group, followed by medium to high rates in the paper group and low to medium rates in the app group[201]. We observed that the differences in swallowing function and muscle strength between groups were mainly due to the differences in adherence.

Our study is however not without limitations. A rather short longitudinal follow-up period prevents us from making any conclusions on the long-term. Since chronic radiation-associated dysphagia is common and highly impacting on health-related QoL in HNC survivors, this prospective study should ideally be conducted up to a year or even several years after RT/CRT. Examining the effects of PSE on swallowing function >1 year and up to five to ten years after RT/CRT, is subject for future research. The lack of data concerning muscle composition prevented us from making statements about actual muscle changes. Although it is an assumption, we were unable to conclude with certainty that muscle hypertrophy occurred. Moreover, no objective measures, e.g. flexible endoscopic swallowing examination or videofluoroscopy, were conducted. It is possible that when PSE is performed, less residue occurs or that specific swallowing characteristics, such as epiglottic inversion or tongue base retraction, are better preserved. It would also be interesting to compare the more detailed OA levels based on Wall et al. (≥75%, 50-75%, 25-50%, ≤25%)[11], however our groups were too small and the associated statistical models too weak. Lastly, a familiarization session with the devices is something to take into account in future studies in order to increase the accuracy of the measurements.

Further steps within our PRESTO trial are to investigate the influencing factors for (non)adherence. Analysis of patient-related factors, e.g. personality, general condition and fatigue, will be done in follow-up studies.

In conclusion, our randomized controlled trial found no effects of service-delivery mode of PSE on swallowing function or muscle strength. However, significant effects were found with respect to the patients' overall adherence level. Patients practicing more than 75% of the prescribed exercises showed significant better results in swallowing function and muscle strength. It can be concluded that a high level of exercise repetitions is essential to achieve benefits of PSE during RT/CRT.

Chapter 9

Summary, discussion and general conclusion

Chapter 9: Summary, discussion and general conclusion

The outline of this general discussion will be as follows: (1) main findings and overall discussion points, (2) limitations of this thesis and future perspectives, (3) implications for clinical practice in speech and language therapy and (4) general conclusion. Finally, a SWOT analysis closes the discussion.

Main findings and discussion

This doctoral thesis aims to improve the quality of healthcare in head and neck cancer (HNC) patients treated with radiotherapy (RT) or chemoradiotherapy (CRT). Dysphagia as a side-effect of the intensive RT/CRT treatment is highly prevalent and impacts on quality of life (QoL) in both patients undergoing treatment and HNC survivors [2; 4; 7; 42]. Interest and knowledge concerning the use of prophylactic swallowing exercises (PSE) to prevent this life-threatening side-effect has been growing in the last decade [8; 66; 67]. However, adherence to these exercises is low, and unfortunately little is known about how to increase adherence rates [11; 76; 79]. The primary aim of this PhD project was therefore to develop an optimized, patient-tailored and evidence-based PSE program, which would increase adherence and could easily be implemented in daily clinical practice. Different research questions needed to be answered.

Increasing insight

Dysphagia during and immediately after RT/CRT is common and widely reported. However, despite the large number of studies concerning acute dysphagia, a relatively small number of studies reported on very late and chronic dysphagia, up to years after RT/CRT treatment. Nevertheless, it is important to know the prevalence, especially as the treatment of late dysphagia after HNC radiotherapy is strenuous. This problem was translated into **research question 1** (chapter 4), describing a retrospective trial concerning the evolution of late toxicity, including radiation-associated dysphagia (RAD), until 8 years after RT/CRT treatment in a single University Hospital setting. Although the severity of dysphagia decreases up to 5 years after follow-up, a large proportion of HNC survivors continue to experience RAD years after treatment. Almost half (48%) of the patients followed ≥8 years exhibit persistent dysphagia, with most patients having difficulties in eating solid foods. However, almost one-third of these patients also experience difficulties with soft foods or can only take liquid foods. These findings are concordant with previous research indicating a high prevalence of RAD years after RT/CRT [3; 57; 111]. The same trial also demonstrated a high prevalence of xerostomia 3 to 8 years after RT/CRT, with more than 60% suffering from this

side-effect after 8 years. Neck fibrosis showed an increase in severity during the follow-up period until 8 years. These two side-effects also contribute to the presence and persistence of RAD.

Developing an evidence-based PSE protocol which increases adherence

Based on this current knowledge concerning the development and persistence of dysphagia in HNC patients as well as the added value of PSE, it can be stated that developing and implementing a PSE program for HNC patients receiving RT/CRT treatment is strongly recommended. In addition, augmenting the program with adherence-improving measures is paramount in order to maximize possible effects. Based on the available literature to date, PSE programs incorporating adherence-improving measures are scarce. The **second research question** (chapter 5) was therefore to develop an optimized, evidence-based and adherence-improving PSE program that can easily be implemented in clinical practice.

Content of prophylactic swallowing therapy.

Studies reporting on PSE differ in treatment content, timing and intensity, including exercise frequency and the duration of the program. Both strengthening exercises and functional training have already been reported. For example, van der Molen et al. used both range of motion and strengthening exercises and participants in the study of Kotz et al. performed functional exercises, namely five different targeted swallowing exercises [9; 67].

A purely instrumental way of rehabilitation was used in our design, given the multitude of clinical and scientific evidence, the expertise within our research group and the importance of visual and tactile feedback for motor learning [153; 208]. Different principles of exercise, allowing efficient and effective rehabilitation, were taken into consideration in building our design [150]. Specificity, related to how closely the task corresponds with the target outcome, was a first principle taken into account. It implies that the greatest gain in training is achieved when the task resembles the end goal as much as possible. The goal of the PSE was to strengthen the swallowing musculature during RT/CRT and to build a reserve, since strength generally decreases during RT/CRT [58]. Van den Steen et al. showed that healthy participants performing solely anterior tongue strengthening exercises (TSE) demonstrated higher anterior tongue strength compared to patients performing posterior TSE, while no differences in posterior tongue strength were observed [153]. This, in combination with the more difficult placement posteriorly, led to the decision of only practicing anteriorly. The goal of the exercises, i.e. to build strength, was based on the second important principle of exercise: transference. It refers to the transfer of strength

building to improved functional tasks; isolated strength training with progressive resistance leads to improved performance in functional activities. This might explain how non-specific swallowing tasks can improve swallowing function. Strength training may impact the abilities during functional tasks by building a foundation of force-producing capacity, improving functional reserve and priming the neuromuscular system for activity [150; 209; 210]. Buchner and de Lateur stated that improvements in functional tasks after isolated strength exercises would be the result of an increased physiological reserve (i.e. the ratio of potentially generated strength to the effort required to perform a task) [150; 211]. Therefore, the goal of the exercises used in our study design was also to build up this physiological reserve. The third principle of exercise is intensity and encompasses the amount of load, volume and duration of the exercise stimulus. This principle is based on the rationale that an exercise task must exceed usual activity levels and should be performed long enough (both within a session and over time) to trigger a change in the system [150]. The load on the muscles must be gradually adjusted during the exercise program to maximize gains. The current design uses an initial resistive load of 60-80% of the 1-repetition maximum (1RM), depending on the exercise, and is adjusted weekly, based on the new 1RM (progressive overload). For the chin tuck against resistance (CTAR) exercises, we used a 1RM of 60-70% according to Kraaijenga et al. [150; 151]. The choice to practice at 80% of the 1RM during the TSE exercises, was based on Van den Steen et al [212]. Next to the amount of load, the intensity can also be manipulated by adjusting the frequency of practicing and the number of exercise repetitions within a session. Different studies report an exercise frequency of seven days a week, with a repetition of exercises several times a day; some studies use a design that required patients to exercise until the end of RT/CRT and others practiced until weeks after treatment [9; 67; 78; 192; 213]. Since one group was therapist-dependent in our study, the exercise frequency was limited to five days a week. A rest period during the weekend was also assumed to make it easier for the patient to maintain the exercises and thus to increase feasibility. Building on this, it was also decided to limit the PSE to the first four weeks of RT/CRT (see below). A high level of repetitions, 120 for TSE and 150 for CTAR, was chosen since the principle of intensity also refers to the volume of exercises, which can also be manipulated by adjusting the number of repetitions performed. Since Van den Steen et al. already published the effects of TSE in several studies, both in healthy participants and HNC patients, using 120 repetitions per session each time and showing positive effects, we also chose this approach [75; 153; 212]. The protocol for the CTAR exercises was based on Kraaijenga et al. [151]. However, we chose to extend the duration (and repetitions), comparable to the TSE.

Assessing side-effects of RT/CRT during the execution of the PSE program

During RT/CRT, different side-effects occur, which can have a possible impact on adherence to PSE and the effective outcomes of PSE. Oral mucositis (OM) is a common side-effect, causing pain and thus possibly influencing adherence to PSE. Therefore, assessing and evaluating the impact of OM on a patient's wellbeing and QoL is important. The use of patient-reported outcome measures (PROMs) in assisting clinicians to select the best treatment, enriching the understanding of patients' experiences and assessing the quality of health care, is growing [183; 184]. And since no Dutch-language versions of OM PROMs were available, the **third research question** (chapter 6) was to translate the English Oral Mucositis Weekly Questionnaire-Head and Neck Cancer (OMWQ-HN) and to validate this new Dutch version. Since validity and reliability have been demonstrated profoundly, this tool can be used in daily clinical practice and research. Furthermore, cut-off scores were determined to define differences in impact levels. This will facilitate the implementation of the OMWQ-HN in daily clinical practice and can be helpful in choosing and dosing analgesics during RT/CRT.

Increasing adherence to prophylactic swallowing therapy.

Although adherence is generally described as the extent to which a patient's behavior corresponds with recommendations from a health care provider, the content of the definition of this important therapeutic aspect varies widely in PSE literature [76; 79; 140; 192]. Adherence has been measured by the number of training sessions per day [192], by the degree of competence acquired [79], or by the percentage of patients continuing the exercises [76]. Due to these differences in definition, some caution is warranted when interpreting adherence results. However, regardless the definition used and taking into account the heterogeneity described, it is generally accepted that adherence to PSE is moderate to low [76; 79; 192]. The current design defined adherence as the percentage of exercise repetitions completed, based on Wall et al., since this study is the closest in design to our randomized controlled trial (RCT) [11]. Although we observed a significant decrease in adherence rates during the four training weeks, they were found to be higher than the reported rates by Wall et al. and in addition, the paper-group in our study achieved higher adherence rates than the rates found in the study of Messing et al. [10; 11].

Adherence may be influenced by different elements and reasons for nonadherence can be multifactorial (e.g. burdensome RT/CRT treatment, forgetfulness or absence of supervision) [9; 79; 80]. Therefore, it is important to address as many of these factors as possible when developing a prophylactic swallowing program. Furthermore, as research in physical

therapy has already highlighted the positive effect of a combination of continuous supervision, feedback on performance and a close relationship between patient and therapist [82], these strategies are also considered useful in PSE. According to the available literature, programs incorporating adherence-improving measures are scarce. Taking into account these different elements, the design of our protocol considered various general adherence-improving measures. The first general measure considered was the goal setting and the visual and tactile feedback patients experienced when reaching the target [214]. Next, the first exercise session was always supervised and weekly follow-up was provided. Clear instructions and information regarding the exercises were given during this first session, to familiarize the patients with the exercises. The weekly follow-up sessions had the same purpose, as well as ensuring that the patients would not (or would be less likely to) forget the exercises [214]. The third general measure included the limitation of the amount of exercises. Previous research in home-based physical therapy showed that limiting the prescribed exercises to only two different types, might lead to higher adherence rates [199]. The last general measure was, as mentioned above, the limitation of the duration of the exercise protocol and the rest period during the weekend. It was hypothesized that it would be easier for patients to continue practicing when they could rest during the weekends and they would know that the exercises only last for the first four weeks and not until the end of the RT/CRT period, which may seem hardly reachable at the start. Moreover, Van den Steen et al. concluded that the feasibility of tongue strength measures declined during RT/CRT weeks with significant decreases between pre-RT/CRT and week 4, 5 and 6 [75] and Virani et al. and Messing et al. showed progressively downward trends in adherence during RT/CRT and by the end a drop to very low levels [10; 78]. In addition, Jack et al. suggested that patients experiencing pain during exercises are less likely to adhere to the therapy program [81]. Since literature shows that acute toxicities, including oral mucositis causing pain, peak during week 5 of RT/CRT, we set the end at week 4 [10; 180]. Based on this previous research on feasibility and adherence, exercise duration was limited to the first four weeks of RT/CRT, with a weekly rest period during the weekend.

Next to those general measures to increase adherence, **research question 4** (chapter 7) investigated the effect of more specific measures on adherence, namely the service-delivery mode used. Patients were randomly divided into three groups, one practicing face-to-face with an SLP, and two practicing without supervision at home. The paper-supported group received a diary in which they registered their exercises, the app-supported group practiced with an app that used gamification with supporting images and videos. Results showed that therapist-supported PSE reached the highest

adherence rates throughout all training weeks, followed by the paper-supported group and the app-supported group. Based on the adherence levels defined by Wall et al., we concluded that the therapist-group achieved high adherence rates during week 1-3 and moderate during week 4 (73%, just below the 75% threshold) [11]. These findings emphasize the positive effects of continuous supervision, feedback on performance and a close relationship between the patient and therapist, as stated before, and demonstrated in both physical therapy and PSE studies [11; 82-85]. The paper group achieved high adherence rates during week 1 and 2 and moderate rates during week 3 to 4. Contrary to the expectation, the app group had the poorest adherence levels during all training weeks, ranging from 72 to 27% (week 1 and 4 respectively). Wall et al. found a trend towards higher adherence in the app-supported group compared to the home practice group and Starmer et al., working with an app as adjunct to standard therapy, also showed discrepancies with our results [11; 152]. This finding might be explained by the modest appreciation for the game element in addition to the impractical way of performing the exercises with the tablet combined to the devices. However, as stated above, overall adherence rates were found to be higher than the reported rates by Wall et al. and the paper-group achieved higher rates than the rates showed by Messing et al. [10; 11]. Based on this, we can conclude that our general measures increased adherence.

Using the results of the therapist and paper group, we can state that a possible solution for improving adherence might be a hybrid format with a combination of independent home practice and therapist-supervised sessions.

Effect of service-delivery mode and overall adherence on swallowing function and muscle strength.

Previous research showed that swallowing function in patients who are adherent to PSE is better preserved at the end of RT/CRT than in patients who are not adherent [66; 193]. Since service-delivery mode has a significant impact on adherence rates, the question arises whether this mode can also impact on swallowing function and muscle strength. **Research question 5** (chapter 8) was therefore formulated to examine the effect of the three service-delivery modes on swallowing function and muscle strength. In addition, the effect of overall adherence was also assessed. Service-delivery mode did not show a significant impact on swallowing function or muscle strength, however, significant differences were observed when taken into account overall adherence rates. Regardless of service-delivery mode, patients practicing ≥75% of the prescribed exercises (OA75+) showed significantly better muscle strength gain and swallowing function compared to patients performing <75% (OA75-).

The possibility to increase muscle strength during RT/CRT with acute toxicities is a unique finding. It is however important to keep in mind that the level of adherence is key to impact on muscle strength in this patient group. No detraining effects were observed after RT/CRT, moreover, between the end of RT/CRT and 3 months post-RT/CRT, both anterior and posterior tongue strength showed significant increases in the OA75+ group. However, a decrease in acute toxicity and an improved oral intake cannot be the only reasons for this increase since the OA75- group failed to demonstrate this. It can be suggested that an effective improvement in muscle strength in the OA75+ group occurred.

Practicing at a high level (OA75+) resulted in less deterioration of the swallowing function by the end of RT/CRT. Despite the no longer significant effects in swallowing function in the longer term, it can be stated that a high frequency of exercise is essential. The short-term effects are crucial, because it is generally known that it is of utmost importance for patients to continue eating and drinking during RT/CRT treatment. And this not only in terms of maintaining swallowing function, weight and preventing malnutrition and tube feeding, but also in terms of psychosocial QoL.

In conclusion, this thesis showed the high prevalence of RAD and the need for the development of an optimized, evidence-based and adherence-improving prophylactic swallowing program. We were able to develop a program that improved adherence through face-to-face therapy and showed that a high level of adherence is key to benefit from PSE.

Limitations of this thesis and future research perspectives

Despite the proven added value of this research, there are some inherent limitations, often leading towards new research questions.

Although our research concerning very late toxicity included data prospectively scored by experienced radiation oncologists, its retrospective character is prone to cause bias. Prospective trials incorporating large patients groups are thus needed to focus on very late toxicity and QoL >3 years after finishing RT/CRT.

For translation of an already existing questionnaire, three main steps need to be followed. The first step concerns the translation and back-translation, the second step involves the expert panel meeting and the third step considers the patients' interpretation. This last step was only done in 2 patients and should ideally have been done in a larger group of patients. This is a limitation of our study which has not yet been addressed in the manuscript itself. After this translation, it is also recommended to assess whether the translated scale is valid and reliable, and it should not be assumed that the

new scale has the same psychometric properties as the original version. Therefore, the second part of our study includes a reliability and validity testing. However, a minimal sample size of 5 patients per questionnaire item is recommended. Since the OMWQ-HN consists of seven items, 35 participants is sufficient, however an absolute minimum. A larger sample size in this study would have been preferable.

An important limitation of the PSE protocol concerns the content of the program. As stated before, we used a solely instrumental way of rehabilitation and did not include functional swallowing training. Since previous retrospective research already showed that keeping an oral diet is, next to exercising, essential to maintain swallowing function [2], future research should assess the effects of strength training in combination with functional training.

A second limitation concerns the duration of the PSE program. The decision to practice only in the first four weeks of RT/CRT was made with the aim to increase adherence. Nonetheless, the question arises whether the PRESTO training protocol of four weeks is sufficient to achieve benefits on swallowing function and muscle strength in the long term (>3 months). Although no clear guidelines exist in how long PSE should last after treatment, the web-based surveys of Roe et al. and Logan and Landera demonstrated that the most frequent recommendation was to continue exercises as an ongoing maintenance program, even after RT/CRT [138; 215]. However, some caution is warranted when comparing, since all previous published protocols differ in design from our study. Taking into account the recent knowledge on adherence, a future study design might be composed with exercises during the first four weeks of RT/CRT, a pause during the most burdensome weeks, and then a continuation of training afterwards. Follow-up research should clarify this.

Another limitation related to the previous one, is the rather short longitudinal follow-up period, preventing us from drawing long-term conclusions. Prospective studies should ideally be performed up to one year or even several years after RT/CRT as the effects of radiotherapy remain visible for years after treatment and can even arise up to years after treatment [1; 3]. Therefore, investigating the effects of PSE on swallowing function >1 year and up to 5-10 years after RT/CRT is a topic for future research.

The absence of collection of objective measures is another limitation of our protocol. It is possible that videofluoroscopy or flexible endoscopic examination of swallowing would show differences in swallowing characteristics, e.g. tongue base retraction, laryngeal elevation or timing, which could not be observed by means of clinical examination [63; 216].

In general, the administration of a test to determine whether the patients included in the studies had sufficient cognitive abilities can be necessary and is important to take into account in follow-up research.

Within the PRESTO trial, data concerning QoL were also collected, in addition to tracking and assessing various possible confounding factors. Further steps within our project will be to analyze all of these collected data. Moreover, the feasibility of the clinical implementation of therapist-supported PSE should be assessed and a cost-effectiveness study must be performed.

Implications for clinical practice in speech and language therapy

The results of this PhD research are clinically relevant and give rise to well-defined clinical guidelines and directions for an optimized, evidence-based and adherence-improving prophylactic swallowing program that is tailored to the patient. The scientific support provided by this research should enable the implementation of new guidelines in daily clinical practice. Based on our results, we want to achieve implementation in standard clinical care. Through the dissemination and publication of our findings, we aim to inform doctors and allied health professionals, both nationally and internationally, about the added value of prophylactic speech-language therapy care in HNC patients, and in particular the added value of face-to-face speech-language pathologist-supported care. This will serve as a support base among healthcare providers and healthcare institutions, as well as the government to realize the implementation. When prophylactic swallowing therapy becomes standard care in the radiotherapy-treated HNC population, the quality of care will increase, resulting in a reduced burden on our healthcare systems and the most important goal, an improved quality of life for HNC survivors.

General conclusion

This PhD research showed the high prevalence of long-term RAD and the need for using evidence-based PSE protocols to increase adherence in HNC patients. We were able to develop a PSE program and indicated the impact of service-delivery mode on adherence and the positive effects of therapist-supported PSE. Moreover, we concluded that only when patients exercise at a very high frequency level, the benefits of PSE can be achieved during and immediately after RT/CRT. The results of this PhD research are clinically relevant and contribute to better clinical care in patients with HNC.

SWOT analysis

Research goal 1: increasing insight in the presence of dysphagia in HNC patients treated with RT/CRT

Main strengths

- Research concerning very late toxicity is scarce; our study contributes significantly to current knowledge in this specific subject
- Data were scored prospectively by experienced radiation oncologists

Main weaknesses

- Retrospective character and possible loss-to-follow-up bias

Main opportunities

- It is important to find new strategies to minimize and prevent late toxicities: prophylactic and therapeutic measures need to be investigated in this patient population

Main threats

- No statements can be made about the impact of very late toxicity on quality of life

Research goal 2: developing an evidence-based PSE protocol that improves adherence

Main strengths

- Prospective randomized controlled trial
- Large sample size, low/acceptable drop-out rate
- Strong methodology supported by a statistical analysis plan
- Multicenter research trial
- Only the second randomized controlled trial to investigate the effect of service-delivery mode on adherence
- Homogeneous study group
- Development of potential exercise protocol with impact on daily clinical practice
- Innovative and clinically relevant

Main weaknesses

- Relatively short observation period
- Adherence in the 2 home-practice groups is solely based on patients' feedback

Main opportunities

- It is promising to implement PSE in daily clinical care of HNC patients treated with RT/CRT
- A major step forward in the development of an evidence-based adherence-improving PSE program
- PSE and counseling with a speech-language pathologist must be considered as standard care in this population

Main threats

- The effectiveness of current protocol was not investigated on the long-term
- Solely patients' information on adherence in the 2 home-practice groups can have created a bias

English summary

English summary

Dysphagia is a common and widely reported complication during and after radiotherapy for head and neck cancer (HNC). The medical and psychosocial consequences have a major impact on the quality of life (QoL) of patients undergoing radiotherapy as well as HNC survivors. In a retrospective analysis, we investigated the prevalence of very late dysphagia (>3 years after treatment) and demonstrated that even eight years after treatment, it can remain a problem. This study also showed a high prevalence of xerostomia and neck fibrosis three to eight years after radiotherapy, both contributing to the presence and persistence of swallowing disorders (manuscript 1).

Since treatment of radiation-associated dysphagia is strenuous, research concerning the use of prophylactic swallowing exercises (PSE) is growing and positive effects on muscle condition, post-treatment swallowing function and QoL have already been demonstrated. However, moderate to low adherence to PSE, along with a lack of accessibility, undermines its beneficial effects. We therefore developed an optimized, patient-tailored and evidence-based prophylactic swallowing program augmented with adherence-improving measures (manuscript 2). The program used an instrumental way of exercising and considered different general, but also more specific methods to increase adherence. The way the exercises were delivered depended on treatment group (diary-supported, app-supported or therapist-supported PSE).

Since different radiotherapy side-effects, e.g. oral mucositis, affect the execution of and the adherence to PSE, it is important to report and track them. Patient-reported outcome measures can provide insight into the impact of different side-effects and are therefore very useful in the development of a new swallowing program. To be able to assess the impact of oral mucositis, we translated the English version of the Oral Mucositis Weekly Questionnaire (manuscript 3).

After implementing this adherence-improving swallowing program in 150 oropharyngeal cancer patients treated at four different hospitals in Flanders, we observed that the adherence towards PSE was high when practicing under the supervision of a speech-language pathologist. Face-to-face therapy may solve the problem of moderate to low adherence rates (manuscript 4). In addition, we observed that only practicing at a high frequency (≥75% of the prescribed exercises) will ensure that the positive effects of the PSE on swallowing function and muscle strength are achieved (manuscript 5). The results of this PhD research are clinically relevant and contribute to the road to better supportive care in patients with HNC.

Nederlandstalige samenvatting

Nederlandstalige samenvatting

Een slikstoornis (dysfagie) is een veel voorkomende complicatie tijdens en na de behandeling met radiotherapie voor hoofd-halskanker (HHK). De medische en psychosociale gevolgen hebben een grote impact op de levenskwaliteit van patiënten, zowel tijdens radiotherapie als gedurende een lange periode na de radiotherapie. In een retrospectieve analyse onderzochten we het voorkomen van zeer laattijdige dysfagie (>3 jaar na de behandeling) en toonden we aan dat het zelfs acht jaar na de behandeling nog frequent aanwezig is. Deze studie stelde ook vast dat xerostomie en halsfibrose drie tot acht jaar na radiotherapie veelvoorkomend is, wat beide bijdraagt tot de aanwezigheid en het voortduren van slikstoornissen (manuscript 1).

Aangezien de behandeling van radiatie-geassocieerde dysfagie moeilijk is, wordt steeds meer onderzoek gedaan naar het effect van preventieve slikoefeningen (PSO) en werden reeds gunstige effecten aangetoond op de spier- en slikfunctie na de behandeling, alsook op de levenskwaliteit van de patiënt. Matige tot lage therapietrouw ten aanzien van PSO, ondermijnt echter de positieve effecten ervan. Daarom ontwikkelden we een geoptimaliseerd, op maat gemaakt en evidence-based preventief slikprogramma, aangevuld met therapietrouw verbeterende maatregelen (manuscript 2). Het programma maakte gebruik van een instrumentele manier van oefenen en onderzocht verschillende algemene, maar ook meer specifieke methoden om de therapietrouw te vergroten. De manier waarop de oefeningen werden aangeboden, was afhankelijk van de behandelingsgroep waarin de patiënten terecht kwamen (dagboek-ondersteunde, app-ondersteunde of therapeut-ondersteunde PSE).

Aangezien verschillende bijwerkingen van de bestraling, bv. orale mucositis, een invloed hebben op de uitvoering en therapietrouw van PSO, is het belangrijk om deze nevenwerkingen te rapporteren en bij te houden. Patient-reported outcome measures kunnen inzicht bieden in de impact van verschillende bijwerkingen en zijn daarom zeer bruikbaar bij het ontwikkelen van een nieuw slikprogramma. Daarom vertaalden wij de Engelstalige versie van de Oral Mucositis Weekly Questionnaire om de impact van orale mucositis te kunnen beoordelen (manuscript 3).

Na implementatie van het therapietrouw-verbeterende slikprogramma bij 150 patiënten met orofarynx kanker, behandeld in vier verschillende ziekenhuizen in Vlaanderen, stelden we vast dat de therapietrouw aan PSO hoog is wanneer geoefend wordt onder begeleiding van een logopedist. Face-to-face therapie kan dus een oplossing zijn voor het probleem van lage

therapietrouw (manuscript 4). Daarnaast leerden we ook dat enkel wanneer er aan een hoge frequentie geoefend wordt (≥75% van de voorgeschreven oefeningen), de positieve effecten van de PSO op de slikfunctie en spierkracht bereikt worden (manuscript 5).

De resultaten van dit doctoraatsonderzoek zijn klinisch relevant en dragen bij aan de weg naar betere ondersteunende zorg bij patiënten met HHK.

Curriculum vitae Margot Baudelet

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EDUCATION

Jan. 2018 – present	Doctoral Schools *University of Ghent, Belgium*
Sept. 2016 – July 2017	Master of Science in Speech Language and Hearing Sciences (Logopaedics) Achieved with greatest distinction *University of Ghent, Belgium* Master thesis: "Determination of the effect of fatigue of tongue muscles on tongue and swallowing strength in healthy adults and the elderly"
Sept. 2016 – Jan. 2017	Erasmus exchange program at the University of A Coruña *University of A Coruña, Spain*
Sept. 2013 – July 2016	Bachelor of Science in Speech Language and Hearing Sciences (Logopaedics) Achieved with greatest distinction *University of Ghent, Belgium*

EXPERIENCE

Jan. 2018 – present	PhD researcher, Joint PhD, University of Ghent and University of Antwerp *University of Ghent and Antwerp, Belgium*
May 2020 – June 2020	Speech and language pathologist at University Hospital Ghent as support during COVID-19 pandemic
March 2017 – Apr. 2017	Internship as speech and language pathologist at the center of ambulant rehabilitation "Ter Kouter" *Deinze, Belgium*
Feb. 2017	Internship as speech and language pathologist at the center of Speech-Language and Psychologic diagnostics "Miël" *Dikkelvenne, Belgium*
July 2016	Internship as speech and language pathologist at the center of Locomotive and Neurological rehabilitation, University Hospital Ghent *Ghent, Belgium*
Apr. 2016 – May 2016	Internship as speech and language pathologist at the center of Hearing- and Speech Rehabilitation "Ter Sprake", University Hospital Ghent *Ghent, Belgium*

POSITIONS

Sept. 2021 – present	Board member of the "Vlaamse Werkgroep voor Hoofd- en Halstumoren" (VWHHT)
May 2021 – present	Board member of the "Belgian Society for Swallowing Disorders" (BSSD)

EDUCATIONAL ACTIVITIES

- Co-promotor of master theses (Master of Science in Speech Language and Hearing Sciences) (Sept. 2018 – now)
- Supervisor in paper-writing (Bachelor of Science in Medicine) (2019-2021)
- Oral presentation at seminars:
    - *Iowa Oral Performance Instrument* (Antwerp, 2018)
    - *Dysphagia in head-and-neck cancer patients treated with (chemo)radiotherapy* (VWHHT-allied health professionals) (online, 2021)

SKILLS

Languages	Dutch (mother tongue), English (fluent), French (average) and Spanish (notions)
Computer skills	Microsoft Office, IBM SPSS statistics 26, Endnote
Certificates	The McNeill Dysphagia Therapy Program Certification Course (MDTP), *online course* First aid: course Basic Life Support, University of Ghent, *Ghent, Belgium*
Doctoral schools courses	English Presentation Skills (2018), Personal Effectiveness (2019), Data Analysis: Module 2 - Introductory Statistics with R or SPSS. Basics of Statistical Inference (2019), 'Start using R' for health scientists (2021)

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Baudelet, M., Van den Steen, L., Tomassen, P., Bonte, K., Deron, P., Huvenne, W., ... & Duprez, F. (2019). Very late xerostomia, dysphagia, and neck fibrosis after head and neck radiotherapy. *Head & neck*, *41*(10), 3594-3603.

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CONTRIBUTION TO SCIENTIFIC CONFERENCES

Oral presentations

- BSSD (Brussels, 2018): *Can we fatigue a healthy tongue?*

- BSSD (online, 2021): *A multicenter, randomized controlled trial on prophylactic swallowing exercises in head and neck cancer patients*
- DRS (online, 2022): *Increasing adherence to prophylactic swallowing exercises during head and neck radiotherapy, the multicenter, randomized controlled PRESTO-trial*
  Head and neck cancer Alliance Award
- Research Lunch (Ghent, 2022): *Prophylactic swallowing exercises during head and neck cancer radiotherapy, the randomized controlled PRESTO-trial*
- BSSD (Brussels, 2022): *Increasing adherence to prophylactic swallowing exercises during head and neck radiotherapy, the multicenter, randomized controlled PRESTO-trial*

Poster presentations

- Research Day and Student Research Symposium (Ghent, 2019): *Study protocol for a randomized controlled trial: prophylactic swallowing exercises in head-and-neck cancer patients treated with (chemo)radiotherapy*
- ESSD (European Society for Swallowing Disorders) (Vienna, 2019): *Study protocol for a randomized controlled trial: prophylactic swallowing exercises in head-and-neck cancer patients treated with (chemo)radiotherapy*

WORK IN PROGRESS

Baudelet M., Van den Steen L., Wouters S., De Bodt M., Vanderveken O., Duprez F., Van Nuffelen G. Supportive care among head and neck cancer patients: validation of the Dutch version of the Performance Status Scale – Head and Neck Cancer (D-PSS-HN). *Submitted in The International Journal of Language & Communication Disorders.*

Baudelet M., Van den Steen L., Duprez F., Goeleven A., Nuyts S., Nevens D., Vandenbruaene C., Massonet H., Vergauwen A., Vauterin T., Verstraete H., Wouters K., Vanderveken O., De Bodt M., Van Nuffelen G. Prophylactic swallowing therapy during head and neck cancer radiotherapy: effect of service-delivery model and overall adherence level on swallowing function and muscle strength. The PRESTO trial. *Submitted in Dysphagia.*

Dankwoord

Dankwoord

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