

Radiation-induced Dysphagia: Intervention and Assessment Tools for Head and Neck Cancer

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UNIVERSITY OF GOTHENBURG

Gothenburg 2025

Cover illustration: Gunilla Hagström

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ISBN 978-91-8069-883-2 (PRINT)
ISBN 978-91-8069-884-9 (PDF)

Printed in Borås, Sweden 2025
Printed by Stema Specialtryck AB



To my daughter Anja,
my best team-mate and the brightest shining star in my universe.

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ABSTRACT

The aim of the thesis was to evaluate the effect of two interventions to prevent or reduce complications of radiation-induced swallowing and mouth opening difficulties among patients with head and neck cancer (HNC). An additional aim was to introduce a valid and reliable tool for assessment of swallowing difficulties among HNC, by translating and validating a Swedish version.

Study I and II is based on an RCT evaluating the effect of the head-lift exercise (HLE) on swallowing function assessed by flexible endoscopic evaluation of swallowing (FEES) after 8 weeks of intervention. No convincing effect was found of the HLE on swallowing function assessed by FEES. In **study II** the effect of the HLE was measured by general and dysphagia-specific health-related quality of life instruments up to 12 months after intervention. No effect of the HLE could be detected, as there were no statistically significant differences attributable between the groups at any follow-up.

In **study III**, the Dynamic Imaging and Grading Assessment Tool for FEES (DIGEST-FEES) was translated and validated by using well-known assessment scales as reference measures. Analyses established that correlations were equal to or better for the Swedish version (Sw-DIGEST-FEES) compared to the reference measures used in the original development. Therefore, the Sw-DIGEST-FEES was deemed to be a psychometrically sound assessment tool.

Study IV is based on an RCT evaluating the effect of preventive muscle-strengthening exercises on swallowing and mouth-opening function. Baseline results from FEES and mouth opening measurement were compared to measures made one month after completion of radiotherapy for HNC. No statistically significant positive effect of the intervention protocol could be determined. Adherence to exercise protocol was 61%. Among participants in the intervention group who had completed $\geq 75\%$ of exercises, there was a trend toward better outcomes.

In conclusion, results from both RCTs are in line with previous research within the field-i.e., improving chronic swallowing difficulties is challenging, and preventive protocols for swallowing and mouth opening function is difficult to evaluate due to low adherence rates. The Sw-DIGEST-FEES can contribute to standardization of clinical and research results and offers psychometrically sound assessments.

Keywords: dysphagia, radiotherapy, head and neck cancer, intervention, mouth opening difficulties, validity

ISBN 978-91-8069-883-2 (PRINT)

ISBN 978-91-8069-884-9 (PDF)

SAMMANFATTNING PÅ SVENSKA

Patienter med huvud- och halscancer drabbas ofta av långvariga komplikationer som dysfagi (sväljsvårigheter) och trismus (nedsatt gapförmåga) efter strålbehandling och cellgiftsbehandling. Både svälj- och gapsvårigheter kan försämra patienternas funktion och livskvalitet avsevärt.

Avhandlingen innehåller fyra studier där tre delarbeten undersöker förebyggande och rehabiliterande insatser för gap- och sväljsvårigheter, och ett delarbete är en metodologisk studie.

I. Effekten av Shakers halsmuskelstärkande övning på sväljfunktion efter strålbehandling

Den första studien utvärderade om Shakers halsmuskelstärkande övning kan förbättra sväljförmågan hos patienter som genomgått strålbehandling. Patienterna delades in i en interventionsgrupp och en kontrollgrupp. Resultaten visade att även om patienterna i interventionsgruppen upplevde vissa subjektiva förbättringar av sväljningen efter 8 veckors träning, fanns få mätbara skillnader vid undersökning av sväljfunktionen. Studien visar att det finns behov av ytterligare forskning kring effektiva metoder för att förbättra sväljfunktionen efter strålbehandling.

II. Långtidseffekter av Shakers halsmuskelstärkande övning på livskvalitet och sväljfunktion

I det andra delarbetet följdes patienterna från delarbete I under ett år för att undersöka effekterna av Shakers halsmuskelstärkande övning på sväljnings- och hälsorelaterad livskvalitet. Resultaten visade inte på bättre livskvalitet hos de som tränat med den halsmuskelstärkande övningen, varken vid kort- eller vid långtidsuppföljningen.

III. Översättning och validering av ett nytt protokoll för att bedöma sväljförmåga

Det tredje delarbetet validerade en svensk version av ett protokoll för flexibel endoskopisk undersökning av sväljfunktion (FUS), "Dynamic Imaging Grade of Swallowing Toxicity for Flexible Endoscopic Evaluation of Swallowing" (DIGEST-FEES). Protokollerna är utarbetat för huvud- och halscancerpatienter och ger en övergripande bedömning av sväljningens säkerhet och effektivitet. Översättningen, DIGEST-FUS, var tillförlitlig, och

möjliggör standardiserad bedömning av sväljfunktion hos patienter med huvud- och halscancer i forskning och klinisk praxis.

IV. Förebyggande träning mot strålningsinducerad dysfagi och trismus

Det fjärde delarbetet undersökte om ett förebyggande träningsprogram, med övningar för svälj- och gapfunktion, kunde minska risken för dysfagi och trismus hos patienter som genomgick strålbehandling. Resultaten visade, som förväntat att svälj- och gapförmågan försämrades under strålbehandlingen i både interventions- och kontrollgruppen. Deltagare i interventionsgruppen som tränat mer under strålbehandlingen hade dock bättre resultat, framför allt gällande sväljfunktion. Träningen gav ingen statistiskt säkerställd effekt en månad efter avslutad strålbehandling. Fortsatt uppföljning av träningen behövs för att bedöma effekt på längre sikt.

Sammanfattningsvis visar studierna på ett fortsatt behov att utveckla och förbättra metoder för att motverka eller minska förekomsten av dysfagi och trismus för patienter med huvud- och halscancer. DIGEST-FUS kan bidra till forskningsområdet genom att erbjuda en standardiserad utvärdering av sväljfunktion vid FUS och förenkla jämförelse av studieresultat.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

- I. Dotevall H, Tuomi L, Petersson K, Löfhede H, Bergquist H, Finizia C. Treatment with head-lift exercise in head and neck cancer patients with dysphagia: results from a randomized, controlled trial with flexible endoscopic evaluation of swallowing (FEES). *Support Care Cancer*. 2022;31(1):56.
- II. Petersson K, Finizia C, Pauli N, Dotevall H, Tuomi L. A randomized controlled study evaluating the head-lift exercise in head and neck cancer patients with radiation-induced dysphagia: effect on swallowing function and health-related quality of life over 12 months. *Eur Arch Otorhinolaryngol. Eur Arch Otorhinolaryngol*. 2023;280(12):5445-5457.
- III. Petersson K, Finizia C, Pauli N, Tuomi L. Validation of the Swedish Dynamic Imaging Grade of Swallowing Toxicity for Flexible Endoscopic Evaluation of Swallowing (DIGEST-FEES). *Dysphagia*. Published online September 27, 2024.
- IV. Petersson K, Finizia C, Pauli N, Tuomi L. Preventing radiation-induced dysphagia and trismus in head and neck cancer- A randomized controlled trial. *Head Neck*. Published online August 1, 2024.

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ABBREVIATIONS

3D-CRT	Three-Dimensional Conformal Radiation Therapy
DIGEST	Dynamic Imaging Grade of Swallowing Toxicity
EAT-10	Eating Assessment Tool
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life questionnaire Core 30
QLQ-H&N35	EORTC QLQ Head and Neck Module
FEES	Flexible Endoscopic Evaluation of Swallowing
HLE	Head-Lift Exercise
HNC	Head and Neck Cancer
HPV	Human Papilloma Virus
HRQL	Health-Related Quality of Life
IMRT	Intensity Modulated Radiotherapy
ITT	Intention-To Treat
MDADI	MD Anderson Dysphagia Inventory
MIO	Maximum Interincisal Opening
PAS	Penetration Aspiration Scale
RCT	Randomized Controlled Trial
UES	Upper Esophageal Sphincter
VFS	Video Fluoroscopic evaluation of Swallowing
VMAT	Volumetric Modulated Arc Therapy

FUNDING AND GRANTS

The studies in this thesis were funded by grants from the following foundations.

Anna-Lisa and Bror Björnsson Foundation

The Assar Gabrielsson Foundation

The Department of Otorhinolaryngology at Sahlgrenska University Hospital

Operational Healthcare Committee, Region Västra Götaland,

Lions Cancer foundation West

Sjöberg Foundation

Sahlgrenska University Hospital foundation

The Swedish Cancer Society

Grants from the Swedish state under the agreement between the Swedish government and the county councils, the ALF agreement.

1 INTRODUCTION

Dysphagia is a medical term for difficulties passing food, drink, and saliva from the mouth to the esophagus.¹ Swallowing is something we take for granted. Eating and drinking is a large part of our everyday lives and a way to socialize and create well-being. Dysphagia occurs in a variety of medical conditions such as neurological disease, stroke, traumatic brain injury, autoimmune diseases, and head and neck cancers (HNC). This thesis focuses on swallowing difficulties as a consequence of radiotherapy for HNC. Typically, patients who develop dysphagia after radiotherapy are 65–70 years old and live with the impairment for a long time.² Effective interventions for dysphagia are needed to enable survival following HNC with as little negative impact following radiotherapy as possible.

1.1 SWALLOWING AND MASTICATION

Eating and drinking is a complex task where more than 30 muscles and six cranial nerves are working together with precision.³ Swallowing is divided into three phases: oral, pharyngeal, and esophageal (Figure 1).

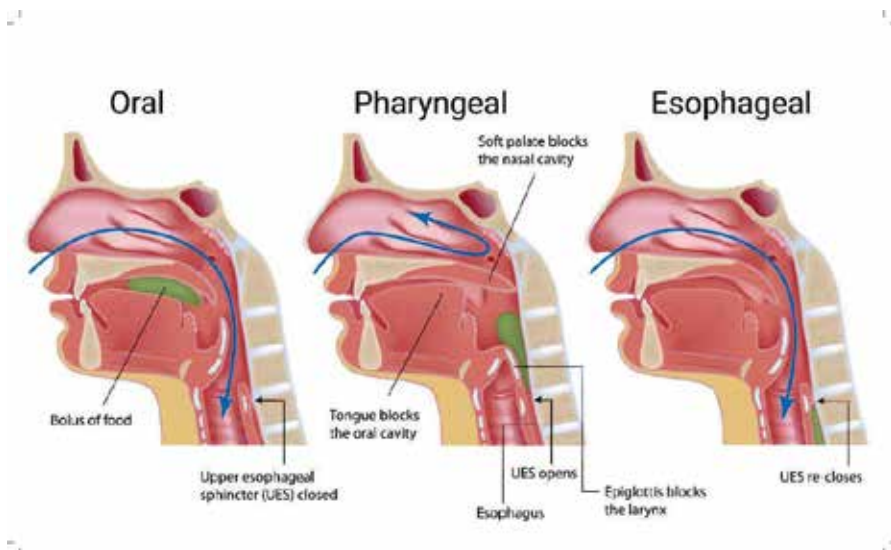


Figure 1. Illustration of three swallowing phases. Alila Medical Media/shutterstock.com.

In the **oral phase**, the bolus is prepared through a series of controlled, voluntary movements. Solid consistencies are masticated by cyclic movement of the jaw and mixed with saliva. The tongue actively passes the bolus through the oral cavity back towards the pharynx. The following structures are important in the oral phase: lips, tongue, teeth, the hard and soft palate, the mandibula, cheeks, and the anterior and posterior palatine arches.

When the bolus reaches the palatine arche (i.e., at the tongue base level), the **pharyngeal phase** starts. In the pharyngeal phase, movements are reflexive and occur almost simultaneously. The movements pass the bolus into the esophagus and protect the airway from the ingested material. First, the soft palate pushes against the pharyngeal walls and seals towards the nasopharynx. This sealing prevents leakage of food and drink into the nose. At the same time, the base of the tongue is pressed against the posterior pharyngeal wall, pushing the bolus down into the pharynx. The pharyngeal constrictor muscles peristaltically squeeze the bolus downward to the upper esophageal sphincter (UES). To protect the airway from the ingested material, the true and false vocal folds squeeze together, the arytenoids tilt forward, and the UES opens. Alongside these motions, the suprahyoid muscles contract and the thyrohyoid muscle creates a forward and upward motion in the hyoid bone and the larynx. The epiglottis tilts backwards and closes against the laryngeal vestibule to further protect the airway.^{1,3} At this time, there is a short pause in breathing. These simultaneous actions in the pharyngeal phase take place in less than a second.³

The **esophageal phase** starts when the bolus enters the sphincter and is transported downwards through the esophagus towards the stomach by peristaltic movements.

1.2 HEAD AND NECK CANCER

Head and neck cancer concerns tumors located between the clavicles and the base of skull (Figure 2, Table 1). Incidence of HNC is increasing globally, including in Sweden, mainly due to an increase of oropharyngeal cancers caused by human papilloma virus (HPV). Other

major risk factors for HNC are frequent alcohol and tobacco exposure.^{4,5} The relative five-year survival rate is currently 67% in Sweden but varies depending on tumor site and etiology of disease.² Main treatment methods are surgical removal, radiotherapy, and chemotherapy, either alone or in combination. The research results in the present thesis are based on patients with tumors located in the oropharynx (base of tongue and tonsil), hypopharynx, or larynx. All were treated with radiotherapy and a majority in combination with chemotherapy.

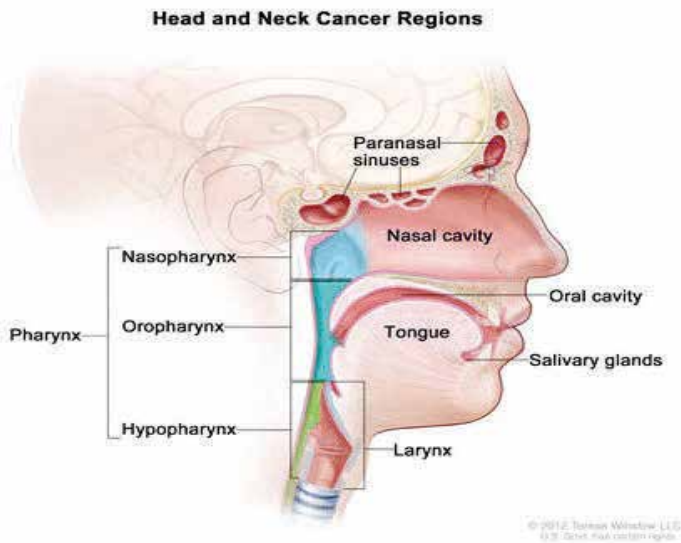


Figure 2. © (2012) Terese Winslow LLC, U.S. Govt. has certain rights.

Table 1. Data from the Swedish head and neck cancer register, 2023², incidence of selected subtypes in relation to total incidence of HNC.

Cancer subtype	Incidence
Oral cavity/ lip	40%
Nasopharynx	2%
Oropharynx	30%
Hypopharynx	3%
Larynx	11%

1.3 RADIATION-INDUCED DYSPHAGIA AND TRISMUS

Radiotherapy is effective in killing cancerous cells but impacts all tissue in the irradiated area. During treatment, acute side effects such as pain in the irradiated area, edema, mucositis, altered taste perception, dryness of mouth (xerostomia), and loss of appetite are common and often restrict a patient's dietary intake. Other common complaints are impaired swallowing function and mouth opening ability.⁶ In some patients, dysphagia and restricted mouth opening (i.e., trismus) subsides after completing radiotherapy. For others, however, the symptoms persist or arise after treatment.

Around 40–70% of patients develop dysphagia and 30% develop trismus following radiotherapy for HNC.⁷⁻⁹ However, reports from current cohorts suggest that prevalence of trismus is decreasing, most likely due to advances in radiation technique.¹⁰ Since the absorbed radiation continues to affect tissue, some patients develop dysphagia and trismus years after treatment.^{6,11} Trismus can be defined as a maximum interincisal opening (MIO) of ≤ 35 mm.¹² Chronic swallowing and mouth opening difficulties are usually ascribed to fibrotic changes in irradiated tissue. Radiation-induced fibrosis can cause muscle weakness, restricted range of movement, and stiffness. Also, damage to the peripheral nerves involved in the innervation of swallowing musculature and transmitting information to and from the central nervous system can contribute to impaired function.¹¹ Patients who are treated with chemotherapy in addition to radiotherapy can have more severe swallowing difficulties.¹³

Studies on swallowing kinematics after radiotherapy for HNC have found reduced movement and strength in the tongue, impaired mastication, reduced contact between tongue base and pharyngeal wall, delayed onset of swallowing, reduced laryngeal elevation, reduced pharyngeal contraction, and delayed vestibular closing.¹³⁻¹⁷ In turn, these restrictions make the swallowing function less efficient and less safe.

Swallowing is unsafe if patients have trouble protecting their airway—i.e., if part of the bolus penetrates to the larynx or is aspirated into the trachea. A meta-analysis reported a 20% prevalence of aspiration

during the first year after radiotherapy.¹⁵ A normal reaction to penetration and aspiration is to reflexively cough or clear the throat. This reflex helps expel the material and protects the airway. However, when this sensate response is compromised, silent aspiration can be the result—i.e., aspiration without reflexive response to expel the material.¹⁸

Reduced swallowing efficiency means difficulty passing all of the bolus into the esophagus. In the first year after radiotherapy for HNC, around 70–94% of patients have residues left in the pharynx after swallowing.^{15,19} Mild residue mostly causes discomfort while more substantial residue might leak into the airway causing penetration or aspiration.²⁰

Restricted mouth opening and trismus after radiotherapy for HNC is usually attributed to fibrosis in musculature involved in mastication and typically develops during the first 12 months after treatment.⁹ Tumor sites with high risk of developing trismus are the oral cavity, oropharynx, nasopharynx, and salivary glands.²¹

Recent developments in radiation techniques such as intensity-modulated radiotherapy (IMRT) and volumetric-modulated arc therapy (VMAT) have made it possible to better regulate the intensity of radiation beams compared to older techniques such as three-dimensional conformal radiation therapy (3D-CRT).²² These advances make it possible to more precisely direct the highest dose of radiation to the tumor and a lower dose to the healthy surrounding tissue. Concerning dysphagia, a higher dose of radiation to the pharyngeal constrictors and glottic/supraglottic larynx seems to affect swallowing function negatively.²³⁻²⁵ For radiation-induced trismus, dose to the masseter muscles and pterygoid muscles seems to impact mouth opening outcomes.^{26,27}

1.4 IMPACT ON HEALTH

Both dysphagia and trismus lead to eating and drinking difficulties and are associated with several negative health effects. Patients with restricted mouth opening often have difficulty taking larger bites as well as chewing. Mouth dryness and difficulties with residue can make mealtimes long and effortful, as a consequence many patients with dysphagia must exclude certain foods that are difficult to eat. Diet

modifications can range from choosing soft foods to pureed food rather than meat and raw vegetables. Patients who suffer from penetration and/or aspiration may also require modified consistencies. For safer ingestion, for example, thickeners can be added to liquids for patients who tend to aspirate on liquid consistencies.¹⁸ Extensive mealtimes and modified diets can negatively affect nutritional intake, increasing the risk of malnutrition, dehydration, and weight loss.²⁸ If diet modifications are not enough to ensure safe swallowing or eating takes too much effort, a feeding tube can be used. The most serious and sometimes fatal complication of dysphagia is aspiration pneumonia. Reported prevalence after radiotherapy ranges from 8–20%.^{7,29,30} Although penetration and aspiration events are associated with increased risk of aspiration pneumonia, the patients underlying medical conditions play a role in whether infection will develop. Therefore, it is not certain that a patient who aspirates will develop aspiration pneumonia.^{31,32} One other contributing factor to aspiration pneumonia is poor oral hygiene and aspiration of bacterial saliva.³³ These factors put patients suffering from both dysphagia and trismus especially at risk as restrictions in mouth opening make oral hygiene challenging.

Dysphagia and trismus also negatively impact patients' mental health and health-related quality of life (HRQL).^{34,35} HNC patients often experience eating as unpleasurable. Many are embarrassed of food modifications or over coughing while eating. They may decline dinner invitations or refrain from eating out, preferring to eat alone or with the immediate family. Fear of choking is also common.³⁶ Impaired swallowing and closely related abilities (chewing, salivation, and taste) have been identified as one of the most important factors affecting HRQL one year after radiotherapy.³⁷ In the first year after treatment, HRQL is reported to deteriorate in the first six months, after which the negative trend is reversed and an improvement occurs up to twelve months. Results at twelve months are in general lower-i.e., worse than before treatment and remain stable at two years.^{38,39}

1.5 TREATMENT FOR DYSPHAGIA AND TRISMUS

Diet modification is a common intervention for patients with dysphagia. Another measure is specific swallowing maneuvers (e.g.,

supraglottic and Mendelsohn) and changes in head position. In some patients, these changes alter bolus flow in the pharynx and help increase the safety and efficiency of the swallow.¹⁸ However, none of these measures improve the actual swallowing function, and food modifications are associated with reduced HRQL.⁴⁰

In order to improve long-term function there are some different approaches in dysphagia management such as neuromuscular electrical stimulation, skill-based training (which focuses on timing and strength of the swallow with or without biofeedback), range of motion exercises, and exercises designed to strengthen the muscles involved in swallowing.⁴¹⁻⁴³ This thesis focuses on the latter approach– i.e., strength-based swallowing intervention.

Several randomized controlled trials (RCTs) have established the positive effect of swallowing exercises with reports of decreased aspiration⁴⁴⁻⁵³ and residue,^{46,48-50} improved swallowing kinematics,^{49,53,54} and better ability to eat a normal diet.^{44,45,52,55,56} However, most of these research results are from RCTs on stroke cohorts. Tables 2a and 2b give an overview of results from a number of RCTs evaluating strength-based interventions, mainly for stroke and HNC patients.

Trismus interventions are often based on active and passive jaw stretches with or without an exercise device. Examples of devices used in stretches are wooden tongue depressors and task specific jaw-opening devices such as Therabite, Jaw-Trainer, or Dynasplint.⁵⁷ Several studies have established the positive effect of jaw exercises on mouth opening function and HRQL.^{58,59 54,60,61}

Table 2a. Overview of results from selected randomized controlled trials on strength-based exercises for swallowing function stroke, neurological disease and mixed cohorts.

Disease	Author	Intervention	n	Diet	Kine- matics	Capa- city	Aspira- tion	Residue	HRQL
	Carnaby ⁵⁵	Active group 1: Effortful swallow and supraglottic swallow Active group 2: Modification, advice on safe swallowing. Control group: Advice safe swallow, or none	306	+	n/a	n/a	n/a	n/a	n/a
	Kim ⁶²	Active group 1: Proprioceptive Neuromuscular Facilitation Active group 2: HLE*	26	=	=	n/a	=	=	n/a
	Park ⁵³	Active group: EMST* Placebo group: Sham device	27	=	+	n/a	+	n/a	n/a
	Choi ⁴⁵	Active group: HLE*	32	+	n/a	n/a	+	n/a	n/a
	Eom ⁴⁶	Active group: EMST* Placebo group: Sham exercise	26	n/a	n/a	n/a	+	+	n/a
	Gao and Zhang ⁴⁷	Active group 1: HLE* Active group 2: CTAR* Control group: Traditional dysphagia therapy	90	n/a	n/a	n/a	+	n/a	+
	Guillén-Solà ⁴⁸	Active group 1: IEMT* Active group 2: NIMES* + Sham IEMT* Control group: Standard swallow therapy	62	=	n/a	n/a	+	+	n/a
	Park ⁴⁹	Active group: CTAR* Control group: Conventional dysphagia treatment	22	n/a	+	n/a	+	+	n/a
	Kim and Park ⁵²	Active group: Modified CTAR* Control group: Traditional dysphagia treatment	30	+	n/a	n/a	+	n/a	n/a
	Krajczyk ⁶³	Active group: Strengthening and breathing exercises + thermal stimulation Control group: Safe food education, physiotherapy	60	n/a	n/a	+	n/a	n/a	n/a
Stroke	Park ⁶⁴	Active group: Effortful swallow Control group: Natural swallow	24	n/a	+	n/a	=	=	n/a
	Park ⁶⁵	Active group 1: Game-based CTAR* Active group 2: HLE*	37	=	=	n/a	=	=	n/a
	Carnaby ⁴⁴	Active group: NIMES* + MDTP* Control group: Usual care Placebo group: Sham exercise	53	+	n/a	n/a	+	n/a	n/a

Disease	Author	Intervention	n	Diet	Kine- matics	Capa- city	Aspira- tion	Residue	HRQL
	Hägglund ⁶⁶	Active group: Orofacial sensory-vibration stimulation + Oral device (Muppy®) Control group: Orofacial sensory-vibration stimulation	40	n/a	n/a	+	=	n/a	n/a
Parkinsons disease	Troche ⁶⁷	Active group: EMST* Placebo group: Sham EMST*	60	n/a	=	n/a	=	n/a	=
Multiple sclerosis	Tarameshlu ⁵⁰	Active group: Traditional dysphagia therapy Control group: Postural changes, diet modification, sensory stimulation	20	n/a	n/a	n/a	+	+	n/a
Elderly with dysphagia	Wakabayashi ⁶⁸	Active group: Resistance exercises for swallowing muscles instructed once Control group: Brochure on oral hygiene and resistance exercises	91	n/a	n/a	n/a	n/a	n/a	=
	Hägglund ⁵¹	Active group: Oral device (Qoro®) Control group: Usual care	116	n/a	n/a	+	+	n/a	=
Mixed stroke and HNC	Logemann ⁶⁹	Active group: HLE* Control group: Traditional swallowing exercises	19	=	=	n/a	+	=	n/a

(+) = Statistically significant positive effect in the active group. (=) = No statistically significant difference between groups.
Abbreviations: EMST = Expiratory muscle strength training, IEMT = Inspiratory/Expiratory muscle training, CTAR = Chin tuck against resistance, NMES = Neuromuscular electrical stimulation, HLE = Head lift exercise, MDTP = McNeil Dysphagia Therapy.

Table 2b. Overview of results from selected randomized controlled trials on strength-based exercises for swallowing function among head and neck cancer patients.

Disease	Author	Intervention	n	Diet	Kinematics	Capacity	Aspiration	Residue	HRQL
HNC Prevention	Carnaby-Mann ⁵⁴	Active group: Pharyngocise Placebo group: Sham exercise Control group: Usual care	58	=	+	n/a	n/a	n/a	n/a
	Kotz ⁷⁰	Active group: Swallow exercises Control group: Usual care	26	=	n/a	n/a	n/a	n/a	n/a
	Mortensen ⁷¹	Active group: Swallowing exercises Control group: Usual care (no exercise)	39	=	n/a	n/a	=	=	=
	Messing ⁷²	Active group: Swallowing exercises, ROM* exercises, Therabite Control group: Prophylactic Therabite, no swallow exercises	60	=	=	n/a	=	=	=
	Kumar ⁵⁶	Active group: Swallowing exercises Control group: Usual care (no exercise)	50	+	n/a	n/a	=	n/a	+
	Hajdu ⁷³	Active group: Individually prescribed swallowing exercises Control group 1: Usual treatment Control group 2: No treatment	235	=	n/a	n/a	=	=	= (+ / - at some follow-ups)
	Lin ⁷⁴	Active group 1: Functional electrical stimulation of the suprahyoid muscles while swallowing Active group 2: Swallowing exercises, ROM* exercises	20	n/a	+	n/a	+	=	=
HNC Rehabilitation	Tang ⁷⁵	Active group: Swallowing exercises Control group: No swallowing exercises	43	n/a	n/a	+	n/a	n/a	n/a
	Langmore ⁷⁶	Active group 1: NIMES* and swallow exercise Active group 2: NIMES* sham and swallowing exercises	170	=	n/a	n/a	-	n/a	=
	Chen ⁷⁷	Active group: Swallow exercises Control group: Usual care (no exercise)	76	n/a	n/a	n/a	n/a	n/a	= (+)
	(+) = Statistically significant positive effect in the active group, (=) = No statistically significant difference between groups, (-) = Statistically significant worse result in the active group. Abbreviations: ROM = Range of motion, NIMES = Neuromuscular electrical stimulation								

1.5.1 THE HEAD LIFT EXERCISE

The head-lift exercise (HLE), also called the Shaker exercise, has been evaluated in RCTs with positive results on aspiration, swallowing kinematics, and normalcy of diet.^{45,78,79} These positive results are further supported by a meta-analysis on RCTs evaluating dysphagia intervention, which established large effects of HLE on swallowing function. However, the studies included in the meta-analysis were mainly based on stroke cohorts, and it is not certain that they can be generalized to radiation-induced dysphagia.⁴³

The head-lift exercise was originally developed to target impaired opening of the upper esophageal sphincter by improving hyoid and laryngeal elevation during the swallow.⁷⁸ The exercise consists of static and repetitive head lifts aimed at strengthening the suprahyoid muscles (the digastric posterior and anterior belly, mylohyoid, geniohyoid, and stylohyoid muscles (Figure 3) and the thyrohyoid muscle.⁷⁹ Some promising results have been noted in studies on HNC patients concerning swallowing kinematics, aspiration, and residues.^{69,79,80} However, effect of HLE on chronic radiation-induced dysphagia alone has not previously been evaluated in a RCT.

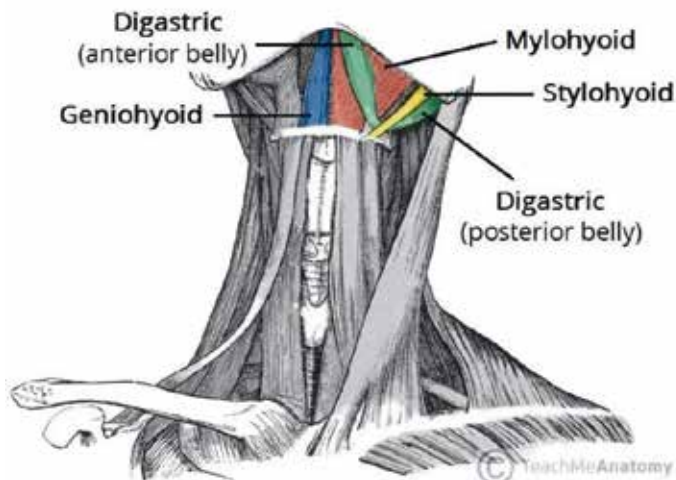


Figure 3. Anterior view of the neck with the suprahyoid muscles highlighted. © TeachMeAnatomy

1.5.2 THE TONGUE HOLD EXERCISE

The tongue hold exercise, also called the Masako maneuver, is included in most protocols for swallowing exercises for HNC patients.^{81,82} One advantage of the tongue hold is that it meets two important training principles: it is task-specific (swallowing) and it provides overload to the swallowing musculature. The exercise is designed to strengthen the pharyngeal contraction and the muscles at the base of the tongue to improve the swallowing efficiency.^{81,83,84} Thus, the exercise has the potential to reduce patient discomfort as well as risk of aspiration of excess residue. A recent study also found that the tongue hold exercise increased muscle strength and thickness in three of the suprahyoid muscles (the mylohyoid, geniohyoid and anterior belly of the digastric muscle).⁸⁵

1.5.3 TIMING OF INTERVENTION: PREVENTION OR REHABILITATION

Despite many years of research on muscle strengthening exercise for radiation-induced dysphagia, there are still no clear answers for when to start an intervention to make the most beneficial impact and what are the most effective exercises. Traditionally, swallowing exercises were offered as rehabilitation to patients with chronic dysphagia following radiotherapy for HNC. However, over the last 10–15 years there has been a trend to offer exercises as a preventive intervention.¹⁸

In preventive intervention, the patients perform exercises before, during, and after completion of oncological treatment. Depending on the onset of intervention (i.e., before or after radiotherapy), the rationale for using strength-based exercises in radiation-induced dysphagia is to prevent or counteract the negative impact of fibrosis and muscle atrophy on swallowing function.^{11,18} Positive results from RCTs evaluating preventive swallowing exercises include better maintained swallowing kinematics, better ability to eat a normal diet, and improved dysphagia-specific HRQL.^{54,56} A meta-analysis comparing timing of intervention based on pooled data on a variety of outcomes measuring swallowing function concluded that results pointed towards better effect of preventive than rehabilitative intervention.⁸⁶ In addition, a recent report found strong agreement among experts in favor of preventive interventions.⁸⁷ However, to determine whether preventive

or rehabilitative intervention is best for radiation-induced dysphagia will require more evidence from high quality studies.^{18,86}

An obstacle to determining the effect of preventive exercise is low adherence. Many protocols are extensive, typically recommending 3–5 sessions of 2–7 exercises (typically 10 repetitions each) per day.⁸⁸ Including multiple exercises is reasonable given the lack of knowledge about which exercises have the best effect, but it has at least two disadvantages. Requiring multiple exercises affects adherence to the exercise protocol negatively as it introduces a barrier to compliance, which undermines the effect, and makes it impossible to evaluate the effectiveness of individual exercises.^{89,90}

Another preventive measure that has gained support over the last ten years is to encourage patients to continue with an oral intake of food and as normal a diet as possible during radiotherapy.⁹¹ These goals aim to prevent atrophy of the swallowing muscles and therefore promote swallowing function. For example, a full liquid diet of nutritional supplements is less challenging on the swallowing musculature than solid consistencies.⁹¹ However, consideration must be given to acute radiation toxicities in the mouth and throat and for some patients, encouraging any oral intake alongside a nasogastric feeding tube might be the appropriate goal.

Mouth opening exercises are also focused on counteracting or preventing the effects of fibrosis and atrophy caused by radiotherapy. It seems that using a jaw-opening device to perform exercises is more favorable to mouth opening outcomes than stretches alone.⁹² Results from RCTs, reviews, and meta-analyses on preventive exercises for mouth opening do not agree, so it is debated whether restricted mouth opening can be avoided through the use of preventive measures.^{54,57,92-96} Concerning chronic trismus after radiotherapy structured training with a mouth opening device can decrease pain and improve opening ability, trismus-related symptoms, and HRQL.^{58,59}

Conclusive evidence on the general effectiveness of exercises, best type of interventions, and treatment onset is lacking concerning swallowing exercises and, to some extent, mouth opening exercises. Many studies that focus on these issues are limited due to their small study populations, heterogeneity in assessment and outcome measures, and

retrospective study designs, limitations that make results unclear and difficult to evaluate.^{18,57,92,95,97}

1.6 EVALUATION OF DYSPHAGIA AND TRISMUS

There are different ways to evaluate swallowing. During an assessment, patients are typically given boluses of different consistencies and sizes (both liquid and solid) to swallow while the clinician looks for signs of airway invasion (aspiration or penetration) and residues. Usually, oral motor and sensory abilities are also assessed. Patients' medical history and self-report of dysphagic symptoms while eating and drinking are also important to evaluate.⁹⁸ Assessment can be done through clinical observation, which is performed without advanced equipment. Findings from clinical observation are less reliable than those from instrumental assessments such as flexible endoscopic evaluation of swallowing (FEES) and video fluoroscopic evaluation of swallowing (VFS).^{98,99}

Measuring mouth-opening ability is less complex and represents the distance between the lower and upper incisors. Examples of outcome measures of interventions are change in MIO, trismus incidence, and a 5-mm increase in mouth opening, which represents a minimal clinical difference.^{61,100,101} Trismus defined as a mouth opening ≤ 35 mm is a well-established cut-off, although alternative definitions such as a 15% decrease in MIO are sometimes used.⁹³

1.6.1 INSTRUMENTAL ASSESSMENT

Both VFS and FEES are well-established methods for assessing dysphagia after HNC. Both methods provide real time images of the patient swallowing and enable better assessment of the amount of residue and severity of penetration/aspiration. Furthermore, silent aspiration is only possible to determine by instrumental assessment.¹⁸ VFS produces a gray scale film over the oral cavity, pharynx, and top part of the esophagus, typically in lateral projection, while the patient swallows liquid and solid boluses of radiocontrast. VFS visualizes the bolus transport, from the oral cavity to the esophagus, and the trachea can be seen during the whole assessment.¹ FEES requires inserting an endoscopy through the nasal cavity to the pharynx. The video is in color and presents a bird's eye view of the oropharynx and hypopharynx as well as the larynx. The liquid and solid boluses are

dyed (e.g., green) to be easily visible on the mucosa (Figure 4).¹

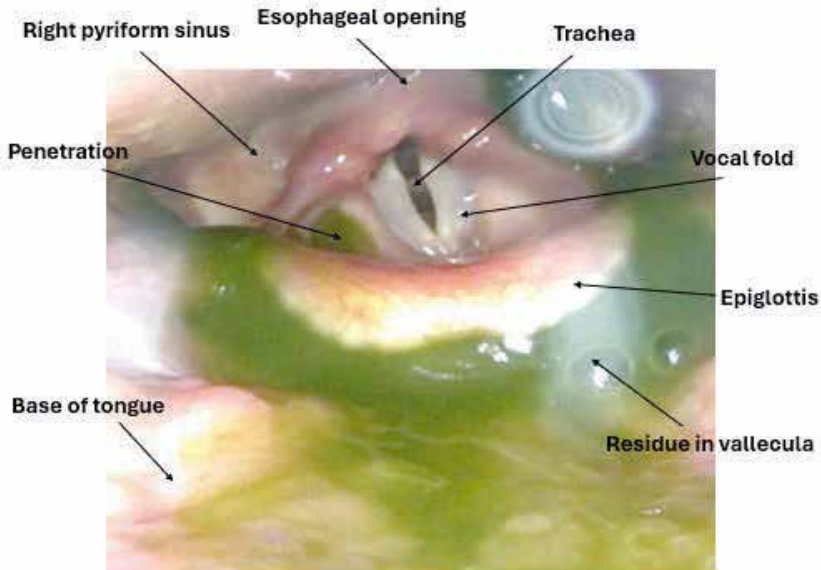


Figure 4. View over the larynx during a FEES. Some structures and swallowing variables are labeled in text.

Swallowing function can be described in different ways, which is reflected in the variety of outcome measures used in research to capture effect of dysphagia intervention.^{86,102} Positive health aspects such as better maintained weight and fewer patients' dependent on a feeding tube for nutrition can be used to determine swallowing ability.^{91,103} In addition, some measures rate swallowing function according to the patient's ability to include all food consistencies in their diet.^{42,104} These measures are fairly easy to attain from a patient's chart or a patient interview and represent results that are desirable and relatable to patients but might be influenced by factors other than swallowing ability.

Ratings on instrumental assessment of penetration, residue, swallowing kinematics, and secretions are more specific to swallowing function, and several scales are available that rate these aspects.¹⁰⁵⁻¹⁰⁸ However, using several scales to describe different aspects of swallowing does not offer a coherent overall assessment of swallowing function. Furthermore, the variety of outcome measures and rating scales used in research on dysphagia intervention for HNC makes it difficult to draw general conclusions from research findings.^{86,102,109}

1.6.2 DYSPHAGIA PROTOCOL FOR HNC

A gold standard for psychometrically sound measures for FEES and VFS is needed.¹⁰⁹ However, over the last decade protocols that include several aspects of swallowing within the same framework have been developed and validated both for VFS and FEES and their use in research contexts and clinical settings are increasing.¹¹⁰⁻¹¹⁴ One such protocol, developed specifically for HNC patients in 2021, is the Dynamic Imaging Grade of Swallowing Toxicity for FEES (DIGEST-FEES). The DIGEST-FEES offers scales and an overall outcome measure for swallowing ability that could help international standardization of FEES evaluation in HNC both in research and in clinical settings. The psychometric evaluation of the protocol has established that it is a reliable and valid instrument for measuring severity of dysphagia in HNC patients.¹¹¹ Previously, no equivalent Swedish validated protocol has been available.

1.6.3 HEALTH-RELATED QUALITY OF LIFE (HRQL)

Health-related quality of life (HRQL) refers to patients' subjective well-being or quality of life in relation to health or functional status. One way of measuring HRQL is through the use of questionnaires covering different aspects of well-being such as general health, emotional well-being, physical functioning, role functioning, social and psychological factors, cognitive functioning, sexual functioning, and sometimes also spiritual beliefs.¹¹⁵ Each domain includes several items— i.e., questions or statements investigating the patient's perception on the subject.

Successful interventions for trismus and dysphagia would ideally reduce negative impacts on HRQL for HNC patients. As questions (i.e., items) are formulated and answered in a standardized manner, HRQL instruments are well suited to follow trends and for group comparisons. However, a current review has determined that few studies evaluate the long-term effects of swallowing interventions on HRQL.⁹⁷ Using HRQL instruments can complement instrumental assessments by including patients' perceptions and therefore provide a more complete evaluation in clinical trials.

Questionnaires such as the EQ-5D and the 36-Item Short Form Health Survey can address generic HRQL issues.^{116,117} Questionnaires can also be disease-specific such as the European Organization for Research and Treatment of Cancer Quality of Life questionnaire Core 30 (EORTC QLQ-C30) and the University of Washington Quality of life measures

(both instruments measure HRQL related to cancer disease)¹¹⁸⁻¹²⁰ The EORTC QLQ Head and Neck Module (QLQ-H&N35) is a diagnosis-specific questionnaire that address issues specific to HNC populations.¹²¹ In addition, there are symptom-specific questionnaires for dysphagia (e.g., the MD Anderson Dysphagia Inventory (MDADI) and Swallowing Quality of Life Questionnaire) and for trismus (e.g., the Gothenburg Trismus Questionnaire)¹²²⁻¹²⁵. It is important that instruments have sound psychometric properties and results are reliable and stable when conditions are unchanged as well as valid for measuring the intended concepts. Instruments should also be responsive—i.e., able to measure changes over time.¹¹⁵

2 AIM

This thesis aimed to evaluate the effect of two muscle-strengthening protocols in order to rehabilitate or prevent radiation-induced dysphagia and trismus among HNC patients. An additional aim was to improve FEES methodology in Sweden by translating and validating a recently developed assessment framework for HNC patients.

The specific aims of each study are listed below:

Study I: To evaluate short-term effect of the head-lift exercise (HLE) on dysphagia following HNC by flexible endoscopic evaluation of swallowing (FEES) in a randomized controlled trial.

Study II: To evaluate the effect of the HLE on general and dysphagia-specific HRQL up to 12 months after intervention.

Study III: To contribute to international standardization and improved FEES both in clinical and research settings by translating and validating a validated assessment protocol for HNC patients into Swedish.

Study IV: To evaluate the effect of a preventive exercise protocol on swallowing and mouth-opening function.

3 PATIENTS AND METHODS

3.1 STUDY DESIGN

Table 3 presents an overview of the study design (Studies I–IV). Participants in cohort A are included in a randomized controlled trial evaluating the effect of the HLE for patients with dysphagia following radiotherapy for HNC. All patients treated at the Sahlgrenska University Hospital in Gothenburg who met the inclusion criteria were invited to participate in a VFS (Table 3). If a rating on the Penetration Aspiration Scale (PAS) of 2 or higher was noted twice on VFS, patients were invited to participate in the trial.¹⁰⁸ The study included 61 participants; 31 were randomized to the intervention group and 30 to the control group. Studies I–III are based on data collected for cohort A.

Cohort B participants were randomized to evaluate the effect of an exercise protocol designed to prevent radiation-induced dysphagia and restricted mouth opening. Patients who matched inclusion criteria (Table 3) were invited to participate in the study at time of HNC diagnosis. Of the randomized participants, 89 were included in the intention-to-treat analysis (ITT), 45 in the intervention group and 44 in the control group.

Table 3. Overview of study design in study I-IV.

Cohort	Patients included (n=)	Study design	Inclusion criteria	Exclusion criteria	Treatment	Inclusion period	Time point for evaluations	Primary outcome
Cohort A n = 61	I	RCT	Age > 18 years Treatment: Radiotherapy, ± chemo-, ± brachytherapy	Previous surgery for HNC Previous HNC disease Tracheostomy	(C)RT	2011 - 2018	Before and 8 weeks after swallowing intervention	Change in PAS
	II	RCT	6-36 months post radiotherapy Tumor site: tonsil, base of tongue, hypopharynx or larynx PAS ≥ 2 on video fluoroscopy	Neurological/neuro-muscular disease Inability to perform the swallowing exercise. Inability to swallow any bolus at VFS			Before and at 8 weeks as well as 12 months after swallowing intervention	Change in HRQL
	III	Validation study					n/a	Psychometric analysis
Cohort B n = 89	89	RCT	Age > 18 years Treatment: RT ± chemotherapy Tumor site: tonsil, base of tongue, hypopharynx or larynx	Previous history of HNC – Trismus at HNC diagnosis Edentulous Tracheostomy Neurological/neuro-muscular disease Previous dysphagia		2019 - 2022	Before start of radiotherapy and one month post completion	Change in PAS Change in MIO

Study I: Swallowing function was measured at baseline and after eight weeks of HLE intervention by well-established rating scales for FEES and a patient-reported outcome measure. Overall worst PAS was the primary outcome measure. Participants with a FEES at baseline and the eight-week follow-up were included in the analysis (24 in the intervention group and 23 in the control group). Without knowledge of participant allocation, two independent raters used FEES recordings to score swallowing.

Study II: The analysis included reports from general and dysphagia-specific HRQL instruments at baseline, the eight-week follow-up (25 in the intervention group and 27 in the control), and the 12-month follow-up (19 in the intervention group and 24 in the control).

Study III: The DIGEST-FEES was translated into Swedish (Sw-DIGEST-FEES) by forward-backward translation. Two experienced speech and language pathologists rated 89 FEES recordings according to the Sw-DIGEST-FEES and according to well-established rating scales for FEES, which were used as reference measures. Correlations between the Sw-DIGEST-FEES and the reference measures were calculated. To ensure the validity of the Swedish translation, we compared the correlations to the reference measures used in the original version (DIGEST-FEES) and evaluated the inter- and intra-rater reliability.

Study IV: Swallowing function was measured by well-established and validated rating scales for FEES at baseline (before oncological treatment) and at the one-month follow-up. MIO measurements were collected at the same times. ITT analyses were performed for the primary endpoints PAS and MIO comparing differences in change for the intervention and control group (n = 89) between baseline and the one-month follow-up.

3.1.1 HEAD-LIFT EXERCISE PROTOCOL

Speech and language pathologists instructed the intervention group in how to perform the HLE. The participants were asked to lay down on a flat surface and to lift their head “to look at their feet” in a sustained (isometric) and in repetitive (isokinetic) lifts. One HLE session consisted of three static 60 second head-lifts with 60 seconds of rest

between repetitions and of 30 short repetitive head-lifts, similar to a sit-up (Figure 5).⁷⁸

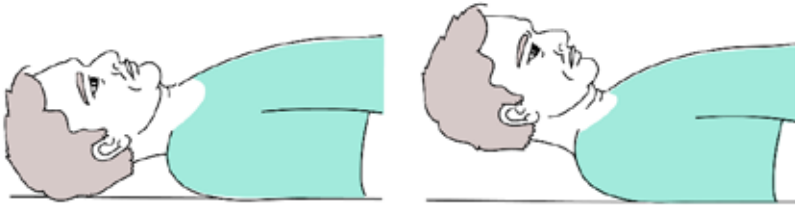


Figure 5. *The Head-Lift Exercise. Illustration by Gunilla Hagström.*

To build strength, the participants started the HLE protocol with an intensive training period. For the first eight weeks participants were instructed to do three HLE sessions per day, and the speech and language pathologists regularly supervised their efforts, providing, for example, advice about their technique. In the following 12 months, the participants were advised to do a minimum of three sessions per week or one daily session to maintain the strength they had developed. Participants reported adherence to the HLE in a diary. FEES, patient reported outcomes, and HRQL data were collected at baseline—i.e., before start of HLE, after the eight-week period of intensive HLE, and after 12 months of maintenance exercise.

3.1.2 PREVENTIVE EXERCISE PROTOCOL

The preventive exercise protocol consisted of one daily session of ten repetitions of the tongue hold exercise and passive and active stretches with a Jaw-Trainer© (Figure 6).¹²⁶ The tongue hold is performed by anchoring the tip of the tongue between the front teeth while swallowing saliva.⁸¹ With the tongue in this position, the resistance increases, so extra muscle effort is required to swallow. Using the Jaw-Trainer©, participants did three passive stretches, which were held for 30 seconds with a short pause in between and 5 active stretches. For the passive stretches, the participant used the device to stretch the jaw in its maximum position. For the active stretches, the device was opened to approximately 1.5 cm and participants bit down on the device for a few seconds with a short pause between each repetition. Training sessions were reported in a diary.

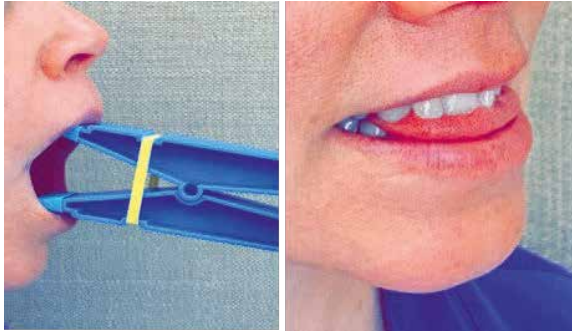


Figure 6. Jaw stretch with a Jaw-Trainer© (left). The tongue hold exercise (right).

All participants had contact with speech and language pathologist every week, and both groups received standard treatment, which meant that they were encouraged to continue eating and drinking as much as they could during treatment and received advice on food modifications if necessary. Both the intervention and control groups recorded daily if they had been eating or drinking anything that day.

3.2 STUDY POPULATIONS

Table 4 presents participant characteristics and treatment delivery for patients included in cohorts A and B. The gender distribution and mean age were similar for both cohorts. There was a larger proportion of participants with HNC stage IV and laryngeal tumors among the participants with chronic dysphagia. Changes in treatment delivery over the last decades concerning radiotherapy can be noted when comparing the cohorts. Most participants in cohort A were treated with IMRT or VMAT, but 15% had 3D-CRT and 33% had additional brachytherapy. All of the participants in cohort B were treated with VMAT and none with brachytherapy. In both cohorts, around 80% received chemotherapy in combination with radiotherapy.

Table 4. Participant characteristics and treatment delivery for patients included in cohort A and cohort B.

	Cohort A n=61	Cohort B n=89
	Mean \pm SD Median (Min; Max)	Mean \pm SD Median (Min; Max)
Age (years)	63.5 \pm 8.1 (44;80)	64.0 \pm 9.4 (42;83)
	n (%)	n (%)
Sex		
Male	45 (74)	68 (76)
Female	16 (26)	21 (24)
Tumor location		
Tonsil	24 (39)	50 (56)
Base of tongue	23 (38)	23 (29)
Hypopharynx	5 (8)	5 (6)
Larynx	9 (15)	8 (9)
Tumor stage*	n (%)	
I	5 (8)	46 (52)
II	7 (11)	7 (8)
III	5 (8)	27 (30)
IV	44 (72)	9 (10)
Smoking		
Smoking	9 (15)	4 (5)
Missing	0	10 (11)
Radiotherapy		
3D-CRT	9 (15)	0 (0)
IMRT	25 (41)	0 (0)
VMAT	27 (44)	89 (100)
Chemotherapy		
Yes	48 (79)	71 (80)
Brachytherapy		
Yes	20 (33)	0 (0)
*TNM classification of malignant tumors 7:th edition was used for Cohort A and 8:th edition for Cohort B		

3.3 OUTCOME MEASURES

Table 5 provides an overview of evaluation methods and the outcome measures used in studies I–IV.

Table 5. Evaluation methods and outcome measures in study I-IV.

Assessment	Outcome measure	I	II	III	IV
Flexible endoscopic evaluation of swallowing (FEES)	Penetration aspiration scale (PAS) ¹⁰⁸	X		X	X
	Yale pharyngeal residue severity rating scale ¹⁰⁵	X		X	
	Murray secretion scale ¹²⁷	X		X	
	Swallowing Performance Scale (SPS) ¹²⁸	X		X	
	Swallowing initiation ¹²⁹	X			
	Swedish translation of the Dynamic Imaging Grade of Swallowing Toxicity (Sw-DIGEST-FEES) ¹³⁰			X	X
Ruler	Maximum interincisal mouth opening (MIO) ¹²	X			X
Symptom specific and health related quality of life instruments	EAT-10 ¹³¹	X			
	The MD Anderson Dysphagia Inventory (MDADI) ¹²²		X		
	European Organization for Research and Treatment of Cancer Quality of Life questionnaire Core 30 (EORTC QLQ-C30) ¹²⁰		X		
	EORTC QLQ Head and Neck Module (QLQ-H&N35) ¹²¹		X		X

3.3.1 MEASURES USED IN FLEXIBLE EVALUATION OF SWALLOWING

The **PAS**, a well-established scale, is used in a majority of studies to reflect swallowing safety (Table 6).^{108,132} The scale ranges from 1 to 8 (normal to silent aspiration).¹⁰⁸ The PAS is usually used as an ordinal scale as ratings largely depend on how far into the airway penetration aspiration occurs. It also makes note of sensory response to penetration and aspiration events. A common way to report the scale is by the maximum PAS rated during the assessment or for each bolus type.

Table 6. *The Penetration Aspiration Scale (PAS).*¹⁰⁸

	PAS	
None	1	Material does not enter the airway
Penetration	2	Material enters the airway, remains above the vocal folds, and is ejected from the airway
	3	Material enters the airway, remains above the vocal folds, and is not ejected from the airway
	4	Material enters the airway, contacts the vocal folds, and is ejected from the airway
	5	Material enters the airway, contacts the vocal folds, and is not ejected from the airway
Aspiration	6	Material enters the airway, passes below the vocal folds and is ejected into the larynx or out of the airway
	7	Material enters the airway, passes below the vocal folds, and is not ejected from the trachea despite effort
	8	Material enters the airway, passes below the vocal folds, and no effort is made to eject

The **Yale pharyngeal residue severity scale** is a five-point ordinal scale ranging from no residue to severe residue. Ratings are made separately for residue in the vallecula and the pyriform sinuses. The scale is considered a valid and reliable instrument.^{105,133}

Initiation of swallowing was rated according to a four-grade scale presented in a previous study: 1 = initiation at the upper epiglottis; 2 = exceeds epiglottis or immediate initiation at pyriform sinus; 3 = initiation at pyriform recess; and 4 = no initiation of swallowing.¹²⁹

The **Murray secretion scale**, used to grade secretions in the pharynx, has been noted to predict aspiration and is considered valid and reliable.^{106,107,127} The scale ranges from 1 to 4 (no visible secretions/transient bubbles to secretions in the laryngeal vestibule).

The **Swallowing performance scale (SPS)** is an overall measure of swallowing ability based on clinicians' grading of oropharyngeal impairment, potential need of therapeutic strategies, as well as recommendations concerning oral intake. The scale ranges from 1 to 7

(normal–severe impairment) and correlates well to physician-rated swallowing ability in an HNC cohort. ^{134,135}

The **DIGEST-FEES protocol** establishes a metric for overall swallowing function using a five-point scale, the DIGEST score. This scale is adapted from the Common Terminology Criteria for Adverse Events (CTCAE), which is commonly used to assess degree of toxicity. The DIGEST score is based on a summary of two scales: DIGEST-safety and DIGEST-efficiency. The score is accompanied by a flowchart guiding the rater in the methodology. The DIGEST-safety rating considers frequency of worst PAS as well as amount and consistency of aspirated material. In the DIGEST-efficiency scale, amount of residue left in the pharynx after swallowing is rated and graded depending on type of consistency.

3.3.2 OBJECTIVE MEASUREMENT OF MOUTH OPENING ABILITY

Mouth opening ability was measured with the patient seated in an upright position. Participants were asked to stretch the jaw twice before the measurement. The maximal distance between the edge of the lower and upper incisors, measured in millimeters with a ruler, was recorded (Figure 7).



Figure 7. Measurement of maximal interincisal mouth opening.

3.3.3 SYMPTOM-SPECIFIC AND GENERAL HRQL INSTRUMENTS

All HRQL instruments used are well-known, considered valid and reliable, and are regularly used in research settings.

The **Eating Assessment Tool (EAT-10)**, reflecting patients' subjective report of swallowing function, has been found to correspond well to functional eating in HNC cohorts.^{131,136} It consists of ten items scored on a range from 0 to 4 (normal function–severe problems). Maximum score is 40 and according to normative data a score ≥ 3 is considered abnormal.¹³¹

The **EORTC QLQ-C30** was designed to evaluate clinical trials of cancer therapy and has been widely used in this capacity.¹²⁰ The instrument consists of 30 items with two single items and five functional and nine symptom scales. Scores range from 0 to 100. Higher scores represent better HRQL in the function scales and higher symptoms (i.e., worse HRQL) on the symptom scales.

The **QLQ-H&N35**, an addition to the EORTC QLQ-C30, was developed to evaluate HRQL in relation to the specific symptoms afflicting HNC patients. The instrument has been used in several research projects.¹²¹ It consists of 35 items and has seven symptom scales with scores ranging from 0 to 100. Lower scores represent better functioning.

The **MD Anderson Dysphagia Inventory (MDADI)**, is an instrument developed to measure HRQL related to swallowing ability in HNC patients.¹²² The instrument is frequently used both in clinical and research contexts.^{137,138} For example, change in MDADI total score has been noted in studies evaluating swallowing interventions and in one or several domains.^{73,139,140} In 2012, a Swedish version of MDADI was translated and validated with retained psychometric properties.¹⁴¹ MDADI consists of four domains–emotional, functional, physical, and global–with a total of 20 items. Scores range from 20 to 100, where higher scores represent better functioning.

3.4 STATISTICAL ANALYSIS

Before inclusion to cohort A and B an 80% power calculation was performed using the Mann–Whitney U test, $\alpha = 0.05$. Sample size calculations for both cohorts were based on a one-point change in PAS with a standard deviation of 1.2. For cohort B, a 5-mm change in MIO with a standard deviation of 5.8 was also considered in the calculation. In cohort A sample size calculation determined that 25 participants per group was needed (inclusion goal was set to 30 to compensate for dropouts). In cohort B the sample size was set to 40 participants in each group including a 25% dropout rate.

All statistical analyses in studies I–IV were performed using SAS version 9.4. In studies I–IV, all tests were two-tailed and non-parametric, with the significance level set to $p < 0.05$. In general statistics for tests between groups (not of primary endpoints) Fisher's exact test was used for dichotomous variables, Mantel-Haenszel chi-square trend test for ordered categorical, Chi-square test for unordered categorical variables, and Mann-Whitney U test for continuous variables. Continuous variables were described by mean, standard deviation, median, and range. Categorical variables were described using number and percentages.

Study I: The Mann–Whitney U test was used to compare the intervention and control groups for outcome variables before and after treatment. The Wilcoxon signed-rank test was used to compare change within each group at the eight-week follow-up. To calculate differences of change between the groups the Fisher non-parametric permutation test was used. Also, 95% confidence interval and effect sizes were calculated. Inter- and intra-rater reliability were calculated using exact agreement in percent, agreement within one scale step in percent, and weighted kappa statistics (κ_w).

Study II: Comparisons of reports on HRQL between the intervention and control group were calculated using Fisher's Non-Parametric Permutation Test. For within group comparisons, the Fisher's Non-Parametric Permutation test for matched pairs was used.

Study III: Correlations between Sw-DIGEST-FEES and each reference measure was calculated using Spearman correlation coefficients. Inter-

and intra-rater reliability were assessed using weighted kappa (κ_w) and exact agreement.

Study IV: The primary outcome variables were analyzed for all eligible participants according to intention-to-treat principles and multiple imputation was applied to missing data. Multiple imputation with 50 samples were performed for the primary outcome change in PAS and MIO. The imputation regression model considered baseline patient characteristics related to the primary variables and to their missingness. General linear models were applied for normally distributed outcome variables adjusted for randomization strata and baseline value of the outcome. Robustness analyses were performed to test the multiple imputation model. As there were two primary variables, the statistical significance level was set to 0.025. For all other tested variables, the statistical significance level was 0.05. The inter- and intra-rater reliability were analyzed using weighted kappa (κ_w).

3.5 ETHICAL CONSIDERATIONS

The study was approved by the Regional Ethical Review Board in Gothenburg, Sweden and was conducted according to the Declaration of Helsinki. To ensure informed consent, we provided participants both oral and written information about the study before inclusion.

4 RESULTS

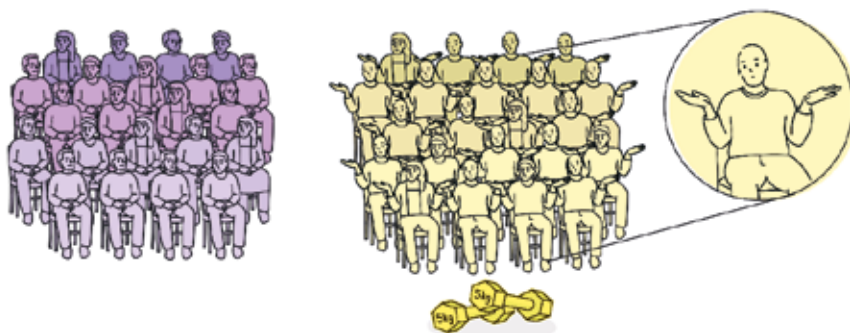


Figure 8. Illustration of the results in study I and II, the control group in purple and intervention group in yellow. Illustration by Gunilla Hagström.

4.1 STUDY I

The purpose of the study I was to determine effect of the HLE on swallowing function after an initial period of intensive intervention. Over eight weeks, the intervention group performed 87% of the prescribed isometric and isokinetic head lifts. No effect was revealed for the HLE on swallowing function when comparing the intervention and control group regarding airway invasion (i.e., PAS), residue, secretions, initiation of swallowing, and overall swallowing function. In addition, statistically significant between-group differences were not seen when comparing patient-reported swallowing function (EAT-10) (Figure 8).

There were two within group changes in the primary outcome PAS: one in favor of the intervention group (3-ml thin liquid) and one in favor of the control group (5-ml thick liquid). There was a trend towards better patient-reported swallowing function after HLE, as the intervention group had a statistically significant improvement in EAT-10 score compared to the control group

4.2 STUDY II

The purpose of study II was to evaluate the short- and long-term effect of HLE on general and dysphagia-specific HRQL. Over the first eight weeks, the participants performed 89% of the 21 recommended sessions/week. Over the following 12 months, the recommended exercise dose was lower: once per day or at least three sessions/week. During this period, participants performed in mean three sessions per week. There were no statistically significant differences between the intervention and control group in any of the included HRQL instruments (MDADI, EORTC QLQ-C30, and QLQ-H&N35) at any time.

There were some within-group differences. At the eight-week follow-up, both groups reported statistically significant better dysphagia-specific HRQL on some MDADI domains and in MDADI total score. However, only the control group still reported statistically significant better results compared to baseline at the 12-month follow-up.



Figure 9. Illustration of flexible endoscopic evaluation of swallowing (FEES). Illustration by Gunilla Hagström.

4.3 STUDY III

The purpose of the study III was to validate a Swedish translation of the DIGEST-FEES protocol (Figure 9). The forward-backward translation of the Sw-DIGEST-FEES was approved by the original developers. The construct validity analysis showed that 79% of the correlations between Sw-DIGEST-FEES ratings and reference measures were equal to or stronger than those in the original validation. Inter- and intra-rater reliability for ratings with the Sw-DIGEST-FEES were high. Inter-rater reliability varied between substantial to almost perfect (κ 0.76–0.81) and intra-rater reliability was almost perfect overall (κ 0.8–1).

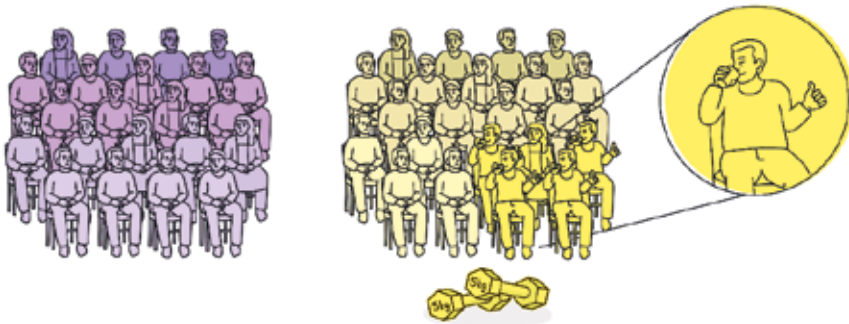


Figure 10. Illustration of results in study IV, the control group in purple, intervention group in yellow and in brighter yellow the part of the intervention group with higher adherence to the exercise protocol. Illustration by Gunilla Hagström.

4.4 STUDY IV

The purpose of the study IV was to evaluate the effect of the preventive protocol on swallowing and mouth opening function at follow-up—i.e., one month after completion of radiotherapy. Adherence to the preventive exercise protocol was 61% (58% for the tongue hold and 62% for the passive and active jaw exercise). There were no statistically significant differences for the primary outcomes PAS and MIO between the intervention and control group (Figure 10). Swallowing function deteriorated and QLQ-H&N35 symptoms were more prevalent in both groups at the one-month follow-up. Explorative analyses were performed assessing PAS and MIO according to level of adherence to the preventive exercise protocol (<50%, 50–75%, and \geq 75%). In the analysis, there was a trend towards better results for swallowing and mouth opening function for those who had done \geq 75% or more of the prescribed exercises.

5 DISCUSSION

5.1 SWALLOWING REHABILITATION

We know that dysphagia is a problem for many patients and that about half of all HNC patients have some degree of swallowing difficulty after radiotherapy. With this background, we wanted to investigate whether an intensive muscle strengthening exercise program could improve swallowing function in patients with chronic dysphagia. As previous studies, including one RCT with a mixed cohort, that included a few HNC patients showed promising results with the HLE, the HLE was chosen as the intervention for this study.^{69,79,80}

The HLE and adaptations of the HLE such as the chin tuck against resistance (CTAR) have been found to improve swallowing in stroke patients and in mixed cohorts.^{43,45,47} However, these encouraging results do not seem transferable to patients with chronic dysphagia after radiotherapy for HNC. Neither speech and language pathologists evaluating swallowing function from FEES recordings nor participants reporting on dysphagia-specific and general HRQL revealed any convincing benefits for the intervention group. Adherence to HLE was good (89%) and not a likely explanation for the lack of effect. Therefore, the effectiveness of the HLE seems to depend on the etiology of dysphagia. The results also suggest that, either it is difficult to rehabilitate the suprahyoid muscles sometime after radiotherapy or, the HLE does not address the cause of radiation induced dysphagia.

These results are in line with other studies on strength-based exercises as rehabilitation for radiation-induced dysphagia. Minor beneficial effect of strength-based exercises on chronic dysphagia have been established in the RCTs listed in Table 2b.^{75,77} It appears challenging to effect change in swallowing muscles sometime after radiotherapy, most likely due to changes in muscle composition such as fibrosis and atrophy.¹¹ However, increases in muscle strength have been established after six weeks of CTAR exercise with the Swallowing Exercise Aid (SEA), a device that made it possible to progressively increase the resistance. Half of the participants (n = 10) had increases in strength measured by a dynamometer.¹⁴² However, the increase in muscle strength did not improve PAS, residue ratings, or swallowing

kinematics and did not enable patients to eat a more varied diet. The authors discuss whether the treatment period was too short, but they note that most improvement in muscle strength took place during the first week of treatment and that it is uncertain whether continued exercise would build more strength. Some participants had larger increases in strength, and the authors discuss that this subgroup might gain more benefit from the exercise and possibly from longer treatment periods.¹⁴² A retrospective case study indicates that strength-based exercises as rehabilitation can improve swallowing function. Patients with chronic dysphagia after radiotherapy (>8 years post treatment) who aspirated on VFS (PAS \geq 6) significantly improved their swallowing safety after eight weeks of expiratory muscle strength training (EMST).¹⁴³

Based on the hypothesis that electrical stimulation could help rehabilitate or strengthen fibrotic muscle tissue in HNC patients, two RCTs evaluated swallowing exercises in combination with electrical stimulation. Between the groups, one positive difference was found (increased velocity in the hyoid bone) and one negative (worse PAS primarily on thin liquid swallows).^{74,76} In addition, electrical stimulation as part of dysphagia therapy for HNC was evaluated in a meta-analysis based on four studies; however, these studies found no convincing effects.¹⁴⁴ The authors did conclude that the settings that stimulate the muscle type responsible for faster contractions would be worth examining and that so far only electrical stimulation of slower muscle fiber has been examined.

In summary, there is no evidence-based treatment for patients who have developed permanent swallowing difficulties after radiotherapy. Focus on dysphagia management largely comprises diet modifications and swallowing maneuvers or head positionings when appropriate.

5.2 DYSPHAGIA PREVENTION

Given that swallowing function is difficult to rehabilitate once it has reached a chronic state, effective preventive intervention would be highly valuable. The consensus among experts in the field of radiation-induced dysphagia is that preventive exercises have the potential to counteract swallowing difficulties, but that more high-quality evidence is needed.⁸⁷ For the RCT in study IV, the intention was to design a

simple, convenient, and effective preventive exercise protocol targeting swallowing function and mouth opening. Unfortunately, this notion could not be substantiated by the short-term results of intervention presented in study IV.

Adhering to preventive exercises is challenging for patients as many are simultaneously suffering from severe side effects after treatment. Consequently, low adherence has limited the possibility to evaluate the impact of interventions. There are reports of participants performing 38–78% of the prescribed exercises.^{54,70-73} Designing a less extensive exercise protocol was hypothesized to increase adherence rates. It seems that even though the exercise protocol was less extensive, participants still found it hard to perform during the second half of radiotherapy— i.e., when side effects are increasing. The overall adherence to the exercise protocol was 61% and adherence was lowest from week four to end of radiotherapy.

High adherence to prescribed exercises have been linked to better swallowing and mouth opening outcomes.¹⁴⁵⁻¹⁴⁸ Swallowing and mouth opening outcomes for the high adherence group ($\geq 75\%$ of the exercise protocol) compared to the control group were better and lend some support to this notion (mean change PAS 0.4 vs 1.4 and MIO -2.8 mm vs -7.0 , respectively). In light of these data, efforts to improve adherence are relevant and need further exploration.

Hajdu et al. report comparatively high adherence rates, 78%, for their preventive intervention. Their exercise protocol was individualized and performed at home and in face-to-face weekly exercise sessions. The authors suggest that the opportunity to motivate and explain the rationale of the exercises was an integral part of the adherence results.¹⁴⁹ In study IV, knowledge of swallowing impairment might have increased motivation to the preventive exercise protocol. The speech and language pathologists performing the FEES gave feedback and advice to all participants after the assessment. The high adherence group had a more impaired swallowing function at baseline (mean PAS = 2.7) compared to the low and moderate group (mean PAS = 1.4 and 2.1, respectively). Further analysis of the adherence group revealed that the high group had in fact done 92% of the prescribed exercises during the intervention period—i.e., the high group was able to exercise between week four and end of radiotherapy. The low and moderate

adherence group had in mean performed 24% and 53% of exercises, respectively. One might suggest that differences in adherence depended on level of radiation toxicity; however, toxicity and performance ratings were reviewed without any evident differences between groups. This finding suggests that perceiving the exercises as important might help patients persevere during the critical weeks of severe radiation toxicities. Also, a study found that one of the most common reasons for not adhering to preventive exercises was that the participants thought there was no need because they did not experience swallowing difficulties at the time.¹⁴⁰ Making sure that patients meet with speech and language pathologists regularly during radiotherapy could be a way to motivate patients and emphasize the importance of the exercises. Regular meetings with speech and language pathologists could enhance adherence in future studies trying to establish the effectiveness of preventive swallowing exercises.

Exercise dose is also fundamental for the effect of an intervention. Dose comprises repetitions per set, intensity (i.e., percent of maximal effort in each repetition and duration of a sustained hold), and frequency of sets per day or week.⁸⁸ The prescribed doses vary considerably between preventive exercise protocols. Therefore, a reported adherence to exercises can reflect quite different doses. Presently, we do not know what dose is required to effect a change in rehabilitative or preventive exercise protocols for radiation-induced dysphagia.⁸⁸ The dose in the preventive protocol investigated in study IV is comparatively low, consisting of one swallowing exercise and passive and active jaw stretches. Many other preventive protocols include several swallowing exercises in one treatment session, and these are often repeated several times a day.⁸⁸ As the goal of preventive exercises is to preserve a function, not to improve an impaired function, and one session three times per week has been seen to build strength in limb muscles, this dose was chosen for the tongue hold exercise.¹⁵⁰ Doses for the jaw-exercises were based on a structured exercise protocol with positive results for chronic mouth opening restrictions, considering that the goal was to preserve a function.^{58,59} The overall adherence rate of 61% makes it difficult to evaluate whether this dose was enough to effect change on swallowing and mouth opening function.

Some positive effects on swallowing function could have been reached in both the intervention and control group by encouraging all

participants to keep eating and drinking as much as possible during radiotherapy. A secondary analysis of prospectively collected data from 595 HNC patients established an effect on swallowing function for both preventive exercises and ability to keep up some oral intake during radiotherapy.¹⁰³ The preventive exercises consisted of jaw stretch, Mendelsohn maneuver, supraglottic swallow, the tongue hold, and the effortful swallowing. Patients who had kept up some oral intake during treatment and those who did swallowing exercises were two and three times, respectively, more likely to manage eating solid food three to six months post treatment compared to those who had not. Long-term results (18–24 months post treatment) revealed that those who had exercised were still twice as likely to manage solid food compared to those who had not, while the effect of oral intake during treatment had levelled off. Analyses were adjusted for tumor and treatment characteristics as well as baseline diet. The results lend support to a previous large retrospective study where both level of oral diet and exercise during radiotherapy was associated to more complex diet long-term and less time using a feeding tube.⁹¹

Furthermore, the ability of the protocol to prevent chronic dysphagia needs long-term evaluation. The protocol intends to prevent muscle changes due to fibrosis and atrophy, which might not have fully developed.¹⁵¹ Also, many participants were affected by acute toxicities following the radiotherapy, for example, edema at the one-month follow-up, which might have influenced the swallowing function. In addition, it is possible that a protocol with a higher dose or another swallowing exercise would have had better results. A review by Vester et al. lists the most prescribed preventive exercises, which are strength and range of motion and exercises for the tongue, the tongue hold exercise, and the effortful swallow.⁸²

5.3 TRISMUS PREVENTION

The development in radiation technique over the last decades seems to have had positive impact on the prevalence of trismus. Comparison between a cohort treated with either 3D-CRT or IMRT and a cohort treated with VMAT reported a reduced rate of trismus the first 12 months after radiotherapy, from 61% to 9%.¹⁰ Studies comparing prevalence of dysphagia between patients treated during a period when mainly older techniques were used to periods when IMRT dominated

have not noted the same clear reduction.^{7,152} However, it is worth noting that the cohorts comparing dysphagia prevalence are not as current as the one on trismus and might not have the same benefits of other advances in treatment planning.

This positive trend is applicable to the participants in study IV as they were treated with VMAT. Consequently, the number of participants at risk of developing a restricted mouth opening was lower than expected at the time the study was planned. Few participants in study IV developed trismus—6% in the intervention group and 18% in the control group. This finding might explain the lack of effect of the jaw exercise. These results from study IV are in line with several other studies evaluating outcomes on mouth opening from preventive exercises.^{93,100,153} Positive and lasting effects of trismus rehabilitation with a jaw-stretching device have been found in participants with established trismus post radiotherapy.^{58,59,61}

Despite that both radiation-induced dysphagia and mouth opening restriction are hypothesized to develop due to fibrosis and atrophy, the most beneficial time for strength-based intervention appears to differ between them. For chronic conditions, mouth opening seems more susceptible to intervention while improving swallowing function has proven to be challenging. On the contrary, for preventive intervention there are more indication of positive effects on swallowing function. However, a recent publication using a part of cohort B found that the preventive intervention during radiotherapy resulted in less pain and temporomandibular joint difficulties as well as less reduction in MIO up to 12 months following radiotherapy.¹⁵⁴

5.4 OUTCOME MEASURES

Instrumental assessment is a more reliable tool than clinical assessment to measure swallowing function, especially when assessing penetration and aspiration. Despite this, a recent review reported that only 30% of research studies used instrumental assessment to evaluate swallowing function for patients with oropharyngeal cancer.¹⁵⁵ However, instrumental assessment is not objective, as the evaluations depend on the rater's judgement and on the reliability and validity of the outcome measures used to describe swallowing function. Outcome measures for instrumental assessments have been critiqued for lacking

robust psychometrical testing and mainly focusing on the reliability of the measurement rather than the validity of the instrument.¹⁰⁹

PAS is a well-established and used in both FEES and VFS to measure swallowing safety, but the scale has some inherent problems.^{108,132} PAS is ordinal in terms of how far into the airway the bolus passes but not necessarily in terms of the severity of the penetration or aspiration event. For example, aspiration that occurs but is expelled from the airway by coughing or clearing the throat might be less severe than penetration left on the vocal folds without any sensory response (i.e., no reaction to clear the airway). Furthermore, the amount of penetration or aspiration also matters when determining the impact of the safety impairment to the patients' health.¹⁵⁶ In addition, there is no consensus on how to report PAS, but a majority of studies use the worst PAS rating to describe the swallowing function.¹³²

The measurements included in study I were chosen because of their comparatively sound psychometrical properties, and five different measurements were used to evaluate swallowing function. This illustrates a challenge within the research field. There is no consensus on which outcome measures to use and studies on dysphagia intervention are often small.¹⁰² The heterogeneity in outcome measures is unfortunate, as it is an obstacle to comparison of results between studies and a challenge for researchers compiling meta-analyses.^{102,157,158} In response to these challenges, it is suggested to develop core outcome sets for dysphagia evaluation and recently a core outcome set of seven items was established for patient-reported outcome measures in HNC.^{102,159}

Outcome measurements such as the DIGEST-FEES have sound psychometrical properties, ensuring that ratings are consistent and that they measure the intended aspects.¹¹¹ An important advantage of the DIGEST-FEES is that it includes several aspects of swallowing, including safety, efficiency, and overall function, within a single system. In study IV, swallowing function was described using two outcome measures, Sw-DIGEST-FEES and PAS. The DIGEST-safety scale is based on PAS and considers how much of the bolus is aspirated or penetrating the larynx and how often it occurs as well as sensory response. Therefore, the ordinal properties concerning swallowing safety are improved compared to PAS.

Increased use of the DIGEST-FEES for swallowing function could help researchers compare results across studies. Also, consistent clinical use could provide a basis for retrospective studies and larger sample sizes. In short, the DIGEST-FEES could be a good candidate as part of a core outcome set for HNC trials.

5.4.1 HEALTH-RELATED QUALITY OF LIFE INSTRUMENTS

Patient-reported swallowing function and ratings based on instrumental assessment generally have weak correlations.¹⁶⁰⁻¹⁶² The use of HRQL instruments adds a valuable perspective to dysphagia evaluation. It is recommended to use both instrumental and patient-reported outcomes of swallowing ability to evaluate an intervention, as was done for the HLE in study I–II and the preventive protocol in study IV.^{18,163} It is also important that the HRQL are sensitive enough to reflect differences between groups, aspects that have been determined for MDADI, EORTC-C30, and H&N-35.^{38,120,121}

The results in study I and IV suggest that HRQL measurements might be influenced by patient expectation. In both studies, FEES assessment could not establish any differences between patients at follow-up compared to baseline, but the HLE participants reported a positive change after eight weeks of intervention and the preventive exercise group had worse function than the control group at the one-month follow-up. These findings should be considered in studies where the active control is not blinded and in clinical settings if patient report is used to evaluate an intervention. Hajdu et al. also reported better results on variables of well-being after intervention within the intervention but not on swallowing function assessed by FEES. As in study I, patients had in-person exercise sessions. These results suggest that support by a dysphagia specialist might benefit HRQL.

Concerning trismus, improved mouth opening measurements have been connected to better reports in HRQL instruments, which adds to understanding of the impact of mouth opening on HRQL. In study IV, few participants developed trismus, in either group, so it is difficult to draw conclusions on how this might have impacted the HRQL outcomes. However, more severely impacted HRQL has been reported for HNC patients suffering from trismus after radiotherapy compared to those who are not.³⁴ Also, increasing reports of pain were detected

over time.³⁴ Positive impact on pain has been reported by improvements in mouth opening by structured exercise ⁵⁸. Better mouth opening ability due to structured exercise has also been found to result in improved general and trismus-specific HRQL^{59,61}

5.5 LIMITATIONS

There were some limitations within the studies. Cohort A, for example, may be limited by the inclusion of participants with PAS 2 or higher, leading to participants with a range of difficulties from mild to severe. Furthermore, the patients who could not swallow at all were excluded. Therefore, the HLE has not been evaluated for participants with the most severe difficulties. However, as the HLE appears to have very slight to no effect on swallowing difficulties induced by radiotherapy, it seems unlikely that HLE would benefit patients with even more impaired function.

Another limitation may be that there was a slightly higher drop-out rate than anticipated in study I. Sample size calculations were based on 50 participants, taking a 20% dropout rate into account. In the follow-up FEES, 47 patients participated. In study II, 52 participants reported their HRQL at the eight-week follow-up and 43 at the 12-month follow-up. Dropout analysis was performed to evaluate attrition bias. No statistically significant differences were found in study I. In study II, two differences were noted among dropouts at the 12-month follow-up—i.e., a higher proportion of hypopharyngeal cancer and no dropouts had brachytherapy. These differences could have skewed the results.

Considering HRQL, reports could have been impacted by the fact that participants in cohort A and B knew that they were part of the intervention group, which might have created expectations influencing reports either positively or negatively. The speech and language pathologists who rated swallowing function based on FEES recordings were blinded to participant allocation and time since treatment. This blinding is considered a strength in the study design.

Concerning the validation of Sw-DIGEST-FEES, the cohort is the same as in study I-II and did not include patients who could not swallow at all and those surgically treated for HNC. The validation did not include

evaluation of sensitivity, responsiveness, and content validity as this has been done by others on corresponding cohorts.^{110,111,164}

A limitation in study IV might be the time of follow-up (i.e., one month post radiotherapy). Differences in mouth opening might have been too early to detect. Therefore, a later follow-up might reveal different results. Also, swallowing function might be impacted by acute side effects such as lymphedema and effects of the intervention might become evident over time.¹⁶⁵ A higher adherence rate to the exercise protocol would have been preferable as this would have improved the certainty of the evaluation.

6 CONCLUSIONS

This thesis contributes to new knowledge concerning intervention for radiation-induced dysphagia and trismus by the use of two randomized controlled trials. It also adds a valuable new assessment tool for FEES for Swedish dysphagia practitioners working with HNC patients.

No effect could be determined for the HLE on swallowing function assessed by FEES after eight-weeks of intensive intervention. In addition, no short- or long-term effect on HRQL could be established for HLE. The consistency of the results makes it possible to conclude with a relatively high degree of certainty that HLE is not a suitable treatment method for patients with chronic radiation-induced dysphagia. This finding should be addressed in clinical guidelines concerning rehabilitation of chronic radiation-induced dysphagia. The HLE was previously mentioned in the Swedish guidelines for HNC care in the context of managing chronic dysphagia but has now been omitted.⁵

Concerning the preventive exercise protocol, no short-term effect could be established for swallowing and mouth opening function. However, there was a trend towards better results for participants who had adhered to $\geq 75\%$ of the exercise protocol. Long-term outcomes need further exploration.

The validation of the Sw-DIGEST-FEES revealed sound psychometrical properties. Consequently, the Sw-DIGEST-FEES is a valid and reliable protocol, which can be used by Swedish clinicians and researchers to evaluate swallowing function in HNC patients.

7 CLINICAL IMPLICATIONS

- ❖ The HLE is not suitable for rehabilitation of radiation-induced dysphagia among HNC patients.
- ❖ The preventive protocol consisting of the tongue hold exercise and passive and active jaw-stretch with a Jaw-Trainer might improve swallowing and mouth opening function if patients adhere to the exercises.
- ❖ The Sw-DIGEST-FEES could be used to standardize FEES and to improve reliability and validity of swallowing assessment in both research and clinical settings for the HNC population.

8 FUTURE PERSPECTIVES

The results in this thesis underline that we need more research studies on intervention for radiation-induced dysphagia and restricted mouth opening for HNC. For patients who develop chronic dysphagia, we have little evidence-based treatments to offer other than compensatory strategies that make swallowing safer and easier. As chronic dysphagia might impact HRQL negatively, effective treatment that improves swallowing function is preferable.

Preventive exercises seem more promising. Therefore, understanding how to improve adherence to preventive exercises during a course of radiotherapy is essential to improving mouth opening function and swallowing. The majority of patients did not experience any difficulties before radiotherapy and might need repeated information on the rationale of the exercises. More support and face-to-face sessions might improve adherence to preventive exercises during radiotherapy. Also, to increase the exercise dose over the whole intervention period, health care providers might need to offer recommendations where the patient can choose a dose depending on their daily form. For example, a higher dose for good days, where the patient does more repetitions and sessions, a medium and a low dose for bad days, where any repetition or session might be the only attainable goal. Furthermore, it seems valuable to plan for analysis of effect based on level of adherence concerning preventive swallowing and mouth opening exercises in addition to the whole intervention group.

A core outcome set in the research area would also help comparison of results between studies and make for better meta-analyses. For example, the DIGEST-FEES and MDADI could be used as they are both developed for the HNC population. Additions to the core outcome set could be made to fit other purposes of the research question. The focus on robust psychometrical testing of outcome measures in swallowing research is positive and will increase the certainty of measures.

Finally, as preventive exercises are part of routine dysphagia management in many facilities, few studies are able to compare outcomes to a non-active control.^{73,153} The outcomes on DIGEST-FEES, PAS, and MIO in study IV from a non-active control group treated with

modern radiation technique, might help other researchers compare results.

9 ACKNOWLEDGEMENTS

I would like to express my gratitude to everyone who has helped me during the work with this thesis.

Lisa Tuomi, for always answering the phone to give insightful advice, guidance and encouragement, many times even while biking. A truly dedicated and supportive main supervisor.

Caterina Finizia, assistant supervisor, for giving me the opportunity to work with research. Also, for your sharp eye for details and for generously sharing your great knowledge and enthusiasm for research. It has been inspirational.

Nina Pauli, assistant supervisor, for your in-depth knowledge of head and neck cancer, careful editing and for conveying calm and confidence.

Hans Dotevall, co-author, for committedly sharing your expertise on swallowing disorders both in clinical and research settings.

To everyone in the research group, who has put great effort and dedication into collecting the data.

To all the participants, for generously sharing your experiences and taking the time to contribute to the research projects.

Johanna Moreno, for your positive attitude, helpfulness and all the laughter. The follow-ups would not have been as fun without you.

To all my wonderful colleagues at the speech and language pathology department. I don't think I have ever been at work without laughing. It is a privilege to have such warm and supportive colleagues.

To my parents, for all the support and love in our everyday life. You have made my work with this thesis possible.

To my brother, for your positive attitude in all kinds of ventures, building projects and life in general.

To Nille and Carina, thank you for all the support and invaluable care, you are so precious in our lives.

To my friends, you light up my life! I am so grateful to have you.

To Anders, for your love and patience. Always happy to try to solve any challenge. **To Ingrid and Hilma**, for being so lovely.

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11 APPENDIX

INSTRUKTION: Detta formulär handlar om hur Du uppfattar Dina problem med att äta, dricka och svälja och hur Du tycker att det påverkar Dig. Besvara frågorna genom att ringa in det svarsalternativ Du tycker stämmer bäst in på Din situation de senaste 7 dagarna. Om Du är osäker, markera det alternativ som känns mest riktigt.

		Stämmer precis	Stämmer ganska bra	Osäker/ har ingen åsikt	Stämmer inte särskilt bra	Stämmer inte alls
1.	Mina vardagsaktiviteter begränsas av mina problem med att äta, dricka, svälja	1	2	3	4	5
E2.	Jag är generad över mitt ätande	1	2	3	4	5
E4.	Jag blir upprörd, illa berörd av mina problem med att äta, dricka, svälja	1	2	3	4	5
F1.	Det är svårt för andra att laga mat åt mig	1	2	3	4	5
P2.	Det är svårare att äta, dricka, svälja mot slutet av dagen	1	2	3	4	5
E7.	Jag känner mig besvärad när jag äter, dricker, sväljer	1	2	3	4	5
F5.	Jag har fått lägre inkomster på grund av mina problem med att äta, dricka, svälja	1	2	3	4	5
P3.	Andra frågar "Varför kan du inte äta det?"	1	2	3	4	5
P7.	Det tar längre tid för mig att äta på grund av mina problem med att äta, dricka, svälja	1	2	3	4	5
E3.	Andra blir irriterade på mina ätproblem	1	2	3	4	5
E6.	Jag har dålig självkänsla på grund av mina problem med att äta, dricka, svälja	1	2	3	4	5

	Stämmer precis	Stämmer ganska bra	Osäker/ har ingen åsikt	Stämmer inte särskilt bra	Stämmer inte alls
P8. Jag hostar när jag försöker dricka	1	2	3	4	5
F3. Mitt privata och sociala liv begränsas av mina problem med att äta, dricka, svälja	1	2	3	4	5
F2. Jag har problem med att gå ut och äta med vänner, grannar eller släktingar	1	2	3	4	5
P6. Det är ansträngande att äta, dricka, svälja	1	2	3	4	5
E5. Jag går inte ut på grund av mina sväljningsproblem	1	2	3	4	5
P5. Jag begränsar mitt födointag på grund av mina problem med att äta, dricka, svälja	1	2	3	4	5
F4. Jag känner mig utanför på grund av mina ätproblem	1	2	3	4	5
P1. Jag kan inte behålla min vikt på grund av mina problem med att äta, dricka, svälja	1	2	3	4	5
P4. Det känns som om jag sväljer för mycket mat åt gången	1	2	3	4	5
X1. Det gör ont när jag äter, dricker, sväljer	1	2	3	4	5
X2. Maten fastnar när jag sväljer	1	2	3	4	5
X3. Jag har svårt att svälja för att jag är torr i munnen och halsen	1	2	3	4	5
X4. Jag måste skölja ned det jag äter för att kunna svälja	1	2	3	4	5

TACK FÖR DIN MEDVERKAN !

Frågeformulär om sväljningsproblem					EAT 10
Ringa in det svarsalternativ som passar bäst in på dina problem					
I vilken utsträckning är följande situationer problematiska för dig?	Inga problem			Svåra problem	
1. Mina problem att äta, dricka och svälja har fått mig att gå ned i vikt	0	1	2	3	4
2. Mina problem att äta, dricka och svälja inverkar på min förmåga att gå ut och äta	0	1	2	3	4
3. Det är extra ansträngande att svälja vätska	0	1	2	3	4
4. Det är extra ansträngande att svälja fast föda	0	1	2	3	4
5. Det är extra ansträngande att svälja tabletter	0	1	2	3	4
6. Det gör ont att svälja	0	1	2	3	4
7. Nöjet med att äta påverkas av min sväljning	0	1	2	3	4
8. När jag sväljer fastnar mat i halsen	0	1	2	3	4
9. Jag hostar när jag äter	0	1	2	3	4
10. Det är stressande att svälja	0	1	2	3	4
Summa per kolumn					
Totalsumma					

EORTC QLQ C30 (version 3.0.)

Vi är intresserade av några saker som har med Dig och Din hälsa att göra. Besvara alla frågor genom att sätta en ring runt den siffra som stämmer bäst in på Dig.

Det finns inga svar som är "rätt" eller 'fel'.

Den information Du lämnar kommer att hållas strikt konfidentiell.

	Inte alls	Lite	En hel del	Mycket
1. Har Du svårt att göra ansträngande saker, som att bära en tung kasse eller väska ?	1	2	3	4
2. Har Du svårt att ta en <u>lång</u> promenad ?	1	2	3	4
3. Har Du svårt att ta en <u>kort</u> promenad utomhus ?	1	2	3	4
4. Måste Du sitta eller ligga på dagarna ?	1	2	3	4
5. Behöver Du hjälp med att äta, klä Dig, tvätta Dig eller gå på toaletten ?	1	2	3	4
Under veckan som gått:	Inte alls	Lite	En hel del	Mycket
6. Har Du varit begränsad i Dina möjligheter att utföra antingen Ditt förvärvsarbete eller andra dagliga aktiviteter ?	1	2	3	4
7. Har Du varit begränsad i Dina möjligheter att utöva Dina hobbies eller andra fritidssysselsättningar ?	1	2	3	4
8. Har Du blivit andfädd ?	1	2	3	4
9. Har Du haft ont ?	1	2	3	4
10. Har Du behövt vila ?	1	2	3	4
11. Har Du haft svårt att sova ?	1	2	3	4
12. Har Du känt dig svag ?	1	2	3	4
13. Har Du haft dålig aptit ?	1	2	3	4
14. Har Du känt dig illamående ?	1	2	3	4
15. Har Du kräkts ?	1	2	3	4
16. Har Du varit förstoppad ?	1	2	3	4

Fortsätt på nästa sida

Under veckan som gått:	Inte alls	Lite	En hel del	Mycket
17. Har Du haft diarré ?	1	2	3	4
18. Har Du varit trött ?	1	2	3	4
19. Har Dina dagliga aktiviteter påverkats av smärta ?	1	2	3	4
20. Har Du haft svårt att koncentrera Dig, t.ex. läsa tidningen eller se på TV ?	1	2	3	4
21. Har Du känt Dig spänd ?	1	2	3	4
22. Har Du oroat Dig ?	1	2	3	4
23. Har Du känt Dig irriterad ?	1	2	3	4
24. Har Du känt Dig nedstämd ?	1	2	3	4
25. Har Du haft svårt att komma ihåg saker ?	1	2	3	4
26. Har Ditt fysiska tillstånd eller den medicinska behandlingen stört Ditt <u>familjeliv</u> ?	1	2	3	4
27. Har Ditt fysiska tillstånd eller den medicinska behandlingen stört Dina <u>sociala</u> aktiviteter ?	1	2	3	4
28. Har Ditt fysiska tillstånd eller den medicinska behandlingen gjort att Du fått ekonomiska ? svårigheter ?	1	2	3	4

Sätt en ring runt den siffran mellan 1 och 7 som stämmer bäst in på Dig för följande frågor:

29. Hur skulle Du vilja beskriva Din hälsa totalt sett under den vecka som gått ?

1	2	3	4	5	6	7
Mycket dålig						Utmärkt

30. Hur skulle Du vilja beskriva Din totala livskvalitet under den vecka som gått ?

1	2	3	4	5	6	7
Mycket dålig						Utmärkt

Patienter uppger ibland att de har följande symptom eller problem.

Var vänlig och ange i vilken grad Du har haft dessa besvär under veckan som gått.

Sätt en ring runt den siffra som stämmer för Dig.

Under veckan som gått:	Inte alls	Lite	En hel del	Mycket
31. Har Du haft smärtor i munnen ?	1	2	3	4
32. Har Du haft smärtor i käken ?	1	2	3	4
33. Har Du haft sveda i munnen ?	1	2	3	4
34. Har Du haft smärtor i svalget ?	1	2	3	4
35. Har Du haft problem med att svälja flytande ?	1	2	3	4
36. Har Du haft problem med att svälja mosad mat ?	1	2	3	4
37. Har Du haft problem med att svälja fast föda ?	1	2	3	4
38. Har Du "satt i halsen" när Du svalt ?	1	2	3	4
39. Har Du haft problem med tänderna ?	1	2	3	4
40. Har Du haft problem med att gapa ?	1	2	3	4
41. Har Du varit torr i munnen ?	1	2	3	4
42. Har saliven varit seg ?	1	2	3	4
43. Har Du haft problem med luktsinnet ?	1	2	3	4
44. Har Du haft problem med smaksinnet ?	1	2	3	4
45. Har Du hostat ?	1	2	3	4
46. Har Du varit hes ?	1	2	3	4
47. Har Du känt Dig sjuk ?	1	2	3	4
48. Har Ditt utseende besvärat Dig ?	1	2	3	4

Under veckan som gått:	Inte alls	Lite	En hel del	Mycket
49. Har Du haft problem med att äta ?	1	2	3	4
50. Har Du haft svårt att äta inför familjen ?	1	2	3	4
51. Har Du haft svårt att äta inför andra människor ?	1	2	3	4
52. Har Du haft svårt att njuta av måltiderna ?	1	2	3	4
53. Har Du haft svårt att prata med andra människor ?	1	2	3	4
54. Har Du haft problem med att prata i telefon ?	1	2	3	4
55. Har Du haft svårt att umgås med Din familj ?	1	2	3	4
56. Har Du haft svårt att umgås med Dina vänner ?	1	2	3	4
57. Har Du haft svårt för att gå ut offentligt bland andra människor ?	1	2	3	4
58. Har Du haft svårt för fysisk kontakt med Din familj eller Dina vänner ?	1	2	3	4
59. Har Du känt Dig mindre intresserad av sex ?	1	2	3	4
60. Har Du känt mindre sexuell njutning ?	1	2	3	4

Under veckan som gått:	Nej	Ja
61. Har Du använt smärtstillande mediciner ?	1	2
62. Har Du tagit något näringstillskott (förutom vitaminer) ?	1	2
63. Har Du haft matsond ?	1	2
64. Har Du gått ner i vikt ?	1	2
65. Har Du gått upp i vikt ?	1	2

Bedömare:

Sample:

Flödesschema DIGEST-FUS

Skattning av säkerhet

Maxpoäng på penetrations-aspirationsskalan (PAS)

- Maximal PAS över samtliga bolussväljningar

- Basera skattningen på bolusgivor i konsistenserna flytande (IDDSI 0-3), puré/timbal (IDDSI 4) och fast (kex/kaka (IDDSI 7))

- Skatta ej sväljningar efter att strategier tillämpats.

PAS: 1-2

Ingen pen/asp eller övergående penetration ovan stämbanden → Grad 0

PAS: 3-4

Tyst penetration ovan stämbandsnivå eller övergående penetration till stämbandsnivå
→ Enstaka händelse → Grad 0
→ Intermittent eller kronisk → Grad 1

PAS: 5-6

Tyst penetration till stämbandsnivå eller övergående aspiration
→ Enstaka händelse, ej riklig → Grad 1
→ Intermittent eller kronisk → Grad 2

PAS: 7-8

Aspiration renas ej, tyst eller trots ansträngning
→ Enstaka händelse, ej riklig → Grad 1
→ Intermittent, ej riklig → Grad 2
→ Kronisk, ej riklig → Grad 3
→ Riklig, ej kronisk → Grad 3
→ Kronisk och riklig → Grad 4

Om någon ytterligare bolussväljning(ar) ger PAS=5-6, skatta som grad 2

Faktorer som tillsammans med PAS reglerar skattning av säkerhet (frekvens/mängd)

Säkerhetsgrad

Frekvens/mönster för PAS - vid max PAS ≥ 3 (PAS 3-4, 5-6 or PAS 7-8)

- Enstaka händelse
- Enstaka+ (enbart vid max PAS 7-8)
- Intermittent (vid flera, men <50% av bolussväljningarna vid en enda konsistens)
- Kronisk (majoriteten (≥ 50 %) av tunnflytande bolussväljningar och/eller vid > 1 konsistens)

Mängd av penetration/aspiration - vid max PAS ≥ 5

- Spår av (liknar diskret beläggning, droppar eller minimal mängd som spripar ned på/under stämbanden)
- Varken spår av eller riklig
- Riklig (> 25% av bolusvolymen)

1= lätt

2=måttlig

3=grav

4=mycket grav/livshotande

Skattning av effektivitet

Maximal andel av faryngeal retention

- Maximal uppskattad andel av bolus i farynx över samtliga bolussväljningar

- Basera skattningen på bolusgivor i konsistenserna flytande (IDDSI 0-3), puré/timbal (IDDSI 4) och fast (kex/kaka (IDDSI 7))

- Basera skattningen på uppskattad andel faryngeal retention efter första sväljförsöket för varje bolus (generellt, hur mycket retention ser du?)

- Skatta ej (bolus)sväljningar efter att strategier tillämpats.

Retentionsmönster (över samtliga bolussväljningar)

Effektivitetsgrad

<10% retention → Ses för samtliga bolustyper → Grad 0
"minimal till ingen retention"

10%-33% retention → Oavsett bolustyp (tunnflytande, lätt trögflytande, puré/timbal och kex/kaka) → Grad 1
"mindre än 1/3"

34%-66% retention → Kex och/eller kaka → Grad 2
"större delen"
→ Flytande och/eller puré/timbal → Grad 3

>66% retention → På någon/några (men inte samtliga) bolustyper → Grad 3
"nästan allt"
→ Ses för samtliga bolustyper → Grad 4

DIGEST-poäng (sammantagen gradering av säkerhet och effektivitet)

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

1= lätt

2= måttlig

3= grav

4= livshotande