Radiation-induced dysphagia in head and neck cancer

Risk structures and methodological aspects

Johanna Hedström

Department of Otorhinolaryngology
Institute of Clinical Sciences
Sahlgrenska Academy, University of Gothenburg

UNIVERSITY OF GOTHENBURG

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johanna.hedstrom@vgregion.se

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“Whatever you can do or dream you can do, begin it. Boldness has genius, power and magic in it.”

- Johann Wolfgang von Goethe

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ABSTRACT

Background/Aims
Swallowing difficulties are common after radiation therapy (RT) in head and neck cancer (HNC). The overall aim of this thesis was to address radiation-induced late dysphagia with regard to investigating anatomical risk structures related to the development of radiation-induced dysphagia, as well as methodological aspects in the evaluation of swallowing. Another objective was to translate and validate the quality of care instrument Swallowing Quality of Care questionnaire (SWAL-CARE) in a mixed Swedish dysphagia population.

Methods
The studies were conducted at the Sahlgenska University Hospital and included patients from the otorhinolaryngology clinic. In study I-III, patients who had received curative (chemo)RT for HNC underwent a videofluoroscopic examination of swallowing function (VFS) 6-36 months post-RT. Dysphagia severity was measured according to the Penetration-Aspiration Scale (PAS). All patients answered questions regarding difficulties when drinking, eating, swallowing and coughing when eating/drinking (DESdC). **Study I** included 38 patients, and the VFS protocol included six boluses of different consistencies and sizes and two swallowing attempts per bolus. Comparisons were made regarding differences in PAS score between the first and second swallowing attempt for the respective boluses. **Study II** included 118 patients, and associations between DESdC and PAS scores were determined. **Study III** included 90 patients with delineation of potential risk structures for

radiation-induced dysphagia. Associations between radiation dose and dysphagia severity were evaluated and relevant dose predictors were identified. In **Study IV**, translation and validation of the SWAL-CARE was performed. Field testing was conducted including 100 patients with oropharyngeal dysphagia.

Results
In **Study I**, no differences were found between the first and second swallow attempt in VFS regarding PAS score, however large intra-individual dispersion was found. In **Study II**, a discrepancy regarding the severity of self-reported swallowing difficulties and instrumentally measured dysphagia was found. However, half of the patients who reported occurrence of at least three dysphagia symptoms (DESdC) also demonstrated high PAS score (≥6). In **Study III**, the mean dose to the epiglottis had the best discriminative ability for severe dysphagia (PAS≥6). Doses to the larynx and the contralateral submandibular gland as well as the parotid gland were also of importance. In **Study IV**, the validation of the S-SWAL-CARE demonstrated high validity and good internal consistency.

Conclusion
In order to test the swallowing safety, the highest PAS score should be reported in VFS. Furthermore, if a patient reports difficulties eating, drinking and swallowing when asked direct questions it is likely that the patient will present with moderate to severe dysphagia according to PAS. In addition to established dysphagia organs-at-risk (OARs), our data suggest that epiglottic and submandibular gland doses are important for swallowing function post-RT. Finally, the S-SWAL-CARE can be considered a reliable and valid tool to assess the dysphagia-related quality of care.

Keywords: head and neck neoplasms; radiation therapy; dysphagia; videofluoroscopy; Penetration-Aspiration Scale (PAS); patient-reported outcomes (PRO); Quality of Care; validation studies.

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SAMMANFATTNING PÅ SVENSKA

Bakgrund
Huvudhalscancer (HNC) är den åttonde vanligaste cancerformen i världen och i Sverige diagnosticeras ca 1500 personer årligen. Tumörer i huvudhalsregionen påverkar grundläggande funktioner såsom andning, födointag, sväljningsförmåga, lukt- och smaksinne. Behandling av HNC-tumörer innefattar oftast av en kombination av strålning, cytostatika och kirurgi, beroende på tumörens storlek, lokalisation och eventuell spridning. Behandlingen av tumörerna är utmanande eftersom risken för allvarliga och långvariga biverkningar är stor. Många HNC-patienter utvecklar kroniska sväljningssvårigheter (dysfagi), som innebär svårigheter att transportera saliv och föda från munnen till magsäcken. Det är sedan tidigare känt att dysfagi är ett svårbehandlat tillstånd som ofta innebär ett stort lidande för patienten med negativ påverkan på livskvaliteten. Dysfagi kan leda till vätske- och näringsbrist, viktnedgång samt allvarlig lunginflammation, där bland annat studier från Australien har visat att lunginflammation orsakar upp till en femtedel av alla icke-cancerrelaterade dödsfall i denna patientgrupp. Att utvärdera patientens upplevelser av sin hälsa och livskvalitet samt kvaliteten av den vård som patienten erhåller är en viktig del för att förbättra vården för dessa patienter.

Syfte
Avhandlingens övergripande syfte är att på olika sätt utvärdera metoder för att mäta dysfagi samt vårdkvalitet vid dysfagi. Ytterligare ett viktigt syfte är att öka kunskapen om vilka anatomiska strukturer som är mest kritiska för utveckling av dysfagi efter strålbehandling.

Metod
Samtliga fyra studier genomfördes vid Sahlgrenska universitetssjukhuset i Göteborg och omfattade patienter från Öron-näsa-halskliniken. Studie I-III inkluderade patienter med HNC som genomgått strålbehandling och/eller cytostatika under åren 2007-2015, och som minst sex månader efter avslutad behandling genomgått en röntgenundersökning av sväljningsförmågan. I **studie I** fick patienterna svälja sex olika volymer och konsistenser, och studien undersökte om resultatet av sväljningsförsök 1 och 2 för respektive volym/konsistens skiljde sig åt. I **studie II** jämfördes patientrapporterad dysfagi och kliniskt mätt sväljningsfunktion genom sväljningsröntgen för att se om det fanns ett samband mellan dessa utfallsmått. I **studie III** undersöktes om det fanns

ett samband mellan stråldos till sväljningsstrukturer och patientrapporterad samt kliniskt mätt dysfagi. I **studie IV** översattes och validerades ett frågeformulär om vårdkvalitet vid sväljningssvårigheter, Swallowing Quality of Care (SWAL-CARE), som testades på olika patientgrupper med dysfagi.

Resultat

Studie I visade att det på gruppnivå inte fanns någon statistiskt säkerställd skillnad mellan utfallet av de två sväljningsförsöken för någon volym eller konsistens. Dock sågs en variation på individnivå. **Studie II** visade att patienter som rapporterade minst tre dysfagisymptom, i 50% av fallen även uppvisade svår dysfagi på sväljningsröntgen. I **studie III** identifierades stråldos till struplocket (epiglottis) som mest kritisk för svår dysfagi enligt sväljningsröntgen. I tillägg visade dataanalyserna att stråldos till struphuvudet (larynx) och spottkörtlarna också var starkt förknippade med svår dysfagi. I **studie IV** uppvisade översättningen till svenska och valideringen av SWAL-CARE hög tillförlitlighet (reliabilitet) och giltighet (validitet).

Slutsatser

I. Sväljningsförsöket med sämst resultat bör rapporteras vid sväljningsröntgen för att kunna ge adekvata råd till patienten och säkerställa säker sväljning.
II. Samtliga patienter som beskriver att de har flera dysfagisymptom (svårigheter att dricka, äta, svälja och hosta i samband med måltid) efter strålbehandling bör remitteras för vidare utredning av sväljningsfunktionen eftersom dessa löper risk att ha allvarlig dysfagi.
III. Samband mellan stråldos till specifika sväljningsstrukturer och måttlig till svår dysfagi har identifierats. Förhoppningsvis kommer resultaten innebära att stråldos till dessa strukturer kan minskas och på så vis även dysfagiproblematiken.
IV. Den svenska versionen av SWAL-CARE är ett pålitligt frågeformulär för att mäta vårdkvalitet vid dysfagi.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals (I-IV).

I. Hedström J*, Tuomi L*, Andersson M, Dotevall H, Osbeck H, Finizia C (2017). **Within-Bolus Variability of the Penetration-Aspiration Scale Across Two Subsequent Swallows in Patients with Head and Neck Cancer** *Dysphagia*, 32(5): 683-690

II. Hedström J, Tuomi L, Finizia C, Olsson C (2017). **Correlations between patient-reported dysphagia screening and penetration-aspiration scores in head and neck cancer patients post-oncological treatment** *Dysphagia,* 33(2), 206-215

III. Hedström J, Tuomi L, Finizia C*, Olsson C* (2019). **Identifying organs at risk for radiation-induced late dysphagia in head and neck cancer patients** *Manuscript submitted*

IV. Hedström J, Johansson M, Olsson C, Tuomi L*, Finizia C* (2019). **Quality of care in dysphagia patients – translation and validation of the SWAL-CARE questionnaire** *Manuscript submitted*

*Contributed equally

CONTENT

ABBREVIATIONS

ACE-27	Adult Comorbidity Evaluation 27
AUC	Area Under the Receiver Operating Characteristic (ROC) Curve
BMI	Body Mass Index
Chemo-RT	Chemotherapy combined with radiation therapy
DARS	Dysphagia-Aspiration-Related Structures
DESdC	Drinking, Eating, Swallowing difficulties, and Coughing when eating/drinking
DVH	Dose-Volume Histogram
EBRT	External Beam Radiation Therapy
FEES	Fiberoptic Endoscopic Examination of Swallowing
Gy	Gray (joule per kilogram)
HNC	Head and Neck Cancer
HPV	Human Papilloma Virus
HRQL	Health Related Quality of Life
ICC	Intraclass Correlation Coefficient
IDDSI	International Dysphagia Diet Standardization Initiative
IMRT	Intensity-Modulated Radiation Therapy
OAR	Organ-at-risk
PAS	Penetration-Aspiration Scale
PREM	Patient-Reported Experience Measure

PRO	Patient-Reported Outcome
PROM	Patient-Reported Outcome Measure
QoL	Quality of Life
QPP	Quality from the Patient's Perspective questionnaire
RT	Radiation therapy
SWAL-CARE	Swallowing Quality of Care questionnaire
SWAL-QOL	Swallowing Quality of Life questionnaire
TNM	Tumor size, lymph nodes, distant metastasis
UVA/MVA	Univariable/multivariable logistic regression analysis
VFS	Videofluoroscopy
VMAT	Volumetric Modulated Arc Therapy
WHO	World Health Organization
3D-CRT	Conformal radiation therapy

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The Healthcare Board, Region Västra Götaland (Sweden)

The Kamprad Family Foundation for Entrepreneurship Research & Charity and the Medical Faculty of Gothenburg University, Sweden

The King Gustaf V Jubilee Clinic Cancer Foundation in Gothenburg

The Swedish Association for Otorhinolaryngology Head and Neck Surgery

The Swedish Cancer Society

The Swedish Society for Medical Research (SSMF)

1 INTRODUCTION

1.1 SWALLOWING FUNCTION

Eating and swallowing are complex processes requiring perfect coordination of both voluntary and reflexive (autonomous) actions from numerous nerves and muscles [2] to transfer food, liquid and saliva (further on referred to as bolus) from the oral cavity to the stomach while protecting the airway [3, 4] (Figure 1). The normal swallowing (deglutition) can be divided into four separate phases according to the location of the bolus: oral preparatory phase (I), oral propulsive phase (II), pharyngeal phase (III) and esophageal phase (IV) [3] (Figure 2). During the voluntary oral preparatory phase (I) the bolus is tasted and prepared through mastication, saliva secretion and bolus formation [5]. This phase requires intact sensory function in the lips and oral cavity, adequate saliva secretion and muscular activity in the lips, cheeks, jaw and tongue [5]. The bolus is then transported posteriorly (facilitated by retraction of the base of tongue) in the oral cavity (phase II) where it stimulates pharyngeal pressure receptors, initiating the non-voluntary pharyngeal phase of swallowing (III) [3]. Elevation of the soft palate closes the nasopharynx, preventing bolus regurgitation into the nasal cavity [2]. The initiation of the pharyngeal phase is marked by elevation and anterior movement of the hyoid bone and the larynx (hyolaryngeal elevation) making the epiglottis tilt down and ensuring the closure of the laryngeal vestibule [3]. Equally important is the closure of the vocal folds and ventricular folds for laryngeal protection during swallowing [3, 4]. The pharyngeal constrictor muscles contract sequentially, squeezing the bolus downward in the pharynx [2, 5]. The hyolaryngeal elevation together with pressure of the descending bolus and relaxation of the cricopharyngeal muscle enables opening of the upper esophageal sphincter and propulsion of the bolus from the pharynx into the esophagus [3, 4]. In the esophageal phase (IV) a peristalsis wave created by alternating relaxation and contraction of the esophageal muscles and regulated by the autonomic nervous system, drives the bolus down the esophagus to the stomach, through the lower esophagus sphincter [2, 4].

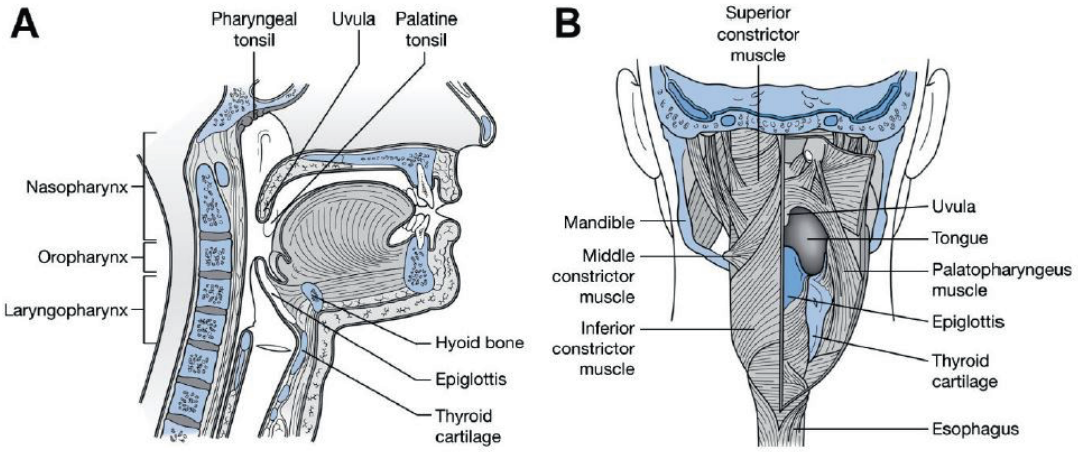

Figure 1. *Anatomy of the oral cavity and pharynx in (A) the lateral view and (B) posterior view. Used with permission from "Atlas of Clinical Gross Anatomy" By Kenneth Moses et al. Elsevier; 2005. ISBN 0323037445 P104, Fig 10.1 Divisions of the pharynx and Fig 10.3 Posterior view of the pharynx.*

Airway protection

Eating, swallowing and breathing are three physiological functions which are tightly coordinated [4]. Protecting the airway and preventing inhalation of bolus in the airway is critical to swallowing. Its failure can have serious consequences such as choking and aspiration pneumonia [2, 4]. Both the hyolaryngeal elevation and retraction of the base of tongue enable the epiglottic inversion, which is crucial for effective vestibular closure (the second level of airway protection after glottic closure) [6]. This is also a necessity for a safe and effective swallowing process without penetration (bolus material above the vocal folds) and aspiration (bolus material below the vocal folds) [7, 8]. Optimal function of retraction of the base of tongue, hyolaryngeal elevation and closure of the vocal folds facilitate closing of the airways on time so that the bolus can be smoothly transported down into the esophagus before the airway opens again [3, 5]. Note that laryngeal penetration sometimes is observed and aspiration of microscopic quantities also may occur in healthy individuals [2].

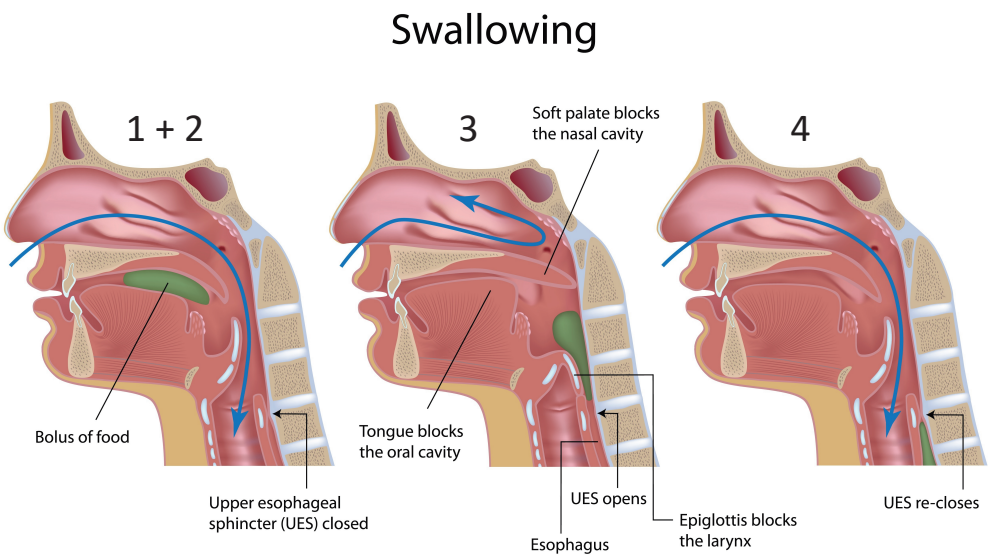

Figure 2. *Schematic presentation of the swallowing process. Swallowing may be divided into four phases: 1. Oral preparatory phase, 2. Oral propulsive phase, 3. Pharyngeal phase, 4. Esophageal phase. Illustration and right to use purchased from 123RF, alila ©123RF.com Abbreviations: UES=Upper esophageal sphincter*

1.2 DYSPHAGIA

Swallowing dysfunction (dysphagia) comprises difficulties transferring saliva, solid foods and liquids from the oral cavity to the stomach, and can result from a wide variety of functional impairments or structural lesions of the oral cavity, pharynx, larynx, esophagus or the esophagus sphincters [2, 4]. Dysphagia may be classified according to the level in the swallowing apparatus at which the problem is located, i.e. oral, oropharyngeal or esophageal dysphagia [4].

Dysphagia represents a common complication in many different medical conditions [4, 5] including stroke [9], neurological and neurodegenerative diseases such as Parkinson's disease [10] and trauma to the head or cervical spine [11]. It is also more common in elderly individuals [12]. In patients with head and neck cancer (HNC), dysphagia marks an important concern. Studies have shown that prior to oncological treatment approximately 40% of HNC patients suffer from mild-moderate-severe tumor-related

dysphagia [13] with higher prevalence after treatment [14-16]. Among patients with HNC, the dysphagia is caused by pain or obstruction from the tumor and/or side effects of the oncological treatment [13, 17, 18].

Structural lesions include for example diverticulae in the pharynx or esophagus and strictures in the pharynx, esophagus or esophagus sphincters. This can cause problems with nasal or pharyngeal regurgitation and obstruction of the bolus passage [2]. Functional impairments affecting the oral cavity (jaw, lips, tongue, cheek) can lead to hampering of the oral phase or the food processing. Weak contraction of the tongue and soft palate may cause premature leakage of the bolus into the pharynx, especially with liquids. Tongue dysfunction (muscular weakness or incoordination), xerostomia and sensory impairment in the oral cavity often lead to impaired mastication, bolus formation and bolus transport in the oral phase. Dysfunction of the pharynx e.g. weakness of the pharyngeal constrictor muscle, can lead to delayed initiation of swallowing, ineffective bolus propulsion and retention of bolus in the pharynx after swallowing [4]. It can also lead to insufficient pharyngeal pressure, resulting in impairment of the bolus transport through the upper esophageal sphincter. Also, incomplete inversion of the epiglottis may obstruct bolus propulsion and result in retention in the valleculae. Furthermore, impaired opening of the upper esophageal sphincter can cause partial or sometimes total obstruction of the passage with retention in the piriform sinuses and hypopharynx, leading to an increased risk of aspiration after the swallow [4]. Potential causes of insufficient upper esophageal sphincter opening include increased stiffness of the sphincter, as in fibrosis or inflammatory conditions, or failure to relax the sphincter musculature [4]. In addition, weakness of the anterior suprahyoid muscles, which normally pull the upper esophageal sphincter open during swallowing, can hinder opening of the sphincter [2]. Last, esophageal dysfunction is another cause of dysphagia and includes conditions of either hyperactivity (e.g. esophageal spasm), hypoactivity (e.g. muscle weakness) or incoordination of the esophageal musculature. These all lead to ineffective peristalsis with bolus retention in the esophagus. Retention can also lead to regurgitation of bolus from the esophagus back into the pharynx, increasing the risk of aspiration [4].

Dysphagia may lead to serious complications including dehydration, malnutrition, choking and aspiration pneumonia [2, 4, 19-21]. Aspiration can occur before, during or after swallowing and is characterized by bolus material being transported below the vocal folds [7, 8] and in the worst scenario not transported back up into the pharynx, causing choking or a

pneumonia [2, 19-21]. Aspiration that is visible on instrumental examination of swallowing (i.e. fluoroscopy or endoscopy) is always pathological with an increased risk of aspiration pneumonia [2, 4]. The normal, adequate response to aspiration is a strong cough reflex, which clears the throat and airway. However, the laryngeal sensation is often impaired in individuals with severe dysphagia, leading to absence of the coughing reflex i.e. silent aspiration [2, 4, 22]. Dysphagia has also been associated with impaired quality of life, depression and anxiety in studies of HNC patient cohorts [4, 23-26].

1.3 INSTRUMENTS FOR PATIENT-REPORTED OUTCOMES

1.3.1 PATIENT-REPORTED OUTCOMES AND HEALTH-RELATED QUALITY OF LIFE

The concept Quality of Life (QoL) has existed since ancient Greece, but still no consensus in the definition of QoL has been reached [1]. As defined by the World Health Organization (WHO), QoL can be defined as "an individual's perception of their position in life in the context of the culture and value system in which they live and in relation to their goals, expectations, standards and concerns" [27]. When applying QoL in the healthcare context, it usually refers to Health-Related Quality of Life (HRQL), measuring QoL in relation to health or functional status [28].

The concept Patient-Reported Outcome (PRO) covers both HRQL and other aspects where information can be obtained from the patients, e.g. treatment compliance and treatment satisfaction [29]. PROs are defined as all information given by the patient him-/herself regarding his/her health status, and should, in the strict meaning of the concept, not include interpretation by health care professionals, relatives or another third party [1]. PRO can be evaluated by conducting open interviews, semi-structured interviews or using validated instruments (questionnaires). Using self-report instruments ensure that the questions are asked in a standardized manner, facilitating comparisons between groups as well as between different timepoints for the same individual. PRO measures give important information on important aspects of health status that cannot be evaluated through clinical/objective assessments, and should be used alongside the latter to ensure a comprehensive assessment [1].

Within the concept of PRO there are two related but conceptually different subdivisions assessing the patients' views: Patient-Reported Outcome Measures (PROM) and Patient-Reported Experience Measures (PREM). PROM addresses the patient's perception of disease/symptoms, quality of life and health, whereas PREM incorporates the patient's experience and satisfaction of the given care, also named quality of care [30]. Assessment of PROM can for example be used to acquire systematic data on self-reported health in a patient population and to compare the effects of different treatments on the patients' self-reported health [31]. Assessment of PREM, on the other hand, is important for evaluation of the provided care and

consequently for identifying the areas that the patients consider subject of improvements [32]. The two concepts might seem well-defined, but in effect it is not always obvious to separate PROMs on experience of the given treatment from PREMs on satisfaction of the given treatment [33].

Approaching HRQL and PROs in clinical studies have become increasingly important during the past decades. This is illustrated by the fact that the American Food and Drug Administration (FDA) recommend drug companies to use PRO instruments in clinical trials when measuring a concept best known by the patient or best assessed from the patient's perspective [34]. Globally, in HNC there has been an extensive development in the oncological treatment, over the last decades, towards more advanced radiation therapy (RT) and chemotherapy treatment regimens [35]. This has resulted in improved loco-regional tumor control, but the overall survival has not been affected and the treatment-related symptom burden (treatment toxicity) is still significant [23, 36]. It is therefore important to address PRO in clinical research and in clinical practice in order to understand the patient's experiences of treatment and treatment-related effects and to identify rehabilitation needs.

1.3.2 DEVELOPMENT AND EVALUATION OF PATIENT-REPORTED OUTCOMES

PRO instruments consist of a number of questions or statements (items) that are relevant for the concept that is intended to be measured. The items are grouped into different scales or domains which all measure different aspects of the same concept. PRO instruments can be subdivided into generic, disease-specific, diagnosis-specific and symptom-specific [37]. The generic instruments assess general health, overall disability and general HRQL, irrespective of the illness or condition of the individual, providing the opportunity to compare scores across groups of patients with different diseases as well as the general population [1]. However, these instruments may fail to identify symptoms specific for certain diagnoses and risk lacking sensitivity to measure clinically significant changes for specific patient cohorts. This has highlighted the need of both disease- (e.g. cancer) and diagnosis-specific (e.g. HNC) instruments. Several HRQL instruments include both generic and disease-specific domains. Furthermore, there are symptom-specific instruments for examining defined issues or symptoms in greater depth i.e. anxiety and depression,

pain, fatigue and, as the focus in this thesis, dysphagia [1]. Figure 3 shows examples of some PRO instruments in use today.

Developing a PRO instrument requires much effort to ensure the accuracy of the instrument. There are guidelines describing the procedure when developing a PRO instrument [1]. In order to ensure accuracy validation needs to be performed [1]. Some central concepts of psychometric properties are explained in Table 1. In order to use an existing PRO instrument in a specific population, the instrument must be translated and validated into the language of the population. The translation and validation procedure should be as thoroughly executed as the original development of the instrument, in order to avoid introducing errors into the questionnaire or shifts in nuances that might affect the way patients respond to items [1]. There are several guidelines describing the translation and validation procedure [1, 38, 39].

The main parts in validation and translation of a PRO instrument can be summarized into translation, pre-testing/pilot study and field testing. The translation process is conducted in a forward-backward manner. First, one or several forward translations are made, i.e. from the original language to the target language, independently by one or several individuals native in the target language. In the translation process it should be stressed to strive for conceptual equivalence i.e. not word for word translation but that the translation is correct in context. Next, a bilingual expert panel with great knowledge in the field as well as translation and adaptation of questionnaires, combine the versions into a consensus version. The consensus version is then retranslated into the original language by an independent bilingual individual with the original language as native language and who is unfamiliar with the questionnaire. Finally, the backward translation and the original questionnaire are compared by one or several bilingual experts in language and the methods of cross-cultural adaptation procedure. Differences are discussed and a final version of the translated questionnaire is established.

It is essential that new PRO instruments are extensively tested on groups of patients before being released for general use. This testing is best carried out in two parts, first a pre-testing/pilot study and then a field testing study. The pilot study involves a smaller yet representative sample of the target population, usually 10-30 patients [1]. The patients are asked to fill out the questionnaire and are then debriefed through a structured interview aiming to identify items that the patients for example thought were lacking, irrelevant, confusing/difficult to understand or upsetting, as

well as the time spent to complete the questionnaire. The results of the pre-testing should identify any potential problems with the instrument, and before the fieldtesting the instrument is revised if needed.

The fieldtesting is conducted in a larger group of patients, according to Fayers and Machin [1] the sample should meet the five patients per item criteria i.e. the minimum sample size is five times the number of items in the instrument. Psychometric testing of the instrument is performed through validity, reliability, sensitivity and responsiveness. More details of the fieldtesting is found in the patients and methods chapter.

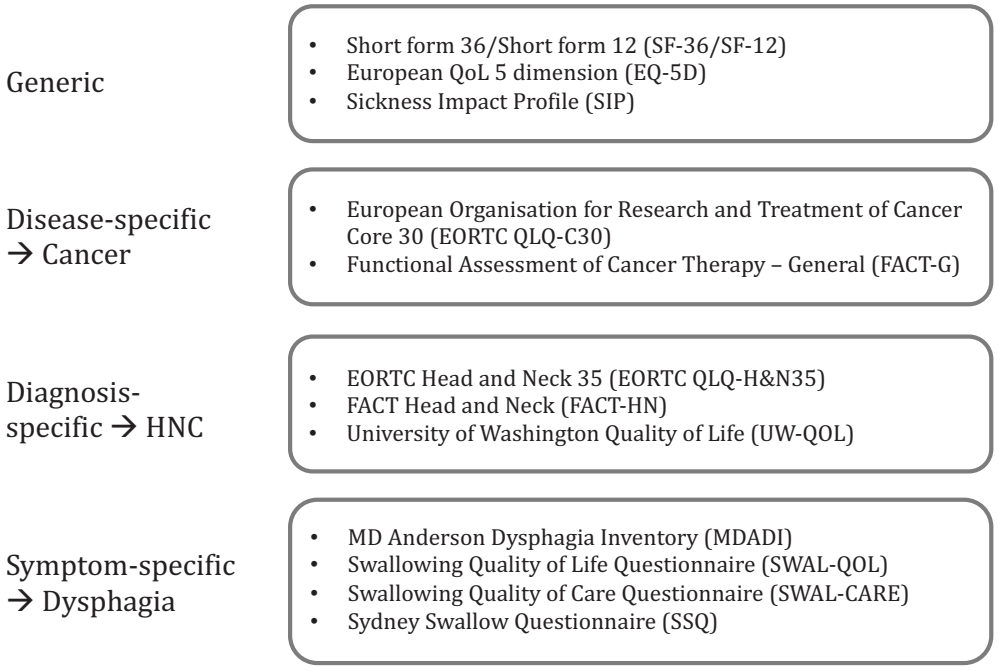

Figure 3. *Examples of some of the PRO instruments in use today. Abbreviations: HNC=Head and Neck cancer*

Table 1. *Psychometric concepts explained* [1]

Concept	Concept explained	How to analyze
Validity	If the instrument measures what it is intended to measure	Consists of different parts: content, criterion and construct validity
Content validity	If the items reflect what they are intended to reflect. High content validity means that the instrument covers all relevant aspects, but does not include irrelevant items	Literature review, exert and patient input. The patient input is a very important step, since the purpose of the PRO instrument is to capture the patient's experience
Criterion validity	If the scale has association with external criteria or "gold standard"	Agreement between two methods (example: external criteria such as blood pressure or blood sample and instrument agreement)
Construct validity	If an instrument measures the theoretically intended constructs. Consists of *convergent and discriminant validity*. That is how well constructs that should be related (or unrelated) in fact are related (or unrelated)	Convergent validity: Correlations of the measured scale with the theoretical construct, i.e. another questionnaire, should demonstrate correlations >0.40. Discriminant validity: Low correlations should be demonstrated
Reliability	Precision and stability of an instrument, i.e. the instrument gives consistent results in repeated measurement	Test-retest through correlations (repeatability) or Cronbach's alpha, which measure internal consistency, how well items are correlated to each other. Alpha >0.70 is considered acceptable
Sensitivity	Ability to detect differences between patients or cohorts	Can be evaluated in cross-sectional or longitudinal studies. If statistically significant differences are detected when comparing groups, the instrument is considered sensitive
Responsiveness	Ability to detect within-patient changes over time	Longitudinal studies required. Measured through e.g. Standardized Response Mean or Effect Size
Factor analysis	Evaluation of construct validity. Analyzing the relationship between individual items and domains	Exploratory factor analysis or Confirmatory factor analysis where the latter imply validation of a specific instrument
Item response distribution	The range of responses and evaluation if there are floor and ceiling effects, which indicate the discriminating ability of the instrument	Presence of floor and ceiling effect i.e. the proportion if patients having the minimum or maximum score, respectively. Floor/ceiling effect >15% indicates that the scale will have poor discrimination and that the item might need to be reconstructed

Interpreting PRO scores

Several studies on HNC patients have shown that perceived experiences rated by patients completing PRO instruments often deviate from clinical measures [18, 40-44]. This is also a general phenomenon [45]. An explanation to this phenomenon is that QoL depends on more aspects than health, as previously described in chapters on PRO and HRQL. Also, ratings of personal QoL/well-being may be influenced by specific circumstances, which sometimes are temporary [1]. Finally, there is the concept of response shift used as an explanation to why PROs do not always correspond to clinical outcome measures [1]. Response shift indicates that we adapt to our surroundings and changed circumstances and redefine important goal concepts [1]. *Nevens et al*. [46], on the other hand, investigated the association between patient- and physician-scored dysphagia and swallowing videofluoroscopy (VFS), and a significant association between patient- and physician scored dysphagia pre- and post-RT for HNC was shown. Also, the risk of observing dysphagia on VFS increased significantly with increasing scores of both patient- as well as physician-scored dysphagia. A study by *Pauloski et al.* also showed that patients who reported swallowing difficulties on a direct question also presented with worse clinical swallowing function by VFS than the patients who did report normal swallowing function [47].

Besides including PROs in clinical research, it is as equally important to implement the use of PROs in clinical practice as routine follow up, for example during as well as after RT to identify acute and late side effects (toxicities). Validated PRO instruments are often quite extensive. To screen for dysphagia in clinical practice, where time is of essence, single questions intercepting problems drinking/eating/swallowing and coughing when eating/drinking, are often used instead of extensive questionnaires. Potentially, individual domains or even items from instruments can be singled out and be of use for this purpose.

1.4 ASSESSMENT OF SWALLOWING FUNCTION

To perform a comprehensive measure to assess the swallowing function is a great challenge due to the complexity in swallowing physiology. Swallowing function may be assessed through clinical or instrumental examinations and physician-rated instruments (such as scales for toxicity scoring post-RT), as well as in combination with patient-reported instruments. Naturally, patient history also provides valuable information on swallowing function that facilitates the diagnostic workup [4]. All clinical and instrumental examinations include observation of swallowing of different volumes and consistencies. In order to achieve a comprehensive evaluation of swallowing it is important to include both patient-reported information and clinical/instrumental assessment [18].

Swallowing examinations

The main goal of swallowing examinations in dysphagia patients is to either identify or exclude the presence of aspiration [4]. A common instrumental approach is to use videofluoroscopy (VFS) or modified barium swallow (MBS), where the swallowing function is assessed by the patient swallowing liquids and solids of various consistencies and quantities (bolus) mixed with contrast [4, 48]. As the patient swallows, the transportation of the bolus through the oral cavity, pharynx and esophagus is visualized via X-ray. The different phases of swallowing are evaluated and events of penetration or aspiration are observed (Figure 4). Airway protection can be evaluated and associated swallowing function scored according to, for example, the penetration-aspiration scale (PAS) [7, 8]. The PAS is an 8-point interval scale where the scores are determined by the depth to which material (bolus) passes in the airway and by whether or not the material entering the airway is expelled [7]. Penetration and aspiration events can also be evaluated by just noting the presence of penetration or aspiration events [4]. The overall swallowing function can also be scored according to different scales, such as the Swallowing Performance Status Scale (SPS) [49] and the Function Oral Intake Scale (FOIS) [50, 51]. The SPS provides assessment of the presence and severity of dysphagia and aspiration risk by combining clinical and radiographic data. Additionally, temporal measurements can be done from the VFS/MBS recording i.e. the time required for the bolus to move through the oral cavity and the pharynx, oral transit time and pharyngeal transit time respectively [4, 48]. Estimates of residue in the oral cavity and pharynx can also be assessed [4, 48].

Examination protocol (consistencies and quantities of the boluses) and the number of swallowing attempts differ between studies, as does the interpretation of the examination results [52-55]. Consensus is lacking on whether to report the mean of several swallowing attempts, chose one specific or analyse all swallowing attempts. To our knowledge, besides Study I in this thesis, there is to this day only one study by *Frowen et al.* investigating the variability between swallowing attempts of the same bolus during VFS [56]. Table 2 lists VFS protocols used in a sample of studies of dysphagia in HNC patients.

Another instrumental examination of swallowing is Fiberoptic Endoscopic Evaluation of Swallowing (FEES), where a flexible endoscope is inserted through the nasal cavity and placed so the pharynx and larynx can be visualized clearly. Similar to VFS, in FEES, the patient is to swallow boluses of different size and consistency, where the boluses are dyed with color to make it easily visible. As in VFS, the pharyngeal phase of swallowing is assessed and penetration/aspiration events are noted. Several different scales can be used in the assessment such as the SPS, FOIS, Yale Pharyngeal Residue Severity Rating Scale [57] and the Murray Secretion scale [58, 59].

The swallowing function may also be evaluated through a clinical examination of swallowing where the clinician assesses oral cavity and pharyngeal sensory and motor function (evaluation of cranial nerve function), in combination with a meal observation or a swallowing test. In the swallowing test the patient gets to swallow different consistencies and volumes just as in VFS and FEES. The clinician observes external signs of aspiration, i.e. coughing, voice disturbance and breathing disturbances. There are also several screening tests, for example the Water Swallow Test [60], the Gugging Swallowing screen [61] and the Toronto bedside Swallowing Screening Test [62].

Important to note is that without instrumental assessment, structural abnormalities of swallowing structures are difficult to identify, which makes VFS and FEES the diagnostic gold standard [3, 4]. Table 3 states a selection of advantages and disadvantages of the clinical examinations of swallowing presented above.

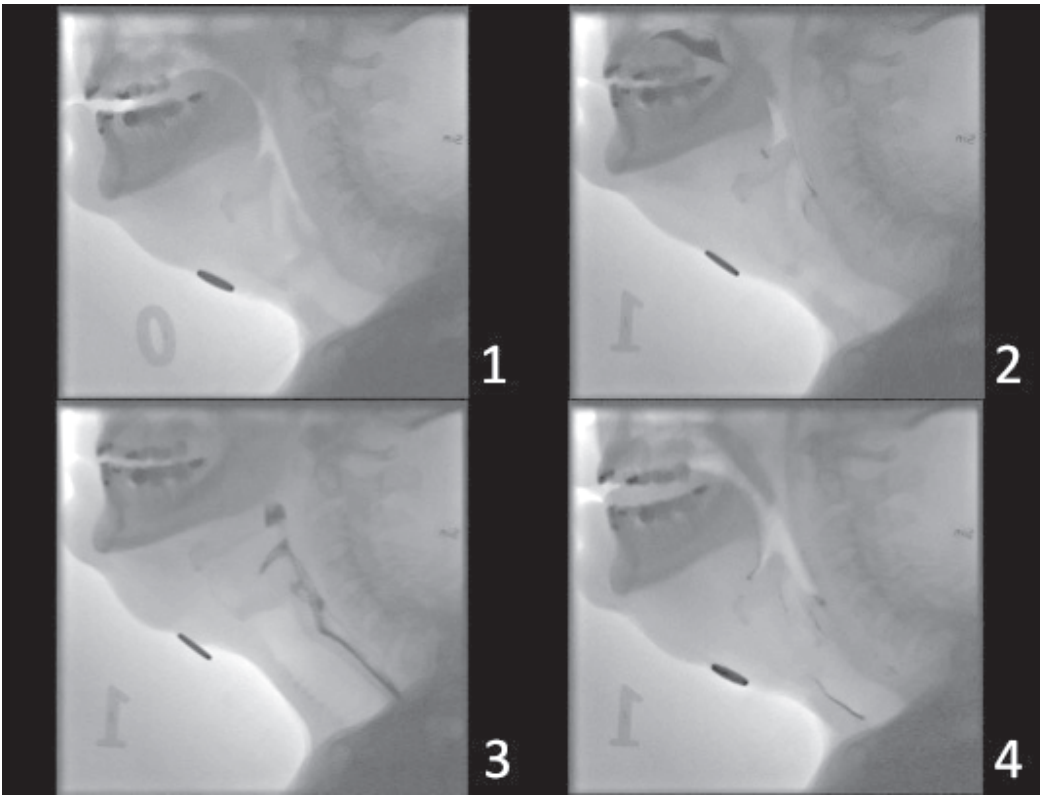

Figure 4. *Swallowing with bolus aspiration as visualized by videofluoroscopy (static images in lateral projection)* ***1.*** *Before start of the swallowing.* ***2.*** *The bolus (black) is seen in the oral cavity with pharyngeal residue from previous.* ***3.*** *The bolus (black) is transported through the pharynx and into the esophagus.* ***4.*** *Residue of the bolus (black) is seen in the larynx, around the vocal folds and in the trachea as well as in the pharynx. © Johanna Hedström*

Table 2. *Boluses used in a selection of studies using videofluoroscopic examination of swallowing*

	Logeman [63]	Frowen [56]	Frowen [52]	Rudberg [53]	Lee [64]	Starmer [16]	Mortensen [15]	Schwartz [65]	Kraaijenga [66]	Logemann [54]	Pauloski [55]
Swallows per bolus	2	3	2	2	1	1	1	1	1	2	2
1 ml thin	-	-	-	-	+	-	-	-	-	+	+
3 ml thin	+	+	+	+*	+	-	+	-	+	+	+
5 ml thin	+	-	-	-	+	+	+	-	+	+	+
10 ml thin	-	-	-	-	+	+	+	+	-	+	+
20 ml thin or Cup sips thin	-	-	+	+*	-	+	-	-	-	+	-
3 ml thick	-	-	+	+	-	-	-	-	-	-	-
5 ml thick	-	-	+	+	-	-	-	-	-	-	-
10 ml thick	-	-	-	-	-	-	-	-	-	-	-
Pudding /paste/semi-solid	3 ml	3 ml	-	-	-	tea-spoon	-	tea-spoon	3 ml	3 ml	3 ml
Cookie/other solid food	-	-	-	-	-	+	+**	+	+	+	+
Total no of swallows	6	6	8	12	4	5	4	3	4	14	12
Which bolus is analyzed	All	All, recommends 2nd	2nd	All	N/A	N/A	N/A	N/A	N/A	All	All

+ = yes; - = no; *=these boluses were observed in both lateral and anterior-posterior view, i.e. four swallows in total; ** = other solid foods: carrot gratin

Table 3. *Advantages and disadvantages with different clinical assessments of swallowing*

Clinical assessment	Advantage	Disadvantage
VFS/MBS	• Analysis of the whole swallowing tract from the oral cavity to the stomach. Gives a topographic overview [4] • Practical, robust and efficient instrumental assessment [4] • Can detect penetration and aspiration [4] • The suitability for specific swallow maneuvers and postural changes can be evaluated [48] • Easily accepted by the patients [50]	• Radiation exposure [4, 50] • Relatively time and resource consuming [5]
FEES	• Direct visualisation of the pharyngeal phase of swallowing [4] • Can indirectly detect penetration and aspiration [4] • Can reveal subtle mucosal abnormalities [4] • Enables evaluation of laryngopharyngeal sensation [48] • No radiation exposure [48] • More easily available than VFS, can be performed at the patient's bedside [4, 48]	• No visualization of the pharynx during the swallow and no visualization of the oral and esophageal phases [4, 48] • Can be somewhat uncomfortable for the patient [5] • Impossible to perform if the patient has strong gag reflex or difficulties to participate [5] • Exact evaluation of penetration or aspiration events are difficult due to no visualization during swallow, and some difficulties of visualization below the vocal folds [5].
Clinical evaluation of swallowing	• Less time and resource consuming compared to VFS and FEES [4] • Can be performed bedside [5] • Can be performed during meal observation [5] • Swallowing will likely be more like the normal eating situation since no instruments are needed during swallowing [5]	• Inadequate information on oropharyngeal swallowing function as well as the anatomy of the pharynx and larynx [5] • Only indirect signs of penetration and aspiration can be detected, hence aspiration cannot be diagnosed or excluded by this evaluation [4] • In order for a more secure evaluation it should be combined with an instrumental assessment [4, 48] • Cannot detect events of silent aspiration [4]

Abbreviations: FEES=Fiberoptic Endoscopic Examination of Swallowing; MBS=Modified Barium Swallow; VFS=Videofluoroscopy

Patient-reported outcomes for swallowing function

The swallowing function may also be evaluated or screened based on the patient's perception of symptoms. In research studies validated instruments (questionnaires) are often used to evaluate patient-reported swallowing, e.g. the diagnosis-specific European Organization of Research and Treatment of Cancer Quality of Life Questionnaire Head and Neck module (EORTC QLQ H&N35) [67] and University of Washington Quality of Life (UW-QOL) questionnaire [68, 69]. The symptom-specific M. D. Anderson Dysphagia Inventory (MDADI) [70, 71], Swallowing Quality of Life Questionnaire (SWAL-QOL) [72, 73] and Sydney Swallow Questionnaire (SSQ) [74] are some examples of instruments used in clinical research and practice to describe the degree of dysphagia and evaluate the effect of dysphagia treatment.

Besides clinical and instrumental diagnostic evaluation of the swallowing function and evaluation of the patient's perception of swallowing, it is also important to evaluate the patient's experience of the given treatment and care. Quality of care is a concept measuring what aspects of the care that the patients consider important as well as their satisfaction with the care given [75]. It brings the opportunity for care givers to receive feedback on the given treatment and care. McHorney et al. have developed a PREM instrument for dysphagia, the Swallowing Quality of Care questionnaire (SWAL-CARE). The SWAL-CARE evaluates the patient's opinion on received clinical information and swallowing safety advice as well as patient satisfaction [72].

1.5 HEAD AND NECK CANCER

HNC is a generic term for a heterogenous group of tumors. According to the ICD-10 classification, HNC tumors can be divided into the following locations [76]: 1. Lip, 2. Oral cavity, 3. Oropharynx, 4. Nasopharynx, 5. Hypopharynx, 6. Larynx, 7. Salivary glands, 8. Nasal cavity and paranasal sinuses, 9. Cancer of unknown primary (CUP) head and neck cancer (Figure 5 [76]). Within the different tumor groups there are sub-groups that differ in way of growth, risk for metastasis, prognosis and treatment. In this thesis the tumor locations studied are: oropharynx (tonsil and base of tongue), hypopharynx and larynx.

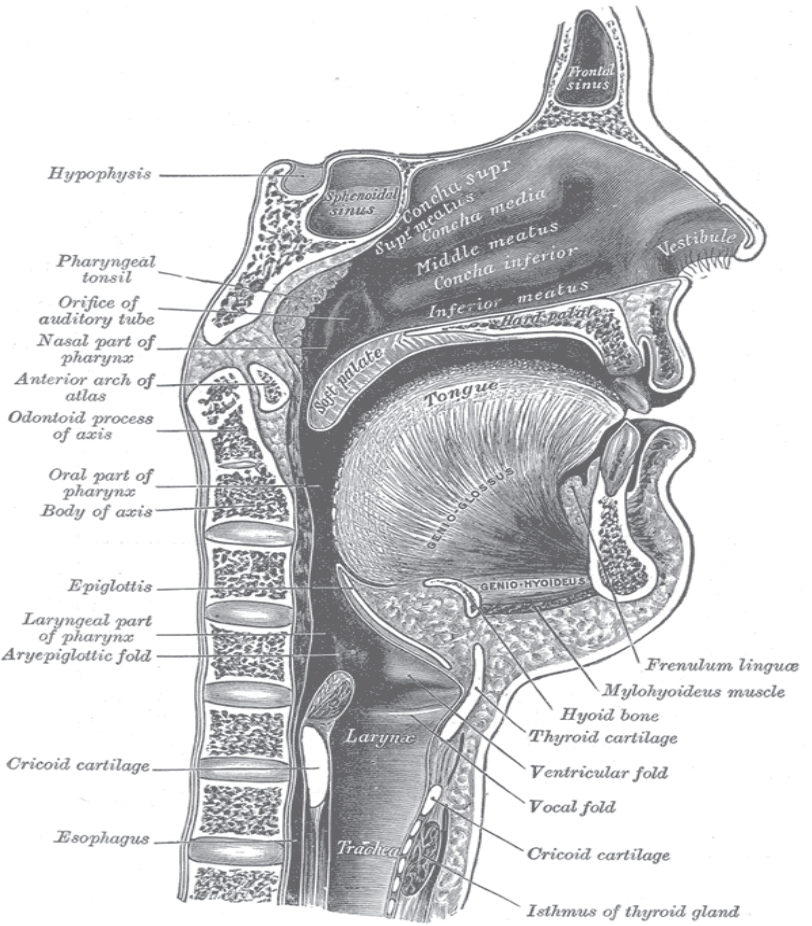

Figure 5. *Head and Neck anatomy, sagittal view. (Source: Henri Gray, Gray's Anatomy)*

1.5.1 EPIDEMIOLOGY

The yearly incidence of HNC in Sweden is approximately 1500 cases [77] and globally more than half a million individuals are diagnosed every year [78]. During the last decade the yearly incidence of HNC in Sweden has increased, making HNC the fifth most rapidly increasing cancer type [79]. The most common tumor location in HNC in Sweden is oral cancer, followed by oropharyngeal cancer [76]. It is well established that the majority of all HNC tumors are squamous cell carcinoma (SCC) or undifferentiated carcinoma.

Since 2008 the number of patients with HNC has increased by 25% in Sweden [76], where the oropharyngeal cancer has the most rapid increase, and here the majority of the cases are induced by human papilloma virus (HPV). The increase of HPV-related tumors is a global trend [76, 80] and in Sweden HPV is detected in 40-90% of the cases of tonsillar and base of tongue cancer [76]. The mean age for patients diagnosed with HNC is approximately 65 years and generally there is a male dominance where approximately two thirds of the patients are males [76].

Risk factors

Established etiological risk factors for HNC are tobacco smoking and alcohol overconsumption [81, 82]. Other possible risk factors are poor dental status and oral hygiene, which in several case-control studies have been shown to be linked to oral and oropharyngeal cancer [83]. In recent years, the HPV (especially high-risk HPV = HPV16) has been highlighted as a precipitating factor for several types of HNC [84, 85].

1.5.2 STAGING AND CLASSIFICATION

Staging is classifying a primary tumor depending on the expansion of the tumor, including the presence or absence of nodal engagement and metastases. Classification and staging of tumors are used to aid treatment planning, provide an indication of prognosis, assist in the evaluation of treatment results, facilitate exchange of information between treatment centers and contribute to collection of comparable data for cancer registries [86]. In Sweden as well as internationally, HNC is classified according to three criteria: the primary tumor size (T), regional lymph node engagement (N) and distant metastases (M), TNM, a classification system developed by the International Union against cancer [86]. A new

version of the TNM classification (8th edition) was released in December 2016, however, the studies in this thesis follow the former TNM classification (7th edition) [87]. A summary of the TNM classification for HNC cancer used in this thesis is shown in Table 4. The TNM-category for a specific tumor is then used to classify the tumor into one of four stages, I-IV.

Table 4. *Generalized TNM classification for HNC (7th edition)*

Classification	T Primary Tumor 0-4	N Lymph Nodes 0-3	M Distant Metastasis 0-1
0	No evidence of tumor	No regional nodes	No metastasis
1	≥ 2 cm	Single ipsilateral <3 cm	Metastasis
2	>2 − ≤4 cm	a. One ipsilateral 3−≤6 cm b. Multiple ipsilateral ≤6 cm c. Bilateral or contralateral ≤6 cm	.
3	>4 cm	>6 cm	.
4	a. Invades adjacent structures b. Invades critical adjacent structures or encases carotid artery	.	.
Stage			
I	T1N0M0		
II	T2N0M0		
III	T3N0M0 or T1-3N1M0		
IV	T4anyNM, N2-3anyTM or M1anyTN		

Abbreviations: HNC=head and neck cancer; TNM=tumor size, lymph nodes, distant metastasis

1.5.3 PROGNOSIS

In Sweden the majority of all new cases of HNC are diagnosed with advanced tumor stage i.e. stage III or IV [76]. The relative 5-year survival for all HNC, between 2008-2016, was 67% in Sweden [76]. Interpretation of survival rates for the whole HNC group should be carried out carefully since it constitutes a merge of nine different tumor locations. The relative 5-year survival is the highest for nasopharyngeal, oropharyngeal, and laryngeal cancer (71%, 70% and 68% respectively), whereas the prognosis for hypopharyngeal cancer is very poor (26% relative 5-year survival) [76].

Apart from the tumor TNM classification and tumor stage, there are several other prognostic factors for HNC survival. As mentioned above tumor location affects the prognosis [76]. The patient's age and performance status are also considered prognostic factors in HNC as well as in cancer generally [88]. Several studies have shown co-morbidity to be a prognostic factor in HNC patients [89-91], where patients with more severe co-morbidity have worse survival rate [90]. The HPV related tumors appear to have a better prognosis and are more sensitive to treatment compared to non-HPV related tumors [92].

1.6 TREATMENT IN HEAD AND NECK CANCER

HNC with its heterogenous tumor locations require a variation of treatment modalities. The treatment and management for this tumor group is challenging due to the location of the tumors at close proximity to vital organs carrying out essential functions such as breathing, swallowing, smelling and tasting. Generally in Sweden, the treatment of HNC patients follows the national clinical recommendations on head and neck cancer diagnosis, treatment and follow-up [76]. Surgery and radiation therapy (RT) constitute the basis of the treatment regimens for HNC, and according to the Swedish Head and Neck Cancer Registry (SweHNCR) 90% of the treatment is given with curative intent [77]. The choice of treatment depends on the tumor site and if the tumor can be surgically removed or resected. Surgery used as the only treatment modality is more common in lip and oral cavity cancer, while RT alone is more common in pharyngeal cancer [76]. The choice of treatment regimen is based on several factors, but generally patients with smaller tumors/early stage disease (Stage I and II) are treated with single therapy. Patients with more advanced tumors (Stage III and IV), which most often are non-resectable, generally receive combined therapy i.e. surgery+RT or RT+chemotherapy (chemoRT). Immunotherapy may also be added to the treatment regimen in selected cases.

The majority of HNC patients (60%) are diagnosed at a more advanced tumor stage (Stage III or IV) [76]. Explanations for this depend on tumor site and are related to the initial absence of symptoms. Typically, a tumor of the lip will often be noted by the patient at an early stage, while a hypopharyngeal tumor can grow until it has become locally advanced [93].

1.6.1 SURGERY

Primary surgical resection of tumors in the head and neck region is used as the standard treatment when possible. However, surgical treatment is often infeasible or cannot be performed radically due to extensive tumor growth or high risk of severe adverse effects, i.e. functional impairments post operatively as a result of tissue defects [48, 94]. Adverse effects and functional impairment after surgery are known to negatively affect the patient's HRQL [48]. Co-morbidity, which affects the post-operative healing and rehabilitation, is also a crucial factor to consider when deciding on treatment regimen [91]. Tumor resectability is determined in the individual patient, but for example tumors infiltrating critical anatomical structures

like the carotid artery, base of scull and prevertebral fascia, are commonly considered unresectable tumors [95]. In addition to resection of the primary tumor, neck dissection is commonly performed to remove regional lymph nodes, hence removing potential micro metastases from the areas draining the tumor. The lymph nodes are then analysed for pathology as well as used for staging the tumor.

1.6.2 CHEMOTHERAPY

Chemotherapy exerts an unselective cytotoxic effect on all tissue cells, more specifically leading to inhibition of the tumor's uncontrolled reproductive capacity by different mechanisms [48]. Different agents have their primary action in different parts of the cell cycle. Chemotherapy is known to potentiate the effect of RT [96] and in Sweden, chemotherapy is used in combination with RT, with or without surgery, in locoregional advanced HNC squamous cell carcinoma stage III-IV. In this context the combined treatment is considered curative [76]. Chemotherapy can also be administered before the start of RT as inductive therapy, during RT as concomitant therapy, or after completion of the primary treatment as adjuvant therapy. In addition, it can be used as a single treatment with palliative intent, here to reduce the tumor volume. Different agents are used in chemotherapy for HNC, mainly cisplatin and 5-Fluorouracil (5-FU). For more advanced tumors, induction chemotherapy is generally given as two cycles (cycle interval 22 days) of Cisplatin (day one) and 5-FU (day one through five), while concomitant chemotherapy consists of six cycles of Cisplatin day one with a cycle interval of seven days [76]. Chemotherapy increases the chance of survival [97], however it exerts toxicity and may induce severe acute adverse effects, such as nausea and vomiting, diarrhea, dehydration as well as bone marrow- and neurotoxicity [48]. In concomitant chemo-RT for HNC, the potentiating effect of the radiation yields an increased risk of acute and late adverse effects, mainly xerostomia and dysphagia [36, 98].

1.6.3 OTHER THERAPIES

A more novel addition to treatment of HNC is immunotherapy, i.e. the use of antibodies targeted at specific cell sites leading to activation of the immune defense system. In contrast to chemotherapy, immunotherapy does not exert a toxic effect on the non-tumorous tissues. The monoclonal

antibody Nivolumab, which inhibits the protein PD1 (Programmed cell Death protein 1), leads to maintained T cell activity and immune response [76]. It is now accepted as second line of treatment in palliative treatment of HNC [76].

Another type of monoclonal antibody therapy, although per definition not immunotherapy, is Erbitux which exerts inhibition of the Epidermal Growth Factor-receptor (EGFR). This is the most common receptor antibody and can be administered as a single regimen or in combination with chemotherapy in palliative treatment, or as an alternative to Cisplatin in concomitant chemo-RT [76].

1.6.4 RADIATION THERAPY

Radiation therapy (RT) plays an essential role in treatment of HNC. The anatomical location of HNC tumors, close to the central nervous system (CNS) including the brain stem and the cranial nerves, demand that the treatment is given with high precision in order to avoid severe radiation-induced complications such as paralysis. Also, important physiological functions such as chewing, swallowing and speech depend strongly on the functionality in the head and neck region, why it is important to apply organ-sparing techniques when possible. Different tumors show different degrees of radiation sensitivity which is reflected in radiation doses needed to eliminate the tumor [96]. HNC tumors generally show a moderate radiation sensitivity and require radiation doses in the range of 60-70Gy (Gy=joule per kilogram) to be eradicated, which imply that the tolerance doses for surrounding non-tumorous tissue e.g. the brain stem are challenged. Doses above 50Gy to the brain stem indicate a risk for paralysis [96]. RT total dose is delivered in fractions and its biological effect depends on numerous factors (described in detail below). Fraction size and overall treatment time can be altered and may result in different tumor responses as well as patterns of early and late toxicity [96, 99]. So called prophylactic dose is applied in areas with suspected microscopic disease, e.g. lymph nodes in the neck, if the risk of local spread is anticipated to be high, and is generally lower (around 45Gy) than the curative dose above.

External beam radiation therapy

In external beam radiation therapy (EBRT) the radiation dose is delivered to the tumor volume from outside the body. During the last two decades there has been a shift in EBRT for HNC from the use of conformal radiation

therapy (3D-CRT) to Intensity-Modulated Radiation Therapy (IMRT) and Volumetric-Modulated Arc Therapy (VMAT). With IMRT/VMAT it is possible to modulate and shape the dose distribution to a greater extent than with 3D-CRT, and thus better conform the dose to the tumor and reduce radiation dose to the surrounding healthy tissue [23], Figure 6. With the use of IMRT/VMAT in HNC it is possible to increase tumor dose and decrease the risk of radiation-induced toxicity (adverse events) [100]. Several studies have shown a reduction of xerostomia with parotid-sparing IMRT/VMAT, leading to this being implemented as a standard approach to deliver RT in HNC [23, 101]. Now, research also focus on other radiation-induced toxicities e.g. dysphagia and trismus.

Brachytherapy

In brachytherapy, the radioactive sources are placed within or in close proximity to the tumor leading to a steep dose fall outside the irradiated volume. This generates a locally intensive treatment and minimizes radiation dose to surrounding tissues, hence giving better chances of preserving organ function than EBRT in certain situations [102]. Brachytherapy can be delivered as high-dose or low-dose rate depending on activity of the implant and if the treatment is delivered as series of short exposures or continuous. The implants are typically inserted through a plastic catheter into the tumor e.g. in a base of tongue tumor. Brachytherapy is generally used in combination with EBRT [102].

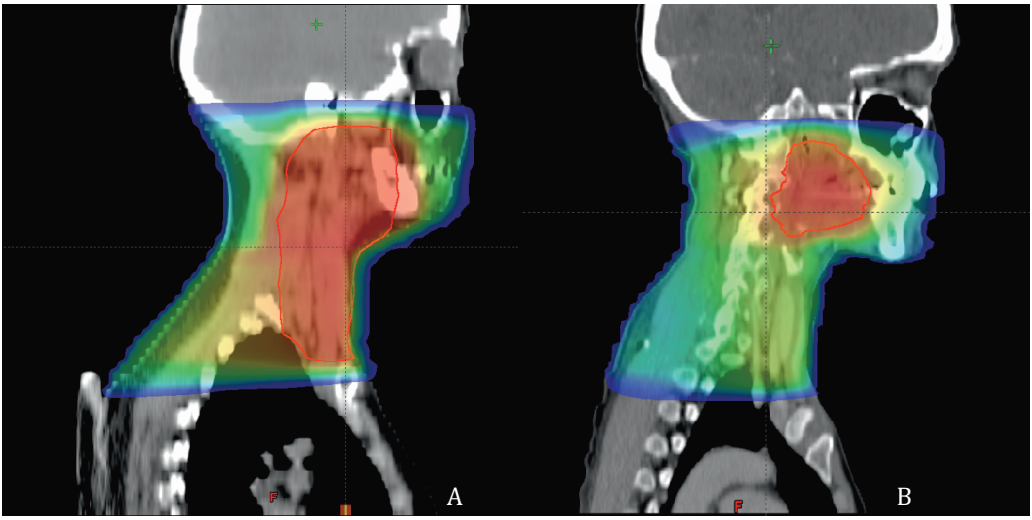

Figure 6. *Comparison of dose distributions with 3D-CRT (A) and IMRT (B). Red=high dose, yellow-green=intermediate dose, blue=low dose.*

Treatment schedules

During a RT treatment session, which takes approximately 10-30 minutes each, a patient to be treated for HNC is immobilized by an individually made thermoplastic head and neck mask. The mask minimizes loss of precision due to movements of the patient and ensures an optimal positioning at every RT session. The RT is prescribed with the assumption that the patient is positioned the exact same way during every treatment session, which makes the preparations before treatment of greatest importance.

RT treatment schedules and guidelines in HNC differ both in between as well as within countries. As mentioned previously, in the Western region of Sweden (VGR) HNC patients are generally treated according to the National care program for head and neck cancer [76]. HNC patients treated with curative intent typically receive 68-70Gy, whereas patients treated pre-operatively receive 46-70Gy and post-operatively 60-70Gy. The dose per fraction is generally 2.0Gy and the patients receive one fraction every day, five days per week. For curative RT the treatment time is generally five to seven weeks.

During the treatment period for the patients included in study I-III in this thesis (2007-2015), RT was initially given as 3D-CRT but for the majority of the period as IMRT or VMAT. Fractionation imply that the total radiation dose is delivered over a period of weeks in a series of fractions instead of being administered as one single large dose. The biological effect depends primarily on the size of fractions, the number of fractions, time between fractions and overall treatment time [96]. Fractionating the radiation dose preserves the normal tissues and can at the same time increase tumor damage. The rationale for this is the fact that normal tissue has a more effective repair system for radiation-induced lesions than tumorous tissue, as long as there is a pause between treatments so that the repair system can be activated [96].

The concept fractionation can be divided into conventional, hyperfractionated, hypofractionated and accelerated fractionation. Conventionally fractionated RT is the general reference treatment schedule for RT where the dose per fraction is around 2.0Gy and the treatment delivered in daily fractions five times per week during a period of five to seven weeks. With respect to conventional fractionated RT, accelerated fractionated RT imply that the overall treatment time is shortened; hyperfractionated RT imply that the number of fractions per day is increased and that the dose per fraction is lowered. The outcome of conventional and hyperfractionated fractionation schedules was studied in the randomized ARTSCAN trial and no statistically significant difference with respect to loco-regional control, overall survival and late toxicity could be shown between the two study arms five years post treatment [103].

Treatment planning and organ-sparing radiotherapy

Planning of the RT is done based on information from the Computed Tomography (CT) scans of the patient and is performed in a computerized treatment planning system. In addition to the tumor and involved lymph nodes, critical structures, so called organs-at-risk (OARs), are identified and delineated in order to assure calculation of the absorbed doses in these structures. Knowing OAR tolerance doses, to not exceed them, is necessary when weighting the desired tumor effect against the risk of treatment complications (toxicity). Examples of OARs in HNC are the spinal cord, the brain stem, the salivary glands, the optic chiasm, the cochlea, the pharynx and larynx [76].

The implementation of IMRT/VMAT has promoted the development of organ-sparing RT. An example is parotid gland-sparing technique aiming

to reduce the risk of xerostomia post-RT. Here, the parotid glands are identified and delineated in the treatment planning system and the dose to the parotid glands is kept below known tolerance doses without jeopardizing tumor control [23, 101, 104]. This is realized by setting specific dose criteria, which are acknowledged by the inverse dose calculation algorithm. For the parotid glands this means keeping the mean dose below 26-30Gy [105].

Investigating relationships between dose to an OAR and a specific complication is a complex process and identified associations need to be carefully evaluated in clinical studies with respect to a secured loco-regional tumor control. In order to decrease the risk of toxicity in healthy tissues tolerance doses (dose-volume constraints) must be established. Dose-volume constraints relate to a certain anatomical structure's probability of radiation-induced toxicity. Dose-volume constraints for dysphagia and potential swallowing structures are being studied but have not yet been as conclusively determined as for the parotid glands.

1.7 RADIATION-INDUCED ADVERSE EFFECTS IN HEAD AND NECK CANCER

Ionizing radiation is the type of radiation most commonly used in the treatment of patients with RT [96]. It exerts its' effect on cancer tumors by damaging the DNA molecule in a cell, e.g. by inducing free-radical and enzyme reactions as well as double-strand breaks, eventually leading to cell death through apoptosis, necrosis, mitotic catastrophe, senescence and autophagy [96]. The tumor cells' impaired ability to repair the damage increases the effect of radiation on the tumor. Different tissues show different sensitivity to radiation leading to the dose-response relationship being different for specific tissues and for tumors versus healthy tissues [96].

The primary goal for RT of cancer patients is tumor eradication and achieving local tumor control, but with the development of more advanced treatment regimens non-lethal treatment-induced adverse effects and preserving organ function have received additional focus. Per definition, a tumor is locally controlled when all tumor cells, with capacity to proliferate and cause recurrence after RT, have been inactivated [96]. If the radiation dose is high enough this will be achieved [96].

Although the intention of RT is to eliminate tumor cells without causing extensive damage in the normal tissue, it is inevitable that normal tissue within the treated volume will be affected to some extent. Depending on the location in the body and the specific tissue type the symptoms will differ. Radiation-induced adverse effects or toxicity is generally divided into acute, late and consequential effects [96]. Acute effects are the side effects appearing during the treatment course and up to 3 months after the completion of RT [96]. Late effects are considered to appear from six months up to several years post-RT. Acute side effects might transcend into a more persistent late effect, usually named a consequential late effect, but a late toxic effect can also surface without being preceded by a corresponding acute effect [96, 106]. The most effective way to limit radiation-induced toxicity in healthy tissues is to decrease the exposure of critical structures adjacent to the tumor from radiation doses that are above the tolerance level of the specific OAR [107].

Acute toxic effects in RT are foremost seen in tissues with a rapid turnover of cells such as epithelial surfaces i.e. skin and intestine mucosa, and are typically reversible [96]. Common acute toxicity in the oral cavity are mucositis (often with secondary opportunistic fungal infections in the

mouth), taste disturbance, xerostomia and dysphagia [48, 108, 109]. Many patients react with dermatitis in the irradiated area and may also develop general fatigue [48, 78]. During the acute toxicity many HNC patients are in need of nutritional support for example through a nasogastric tube and percutaneous endoscopic gastrostomy [48].

Late toxic effects of radiation generally occur in tissues with a slow cell turnover such as bone, muscle, brain and central/peripheral nervous system, fatty tissue and subcutaneous tissue, and may worsen or even become permanent with time [96]. In HNC, the brain, brainstem and spinal cord are considered OARs and they are carefully shielded from excessive radiation dose due to the severity of late toxicity in these structures such as brain edema, necrosis and spinal cord injury [110-112]. Another commonly recognized late radiation-induced toxicity is xerostomia (dry mouth) [104, 113, 114], which together with dysphagia causes substantial suffering for the patients and can be persistent or even deteriorating up to several years after completed RT [104, 115, 116]. Other examples of late effects are osteoradionecrosis of the mandible, trismus, laryngeal edema and thyroid gland dysfunction [96].

1.8 RADIATION-INDUCED DYSPHAGIA IN HEAD AND NECK CANCER

Dysphagia is a complex neuromuscular dose-limiting toxicity after RT for HNC [36, 98] and it may occur as both an acute and late adverse effect [96]. The prevalence of radiation-induced dysphagia varies between 24-89% [14-16, 117-121]. The occurrence differs depending on the swallowing assessment method used (patient-reported instruments, FEES or VFS), the definition of dysphagia chosen as endpoint as well as the assessment time after completed oncological treatment. Before treatment as many as 30-40% of HNC patients experience tumor-related dysphagia [13, 117, 119, 122].

RT for HNC often results in dysfunction in several of the swallowing phases e.g. through reduced oral motor activity, reduced tongue base retraction, pharyngeal dysfunction, reduction of hyolaryngeal elevation, delayed closure of the larynx and impaired opening of the upper esophageal sphincter [3, 4, 48, 54, 123]. This may result in pharyngeal residue and aspiration [119, 120]. Besides malnutrition and dehydration, one of the most serious consequences of dysphagia is aspiration pneumonia, which occurs in up to one in four HNC patients following concurrent chemo-RT [19, 20, 124] and is reported to cause one fifth of the non-cancer related mortality in overall HNC [125]. The patients' general health and HRQL can also be substantially affected [24, 126, 127]. Patients with tumors located in the oropharynx, hypopharynx and larynx more commonly present with dysphagia post-RT [123, 128].

Pathophysiology of radiation-induced dysphagia

The exact mechanisms of late radiation-induced dysphagia are not completely understood. The pathophysiology of radiation-induced dysphagia includes reduced function of so called Dysphagia-Aspiration-Related Structures (DARS), which individually or synergistically cause the symptoms [14, 117, 118, 123]. Soft tissue fibrosis, as an effect of inflammation and reduced blood supply, resulting in decreased muscular compliance as well as reduced muscle strength and contractility has long been considered the primary source of radiation-induced lesions in general [48]. The severity of radiation-induced fibrosis is dependent on radiation dose, fraction size, treatment schedule and the volume irradiated [48]. Muscular atrophy, with associated weakness, may result from disuse of the oropharyngeal musculature during RT when patients often stop eating normal foods while acute RT toxicities are at their peak [107]. Another contributing factor to radiation-induced dysphagia is impaired sensitivity in the

oropharyngeal mucosa. Roughly half of aspirating patients do so silently without normal sensory response and coughing to clear the airway of foreign bolus [107].

Furthermore, radiation-induced xerostomia has been reported to aggravate symptoms of dysphagia [48, 114, 129, 130]. The reduced saliva flow as well as altered composition and properties of the saliva can cause difficulties with bolus manipulation and formation as well as a delayed initiation of the pharyngeal swallow and increased transit times [48]. Trismus (impaired mouth opening) post-RT, also due to fibrosis, can have a negative effect on the swallowing function [4, 48]. Finally, strictures in the pharynx and esophagus may develop after completion of RT, as a consequence of fibrosis, and contribute to dysphagia [48, 131]. A summary of pathophysiological mechanisms in radiation-induced late dysphagia is presented in Figure 7.

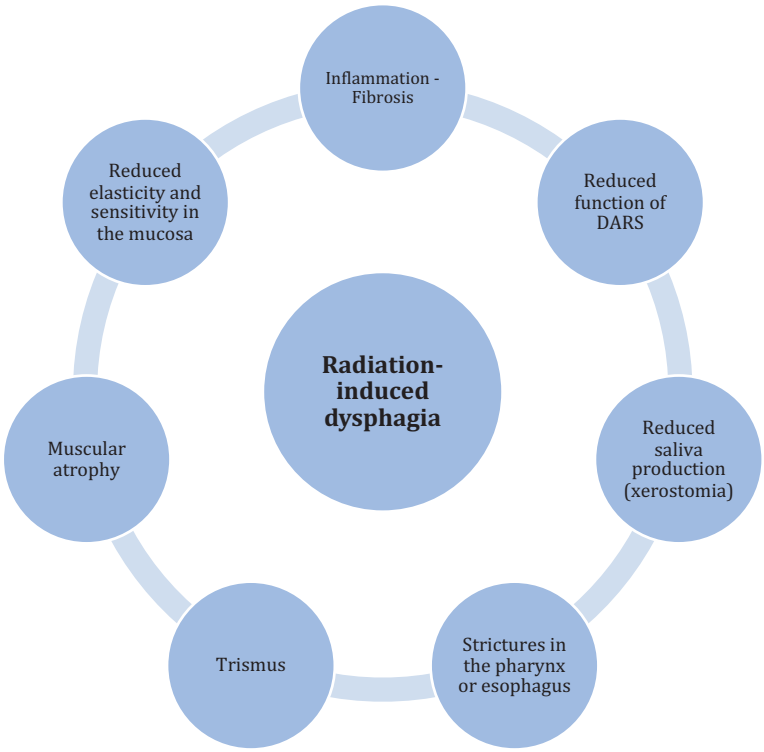

Figure 7. *Pathophysiology in radiation-induced dysphagia*

Dose-volume relationships in radiation-induced dysphagia

The relationship between radiation dose to different specific components of the swallowing apparatus, DARS, and dysphagia has previously been studied. Among previous studies reporting on dysphagia OARs in RT for HNC, radiation doses primarily to the pharyngeal constrictor muscle [15, 113, 115, 124, 132-141] and the larynx [14, 15, 133, 134, 136, 138, 140] have been shown to relate to different aspects of swallowing impairment. Furthermore, doses to the upper esophageal sphincter, the floor of mouth and the genioglossus muscle have also been reported to predict various aspects of swallowing impairment [14, 118, 134, 136, 142].

For the pharyngeal constrictor muscle, mean doses have specifically been reported to predict both clinically determined dysphagia by VFS [15, 115, 134-136, 139, 141] as well as patient-reported dysphagia in terms of specific items of the swallowing domain in EORTC H&N35 [137] and the UW-QOL [141]. Corresponding relationships have been established between mean larynx doses and aspiration by VFS [134, 140, 141] as well as by patient-reported swallowing [14, 15, 134]. Importance of identified substructures for either of these OARs typically depend on which diagnosis is investigated [141]. Specifically, doses above 60Gy to the pharyngeal constrictor muscle and the larynx are reported to predict dysphagia [132, 138, 143, 144]. Table 5 shows a summary of studies investigating dose-volume constraints for DARS.

Table 5. *Summary of research studies evaluating dose-volume constraints for DARS*

Year	Author	No. of patients	OARs delineated	Dysphagia assessment	Results	Dose-volume constraints
2010	Rancati T et al.[138]	QUANTEC review	N/A	N/A	Mean dose to the PCM and larynx >60Gy predicts aspiration.	Minimizing the volume of the PCM and larynx receiving ≥60Gy and when possible ≥50Gy is associated with reduced dysphagia/aspiration.
2011	Eisbruch A et al.[141]	N=73	PCM, glottic and supraglottic larynx, esophagus, oral cavity, major salivary glands	Prospective. Before RT and 3, 12, 24 months post-RT. VFS (aspiration, summary score by SPS); Observer-based CTCAE; eating domain of the HNQOL; swallowing item of the UWQOL	Mean dose to the PCM, supraglottic larynx and esophagus correlated with all dysphagia endpoints. For the subdivided PCM, the superior PCM demonstrated the strongest correlations. For VFS based strictures esophagus mean dose was the most significant predictor.	For increased VFS based aspiration or worsened VFS summary score the tolerance doses $(TDs)_{50}$ were 63Gy for PCM and 56Gy for larynx.
2013	Frowen J et al.[135]	N=55	Superior, middle, inferior PCM. Merged structures of PCM	Prospective. Before RT, 6 months post-RT. VFS (penetration-aspiration, percentage of pharyngeal residue)	Mean dose to the PCM correlated to pharyngeal residue; mean dose superior/middle/inferior and total PCM correlated to penetration-aspiration	Mean PCM dose <60Gy results in better swallowing outcomes.
2013	van der Molen L et al.[139]	N=55 before RT; N=48 10 weeks post-RT; N=36 1 year post-RT	Superior, middle, inferior PCM; mastication structures (e.g. masseter muscle)	Prospective. Before RT, 10 weeks and 1 year post-RT. VFS (PAS-score). Study-specific questionnaire	At 10 weeks: Mean dose to the inferior PCM correlated to PAS. At 1 year post-RT mean dose to the masseter muscle correlated to patient-reported difficulties swallowing solids	V60Gy for PCM predicted PAS at 10 weeks post-RT. V20-60 for the mastication structures were associated with patient-reported difficulties swallowing solids at 1 year post-RT

Year	Author	No. of patients	OARs delineated	Dysphagia assessment	Results	Dose-volume constraints
2015	Christianen ME et al.[144]	N=238	Superior, middle, inferior PCM; cricopharyngeal muscle; esophagus inlet muscle; cervical esophagus, base of tongue, supraglottic and glottic larynx, parotid glands, submandibular glands.	6, 12, 18 and 24 months post-RT. Grade of swallowing dysfunction according to RTOG/EORTC late radiation morbidity scoring criteria. Cut-off ≥2	High dose (>60Gy) to the superior PCM and larynx had the highest risk for severe persistent swallowing dysfunction (grade ≥2 at 6 months and remained up to 2 years post-RT)	V60 for the superior PCM predicted severe persistent swallowing dysfunction
2017	Chera BS et al.[113]	N=45	Bilateral submandibular glands, ipsilateral parotid gland, PCM, cervical esophagus	Before RT and 6 months post-RT. Patient-reported outcome version of the Common Terminology Criteria for Adverse Events (CTCAE)	For the patients reporting a >2 change, V15 to V55 of the combined contralateral glands correlated to xerostomia (N=21; AUC=0.83-0.86); V55-V60 to the PCM correlated to dysphagia (N=9; AUC 0.70-0.75)	Xerostomia: V15 of the combined contralateral salivary glands. Dysphagia: V55 to V60 of the superior PCM.
2017	Soderstrom K et al. [124]	N=124	Superior, middle, inferior PCM, the base of tongue, supraglottic larynx, glottic larynx. Merged structures of the PCM and larynx respectively	Prospective. VFS minimum 25 months after RT-start (aspiration). Patient reported choking (item 38, EORTC H&N 35) 12-60 months post-RT	Mean dose to the PCM correlated to late aspiration (AUC 0.73). Mean dose to the superior PCM correlated to patient-reported choking (AUC 0.66)	Mean dose to the PCM 50Gy. Multivariate model predicting late aspiration: mean dose PCM, age at inclusion in the study and neck dissection post-RT

Year	Author	No. of patients	OARs delineated	Dysphagia assessment	Results	Dose-volume constraints
2018	Kamal M et al.[136]	N=97	Superior, middle, inferior PCM; intrinsic tongue muscle; geniohyoid muscle, genioglossus muscle; mylohyoid muscle, anterior digastric muscle; supraglottic and glottic larynx	Prospective, pre-RT, 3 and 6 months post-RT. VFS (the DIGEST scale)	The geniohyoid/mylohyoid muscle, superior PCM and supraglottic larynx correlated to DIGEST grade ≥2	V61≥18.57% of geniohyoid/mylohyoid muscle predicted DIGEST ≥2
2019	Hutchison AR et al.[143]	Review	N/A	N/A	N/A	Reductions in CTCAE grade 3 dysphagia toxicity were observed when dose to the larynx and PCM was constrained to <50Gy and <60Gy, respectively.

Abbreviations: AUC=area under the Receiver Operating Characteristic (ROC) curve; CTCAE= the Common Terminology Criteria for Adverse Events; DIGEST scale=Dynamic Imaging Grade for Swallowing Toxicity; EORTC H&N 35=European Organization of Research and Treatment of Cancer Quality of Life Questionnaire Head and Neck module; Gy=Gray; HNQOL=Head and Neck Quality of Life questionnaire; N/A= non applicable; OARs=organs-at-risk; PAS=Penetration-Aspiration Scale; PCM=pharyngeal constrictor muscle; RT=radiation therapy; RTOG=The Radiation Therapy Oncology Group; SPS=Swallowing Performance Scale; TD=tolerance dose; UWQOL=University of Washington Quality of Life; VFS=videofluoroscopy; VX=Volume receiving XGy

1.8.1 TREATING RADIATION-INDUCED DYSPHAGIA

The treatment of dysphagia is aimed at maintaining or regaining functional oral feeding while ensuring safe swallowing and preventing aspiration [2, 4, 107]. Dysphagia treatment mainly consists of compensatory and rehabilitative swallowing interventions [48]. Compensatory interventions include head/body postures and modification of food and liquid consistency and bolus size, hence will not change the physiology of swallowing [48]. Rehabilitative interventions, on the other hand, may when used over time result in permanent changes to swallowing physiology. These include range of motion, strength and resistance exercises, as well as specific swallowing maneuvers such as the Mendelsohn maneuver, super-supraglottic swallowing maneuver and the Shaker exercise [48]. To this day randomized studies comparing different swallowing exercises do not provide consensus evidence, although, there are suggestions that procedures aiming to improve strength or coordination of the swallowing act have a positive effect on the swallowing function [131, 145]. In addition, tongue mobility and range of motion exercises have resulted in improved swallowing [131, 145].

Prophylactic swallowing exercises prior to the start of and during RT have gotten increased attention [4, 18, 48, 146]. However, randomized studies comparing different dysphagia-preventive interventions for HNC patients are still few [147, 148]. The prophylactic exercises are believed to minimize the effects of fibrosis on swallowing and are designed to maintain the range of motion, strength, coordination and timing of oral, pharyngeal and laryngeal structural movement [48].

Other treatment options for selected patients with radiation-induced dysphagia include the use of intraoral prosthetic devices, surgery and enteral feeding [4]. Patients with strictures causing the dysphagia may need surgical intervention [145, 149].

2 AIMS OF THE THESIS

The overall aim of this thesis was to investigate various aspects of dysphagia with regard to investigating anatomical risk structures for radiation-induced toxicity, as well as methodological aspects in the evaluation of swallowing function. Another objective was to translate and validate the quality of care instrument SWAL-CARE in a mixed Swedish dysphagia population.

The specific aim for each study was to:

I. Enhance the knowledge about PAS scores for different swallowing attempts as quantified by VFS in HNC patients treated with modern curative (chemo-)RT

II. Investigate relationships between four dysphagia-specific questions and clinically measured swallowing function in HNC after modern curative (chemo-)RT, in order to identify possible alarm symptoms for clinically manifest dysphagia

III. Investigate the relationships between radiation dose to a wide selection of anatomical structures involved in normal swallowing, and late effects quantified by patient-reported as well as by clinically measured swallowing function in HNC patients curatively treated with (chemo-)RT

IV. Translate the instrument SWAL-CARE, measuring quality of care in patients with dysphagia, into a Swedish version (S-SWAL-CARE), and evaluate its psychometric properties in patients with oropharyngeal dysphagia

3 PATIENTS AND METHODS

3.1 STUDY DESIGN

Table 6. *Studies included in the thesis*

	Study design	Subjects (n); Male/Female	Time period for oncological treatment	Oncological treatment given	Inclusion period	Time point for evaluation in the studies	Dysphagia endpoints used
Study I	Prospective, cross sectional	n=38 HNC patients; 26/12	2007-2014	EBRT only or in combination with brachytherapy, with or without chemotherapy, but not with surgery	November 2010 - October 2014	6-36 months after completion of oncological treatment	VFS - PAS Dysphagia defined as PAS ≥2
Study II		n=118 HNC patients; 80/38	2007-2015		November 2010 - January 2016		VFS - PAS DESdC scale Dysphagia defined as: PAS ≥2; DESdC ≥1
Study III		n=90 HNC patients; 60/30		EBRT with or without chemotherapy, but not with surgery	November 2010 - June 2016		
Study IV		n=100 oropharyngeal dysphagia patients; 56/44	N/A	N/A	September 2017 - April 2018	Within 6 months from evaluation of swallowing	N/A

Abbreviations: DESdC = Drinking, Eating, Swallowing difficulties and Coughing when eating/drinking (patient-reported outcome); EBRT=External Beam Radiation Therapy; HNC = Head and Neck cancer; N/A = non applicable; PAS = Penetration-Aspiration Scale; VFS=videofluoroscopy

All patients with newly diagnosed HNC in the Western region of Sweden are referred to the weekly multidisciplinary tumor board at the Otorhinolaryngology clinic at the Sahlgrenska University Hospital, Gothenburg. Participants at the conference include professions involved in the care of HNC patients i.e. head and neck surgeons, oncologists, radiologists and pathologists. At the conference, the cancer diagnosis and treatment are discussed and decided upon. For study I-III, the patients were asked during the conference if they agreed to be contacted after the completion of oncological treatment for potential inclusion in a study.

For study I-III patients with newly diagnosed cancers of the tonsil, base of tongue, hypopharynx or larynx and planned for curative treatment were

identified as potential study participants. Patients having received curative RT +/- chemotherapy were, within 6-36 months post oncological treatment, consecutively offered to undergo a VFS for evaluation of swallowing function. Here after the patients were assessed for eligibility for inclusion. The inclusion period for study I-III diverge, hence the number of patients in the studies differ.

Study I: The VFS for 38 patients were studied. The examination protocol included two swallows each of six different boluses, categorized according to the International Dysphagia Diet Standardization Initiative (IDDSI): 3, 5, 10, 20 ml thin (IDDSI level 0), 5 ml mildly thick (IDDSI level 2) and 3 ml of extremely thick liquid (IDDSI level 4) [150]. All boluses were compared between the first and second swallowing attempt with regard to penetration/aspiration events according to the PAS [7, 8].

Study II: One hundred eighteen patients were enrolled and assessed for dysphagia post-oncological treatment by telephone interview and VFS. A study-specific categorized symptom score was used to determine patient-reported dysphagia (DESdC=presence of Drinking, Eating, Swallowing difficulties, and Coughing when eating/drinking (any combination); scores between 0-4 with 0=no symptom) and the PAS to determine swallowing function by VFS. Swallowing difficulties were defined as DESdC≥1 and PAS≥2. Relationships between clinically relevant cut-offs for DESdC and PAS were explored.

Study III: The 90 patients were assessed for dysphagia post-treatment by telephone interview and VFS. A study-specific categorized symptom score (DESdC, mentioned above) was used to determine patient-reported dysphagia. The PAS was applied to determine swallowing function by VFS (PAS≥4/≥6=moderate/severe dysphagia). Thirteen anatomical structures involved in normal swallowing were individually delineated on the patients' original planning CT scans according to a delineation manual (details in chapter on Treatment-related outcomes). The associated dose-volume histograms (DVHs) for the contoured structures were retrieved. Relationships between structure doses and late toxicity regarding dysphagia were investigated to identify critical anatomical structures for radiation-induced dysphagia.

Study IV: Translation and adaptation of the Swallowing Quality of Care questionnaire (SWAL-CARE) into Swedish was performed using a formal forward-backward translation method according to established international guidelines [1, 38, 39]. A pilot study including a semi-structured

telephone interview was performed in 10 adult oropharyngeal dysphagia patients, selected by the same criteria as the field testing cohort described below. The field testing including psychometric evaluation of the Swedish SWAL-CARE (S-SWAL-CARE, Appendix 1) was performed using 100 patients with oropharyngeal dysphagia due to multiple reasons such as head and neck cancer and neurologic/neuromuscular disease, who had undergone swallowing evaluation within six months prior to the study. The patients answered the patient-reported instruments S-SWAL-CARE, the Quality from the Patient's Perspective (QPP) and the Swallowing Quality of Life (SWAL-QOL). Test-retest was performed in 20% of the participants.

3.2 STUDY PARTICIPANTS

Study I-III

The common inclusion criteria for study I-III were age ≥18, no previous dysphagia, tumor location of the tonsil, base of tongue, hypopharynx or larynx and for the patients to have received curative (chemo-)RT and gone through a VFS examination 6-36 months post-RT.

The common exclusion criteria for study I-III were surgical resection of the tumor, previous oncological treatment prior to HNC diagnosis, tracheostomy as well as presence of neurological or neuromuscular disease.

The specific inclusion and exclusion criteria for the respective studies were as follows:

Study I: Inclusion criteria was PAS score ≥2, indicating abnormal swallowing function according to PAS.

Study III: Exclusion criteria were non-restorable RT treatment plan and for the patient to have received brachytherapy. The rationale behind exclusion of brachytherapy patients was that the brachytherapy dose to the swallowing structures could not be consistently determined.

Study IV: The inclusion criteria for study IV were the participants to be 18 years or above and evaluated for oropharyngeal dysphagia as well as having undergone swallowing examination through VFS, FEES or clinical

evaluation of swallowing by a speech-language pathologist maximum six months prior to contact. Exclusion criteria were insufficient knowledge in the Swedish language in order to complete the questionnaires, severe cognitive impairment and in-patient swallowing examination.

Participant flow chart for the respective studies are shown below (Figure 8 and 9). The patients in study I-III originate from the same cohort, but the number of individuals vary based on different inclusion periods and the different data collections required for the specific research questions. For study II and III the difference in number of patients included is mainly due to patients with brachytherapy as well as non-restorable RT treatment plans being excluded from study III.

An overview of the patient characteristics for study I-III and IV are shown in Table 7 and 8, respectively.

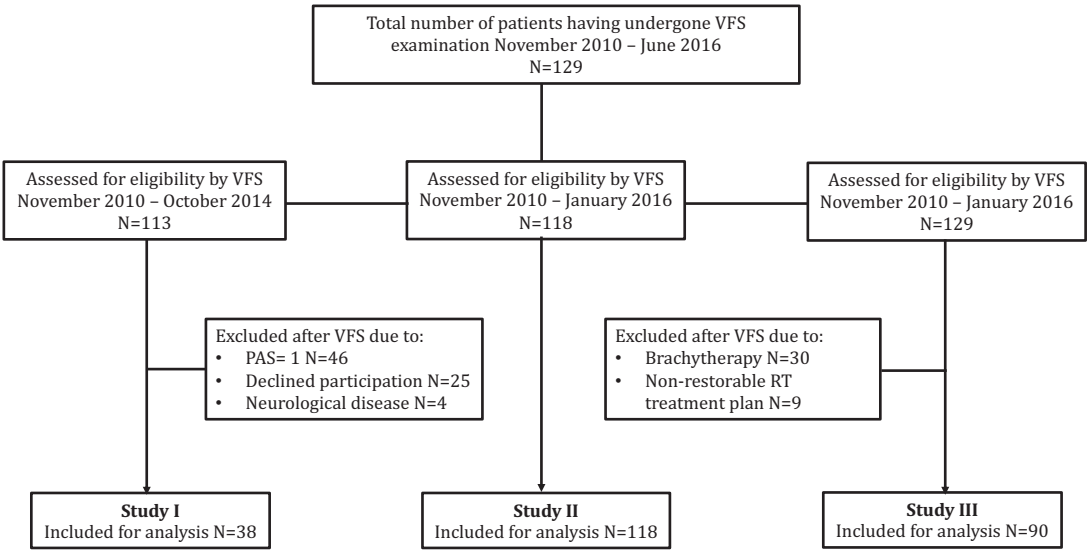

Figure 8. *Participant flow chart for Study I-III*

Abbreviations: N=number of patients; PAS=Penetration-Aspiration Scale; RT=radiation therapy; VFS=videofluoroscopy

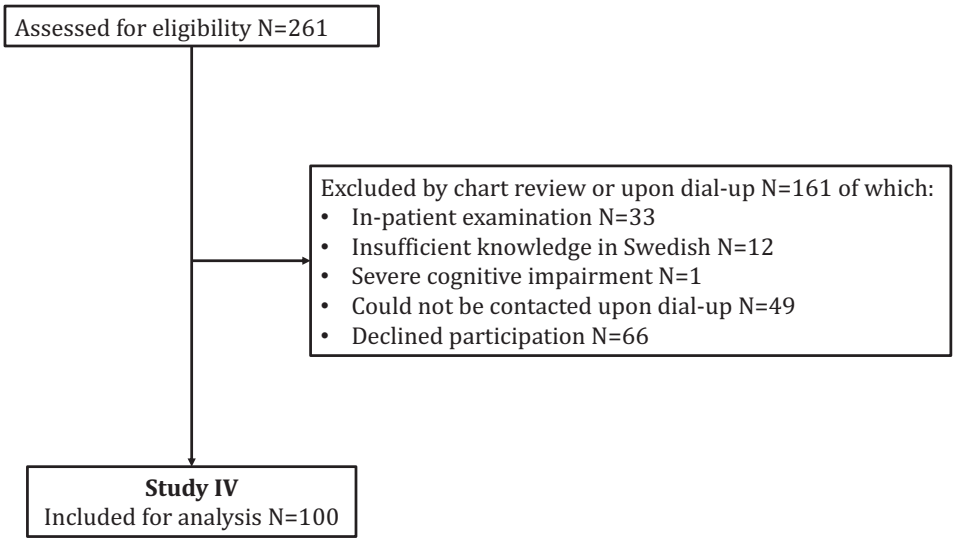

Figure 9. *Participant flow chart for study IV*

Abbreviations: N=number of patients

Table 7. *Patient demographics study I-III*

	Study I	**Study II**	**Study III**
	N=38	N=118	N=90
Assessment time, months post-RT			
Median (range)	7.5 (5-35)	7 (6-36)	7 (5-34)
Age, years			
Median (range)	65 (44-80)	62 (41-88)	62 (37-88)
Gender	n (%)*	n (%)*	n (%)*
Male	26 (68)	80 (68)	60 (67)
Female	12 (32)	38 (32)	30 (33)
Smoking status			
Current smoker	12 (32)	35 (30)	28 (31)
Former smoker**	12 (32)	51 (43)	35 (39)
Never smoked	14 (37)	32 (27)	27 (30)
Tumor location			
Base of tongue	13 (34)	23 (20)	5 (5)
Tonsil	14 (37)	63 (53)	60 (67)
Hypopharynx	4 (11)	8 (7)	6 (7)
Larynx	7 (18)	24 (20)	19 (21)
Tumor stage			
I	5 (13)	16 (14)	12 (13)
II	3 (8)	12 (10)	10 (11)
III	6 (16)	19 (16)	17 (19)
IV	24 (63)	71 (60)	51 (57)
Oncological treatment			
EBRT	7 (18)	27 (23)	26 (29)
EBRT+BT	1 (3)	4 (3)	0 (0)
EBRT+chemotherapy	14 (37)	61 (52)	64 (71)
EBRT+BT+chemotherapy	16 (42)	26 (22)	0 (0)

Abbreviations: BT=brachy therapy; EBRT=external beam radiation therapy; n=number of patients; N/A=non applicable; RT=radiation therapy

* Percentages rounded – therefore it does not always sum up to 100%. ** Former smoker defined as quit smoking > 12 months before start of oncological treatment

Table 8. *Patient demographics study IV*

	N = 100
Age, years	
Median (range)	70 (23-95)
Gender	
Male	56 (56)
Female	44 (44)
Smoking status	
Current smoker	8 (8)
Former smoker*	54 (54)
Never smoked	38 (38)
Primary cause of dysphagia	
Head and neck cancer	28 (28)
Vascular disease (i.e. stroke)	3 (3)
Neurologic or neuromuscular disease	43 (43)
Other cause	26 (26)
Swallowing examination carried out	
Fiberoptic evaluation of swallowing	81 (81)
Videofluoroscopy	9 (9)
Clinical swallowing examination	10 (10)

Abbreviation: n=number of patients
* Former smoker defined as quit smoking > 12 months before start of oncological treatment

3.3 ONCOLOGICAL TREATMENT

The majority of the patients in study I-III in this thesis were treated with IMRT/VMAT, between 70-80%. The reminder of the patients was treated with 3D-CRT. The patients in study I-III in this thesis were generally prescribed conventional fractionation. The prescribed doses were in the range of 64.6-72Gy with 1.9-2.0Gy/fraction once daily, five days a week.

For study I-III, chemotherapy was given as either induction or concomitant therapy. Induction chemotherapy was given to patients with more advanced disease and generally consisted of two cycles of Cisplatin 100 mg/m^2 day one and 5-Fu (5-Fluorouracil) 1000 mg/m^2 per day by continuous infusion day one through five. The cycle interval was 22 days. Concomitant chemotherapy generally consisted of six cycles of Cisplatin 40 mg/m^2 day one, with a cycle interval of seven days.

3.4 OUTCOME MEASURES

Videofluoroscopy of swallowing – the Penetration-Aspiration Scale

In study I-III VFS of the swallowing function was used to clinically score the swallowing ability among the study participants. Details on the procedure are described in Study I and II [151, 152] but in short, the patients were examined seated upright in the lateral position and the field of view included the tip of the tongue anteriorly, the pharyngeal wall posteriorly, the soft palate superiorly, and the seventh cervical vertebra inferiorly. Gastrointestinal radiologists trained in functional assessment of swallowing performed the examinations together with a speech-language pathologist. Six boluses were observed, two swallowing attempts per bolus; 3, 5, 10 and 20 ml of thin barium contrast liquid and 5 ml of a mildly thick iodine contrast and 3 ml extremely thick iodine contrast (categorized according to the IDDSI [150]).

Determination of the PAS score [7, 8] was carried out by two highly experienced gastrointestinal radiologists according to clinical practice at the Sahlgrenska University Hospital. PAS is an equal-appearing interval scale used to describe penetration and aspiration events, ranging from 1 (no material enters the airway) to 8 (material enters the airway, passes below the vocal folds and no effort is made to eject it) [7, 8] (Table 9). For study II and III the worst overall PAS score for each patient, regardless of bolus consistency or swallowing attempt, was used as outcome variable in the statistical analysis.

Table 9. *Rosenbek's Penetration-Aspiration Scale (PAS)* [7].

PAS score	Definition
1	Material does not enter the airway
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
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

Study-specific questions

In study II and III the patient-reported outcome information was collected by a semi-structured telephone interview. The interviews were conducted by speech-language pathologists, following written guidelines. All patients were asked four questions regarding swallowing ability. Do you have difficulties: (1) drinking?; (2) eating?; (3) swallowing?; (4) Do you cough when eating/drinking? From these questions, a study-specific categorised symptom score was constructed, DESdC (acronym for Drinking, Eating, Swallowing difficulties, and Coughing when eating/drinking), describing the presence of any combination of these symptoms. The DESdC score ranges from 0-4; 0=no to all questions; 1=yes

to one question; 2=yes to two questions; 3=yes to three questions; 4=yes to all four questions.

Adult Comorbidity Evaluation-27

The study participants in study II and III were assessed with regards to coexisting somatic and psychiatric illnesses (comorbidity) using the validated instrument Adult Comorbidity Evaluation 27 (ACE-27) [153-155]. The ACE-27 is a comorbidity instrument based on information on the patient's health retrieved from his/her medicinal records. It consists of 27 items divided into twelve categories: cardiovascular system, respiratory system, gastrointestinal system, renal system, endocrine system, neurological system, immunological system, rheumatologic, psychiatric, malignancy, obesity and substance abuse. Each comorbid condition is graded on a four-grade level of severity (none, mild, moderate and severe decompensation).

SWAL-CARE

The SWAL-CARE is a 15-item tool which assesses quality of care and patient satisfaction among patients with oropharyngeal dysphagia. The items are divided into 3 domains: Clinical advice (items 1-6), General advice (items 7-11) and Patient satisfaction (items 12-15). Items 1-11 are answered on a scale from 1-6, where 1=bad; 6=excellent, and items 12-15 are answered on a scale from 1-4, where 1=never; 4=always. Domain scores are calculated by linear transformation to a range from zero to 100, with 0 indicating the least favorable and 100 the most favorable quality of care. All domains in the original SWAL-CARE have been shown to exhibit excellent internal consistency reliability and sufficient short-term reproducibility [72].

The Quality from the Patient's Perspective (QPP)

The QPP is an instrument on quality of care developed and validated in Sweden and it has been adapted to several different health care establishments [156, 157]. In collaboration with the owners of the

questionnaire (IMPROVEIT), the QPP was adapted to be compatible with the care given by swallowing specialists at the otorhinolaryngology clinic at the Sahlgrenska University Hospital (Appendix 2). The QPP consists of 19 items which are answered from two perspectives: perceived reality of quality of care (I have had...) and subjective importance (This is how important it was for me to have...). In the validation of the S-SWAL-CARE questionnaire only the "perceived reality" perspective was used since it matches how the items in the S-SWAL-CARE are phrased. Items 1-16 form four domains: Medical-technical competence, Physical-technical conditions, Identity-oriented approach and Socio-cultural atmosphere. The items are answered on a scale from 1-4, where 1=Completely disagree; 4=Completely agree. A mean score of the items in each domain is calculated, forming the domain score ranging from 1-4 where one (1) indicates poor quality of care and four (4) indicates very good quality of care.

SWAL-QOL

The SWAL-QOL [72] (Appendix 3) is considered the gold standard for evaluating quality of life in individuals with oropharyngeal dysphagia [158, 159]. It has been translated into Swedish and validated by *Finizia et al.* [159]. The SWAL-QOL is a 44-item instrument divided into 10 domains: General burden, Eating desire, Eating duration, Food selection, Communication, Fear, Mental health, Social functioning, Fatigue, Sleep. There is also a symptom-frequency domain, the Symptom scale. The SWAL-QOL Total score is calculated from the general burden, food selection, mental health, social functioning, fear, eating duration and eating desire domains. Domain scores are calculated by linear transformation to a range from zero to 100, indicating an extremely impaired quality of life (0) versus no impairment (100), as experienced by the individual. The domains differentiate normal swallowers from patients with oropharyngeal dysphagia and are sensitive to differences in the severity of dysphagia [7]. The SWAL-QOL has been shown to exhibit good internal-consistency, reliability and short-term reproducibility [72].

Treatment-related outcomes

In study III, the outcome analyses were based on calculated radiation doses to a number of anatomical structures of interest and their relationships to dysphagia. To calculate each structure's absorbed radiation dose, its' volume must be known. For each patient, the volume of each main structure involved in normal swallowing and potentially involved in radiation-induced dysphagia, were defined by delineating its anatomical boundaries on the patient's original planning CT scans. Contouring was performed in the Eclipse™ treatment planning system (version 13.6.6.0, Varian Medical Systems, Palo Alto, U.S.) at the Department of Medical Physics and Biomedical Engineering, Sahlgrenska University Hospital.

A delineation manual for the anatomic boundaries of the OARs, based on review of anatomical literature, discussions with an experienced neuroradiologist, and the guidelines by *Christianen et al*. [160], was developed for study III to ensure contour reproducibility. The potential risk structures identified included both unilateral and bilateral structures: the soft palate, the base of tongue, the genioglossus muscle, the pharyngeal constrictor muscle (superior, middle and inferior), the mylohyoid muscle, the geniohyoid muscle, the hyoglossus muscles, the digastric muscles, the parotid glands, the submandibular glands, the epiglottis, the larynx, the supraglottic larynx, and the upper esophageal sphincter (Figure 10). The delineation guidelines used in study III are attached as Appendix 4. After the contouring was finalized, *Brouwer et al.* [161] published consensus guidelines for delineation of OARs in HNC. These guidelines focus on the main OARs and not all dysphagia risk structures are included. The structures which overlap in the delineation guideline for this thesis and the one of *Brouwer et al.* [161] are the pharyngeal constrictor muscle, the parotid glands, the submandibular glands and the supraglottic larynx. When comparing the two guidelines, the defined anatomical boundaries for the pharyngeal constrictor muscle and the supraglottic larynx are consentient. For the parotid and submandibular glands, the guidelines diverge slightly, mainly regarding the cranial and caudal anatomical borders where our guidelines use the cervical vertebras as anatomical landmarks and *Brouwer at al.* use the soft tissues surrounding the structures.

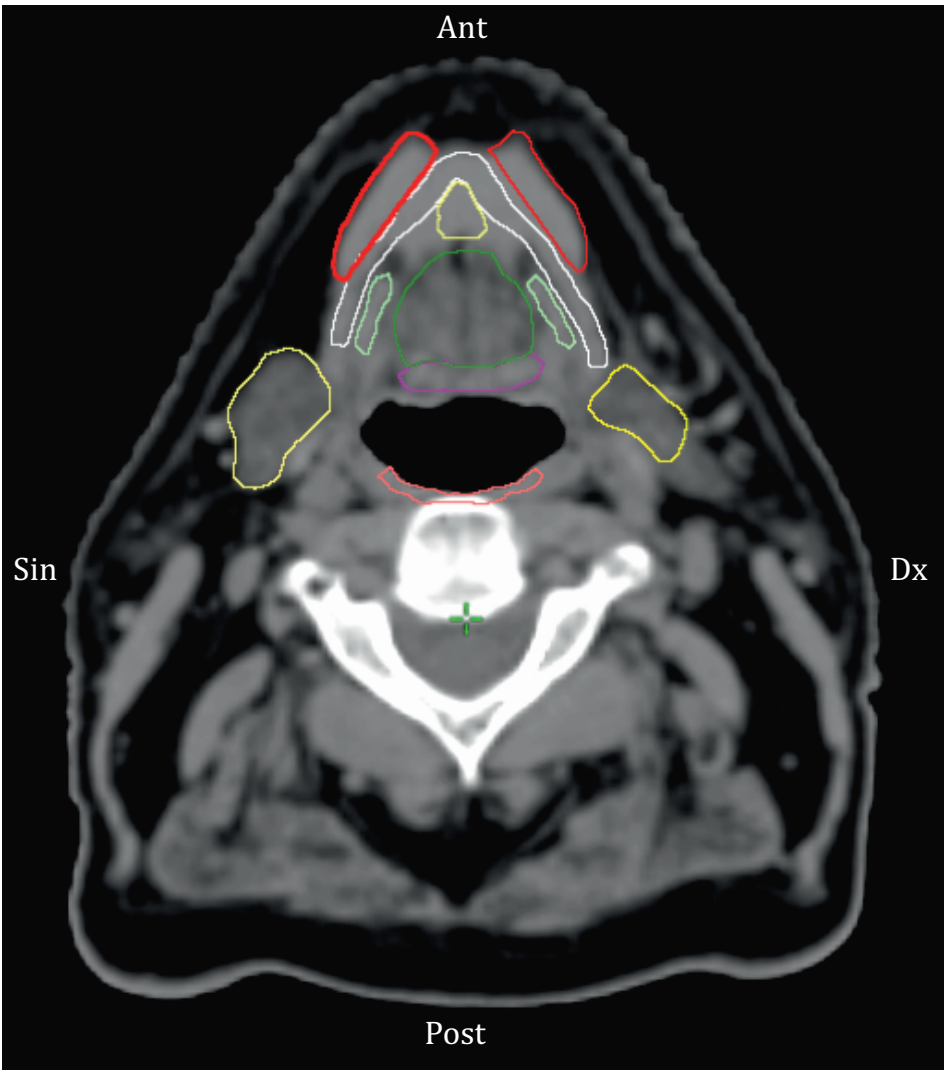

Figure 10. *Delineation of dysphagia risk structures, transversal view. Ant=Anterior (front); Dark green=Genioglossus muscle/Tongue; Dark yellow=Submandibular gland; Dx=Dexter (right); Light green=Hyoglossus muscle; Light yellow=Geniohyoid muscle; Pink=Superior pharyngeal constrictor muscle; Post=Posterior (back); Purple=Base of tongue; Red=Anterior digastric muscle; Sin=Sinister (left); White=Mylohyoid muscle.*

3.5 STATISTICAL ANALYSIS

The distribution of the variables was given as mean and standard deviation (SD) or median and range for continuous variables and as numbers and percentages for categorical variables.

All significance tests were two-tailed and conducted at the 5% significance level ($p<0.05$). SAS® System version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for the statistical analyses in study I, III and IV. In study III, MATLAB v.R2017b (The MathWorks, Inc., Natick, Massachusetts, USA) was also used. For study II Excel (PEARSON function, Microsoft Office Excel 2016) was used for all calculations. Statisticians from Statistiska Konsultgruppen Gothenburg were consulted and performed the statistical analyses for study I, III and IV in this thesis.

Study I: For comparison of change in mean Penetration-Aspiration Scale scores, Wilcoxon signed rank test was used. For comparisons of agreement between the first and second swallow, Intraclass Correlation Coefficient (ICC [2,1] with two-way random and single measure) was calculated. For calculations of the variability between the first and second swallow, intra-individual coefficient of variation (CV) was used. CV was used in order to evaluate within-patient consistency, the variability of the measures in relation to the population mean, where numbers between 0 and 1 were obtained. The CV should generally be low, i.e. close to 0, in order to demonstrate good within-patient consistency.

Study II: The relationships between clinically relevant cut-offs for DESdC and PAS were determined by Pearson's correlation coefficient (Pr). Correlations in the range $Pr \leq 0.39$ were regarded as weak; $Pr=0.4\text{-}0.59$ as moderate and $Pr \geq 0.6$ as strong [162].

Study III: Univariable and multivariable logistic regression analysis (UVA/MVA) was performed with the mean and maximum absorbed doses to the risk structures as predictors for dysphagia, as defined by the two assessment methods (DESdC and PAS). Both forward selection and backward selection MVA was performed. In the MVA potential effects by relevant clinical factors (ACE-27, age, smoking and body mass index [BMI]) was assessed; inclusion criteria for MVA at $p<0.1$ for both dose and clinical factors. Odds-ratios were presented along with their 95% confidence intervals (CI). The discrimination power of each model derived from the MVA was assessed by the area under the Receiver Operating Characteristic (ROC) curve (AUC); Bonferroni-correction for multiple

DVH cutpoint comparisons between patients with and without dysphagia. Relationships between structure doses were determined by Spearman's correlation coefficient (ρ). Correlations in the range ρ≤0.39 were regarded as weak; ρ=0.4-0.59 as moderate and ρ≥0.6 as strong [162].

Study IV: The correlation between each item and its respective domain was assessed through Pearson's correlation coefficient (Pr): Pr≤0.39 correspond to weak correlation; Pr=0.4-0.59 moderate correlation; Pr≥0.6 strong correlation [162]. Internal-consistency reliability was calculated by means of Cronbach's alpha coefficient (range=0–1). Test–retest reliability, as assessed by ICC (2,1), was evaluated for 20 study participants by repeated comparison of the S-SWAL-CARE at the time of enrollment and 2 weeks after. The Spearman correlation coefficient (ρ) was used to assess convergent and discriminant validity. A correlation of ρ<0.3 was considered to be a weak correlation, ρ=0.3–0.7 substantial correlation, and ρ>0.7 strong correlation [163]. Convergent validity was assessed by comparing the respective items and domains in the S-SWAL-CARE with the items and domains in the QPP. Discriminant validity was evaluated through comparison of the S-SWAL-CARE domains to the SWAL-QOL Total score. To evaluate the discriminating ability of the response scales in the S-SWAL-CARE, floor and ceiling effects, i.e. the proportion of patients having the minimum or maximum score, respectively, were explored.

3.6 ETHICAL CONSIDERATIONS

All studies were conducted in accordance with the Declaration of Helsinki and were approved by the Regional Ethical Review Board at the University of Gothenburg, Gothenburg, Sweden. Written informed consent for study participation was obtained from all participants.

4 RESULTS

4.1 STUDY I

The aim of this study was to explore the variation in PAS score, by VFS, between swallowing attempts of the same bolus volume and consistency. For the 38 HNC patients, no statistically significant changes were found when comparing the first and second swallow for any bolus on a group level. However, the ICC for 20 ml thin and 3 ml extremely thick liquid were low (0.3 and 0.1 respectively), indicating that the PAS score for these consistencies varies between swallows. For these boluses, high intra-individual CVs were found (46%-76%). The boluses 3, 5 and 10 ml thin liquid demonstrated similar PAS scores (range 2.2-2.5) as well as ICC (range 0.81-0.86) and intra individual CV (range 17-29%).

4.2 STUDY II

In this patient cohort of 118 HNC patients previously treated with curative modern chemo-RT, 91% of the patients showed swallowing dysfunction according to patient-reported DESdC and 61% according to the PAS, at a median of seven months post oncological treatment. There were weak correlations (Pr≤0.33) between patient-reported DESdC and clinically measured swallowing function by PAS. Every second patient reporting DESdC score ≥3 had severe swallowing difficulties according to PAS (PAS≥6).

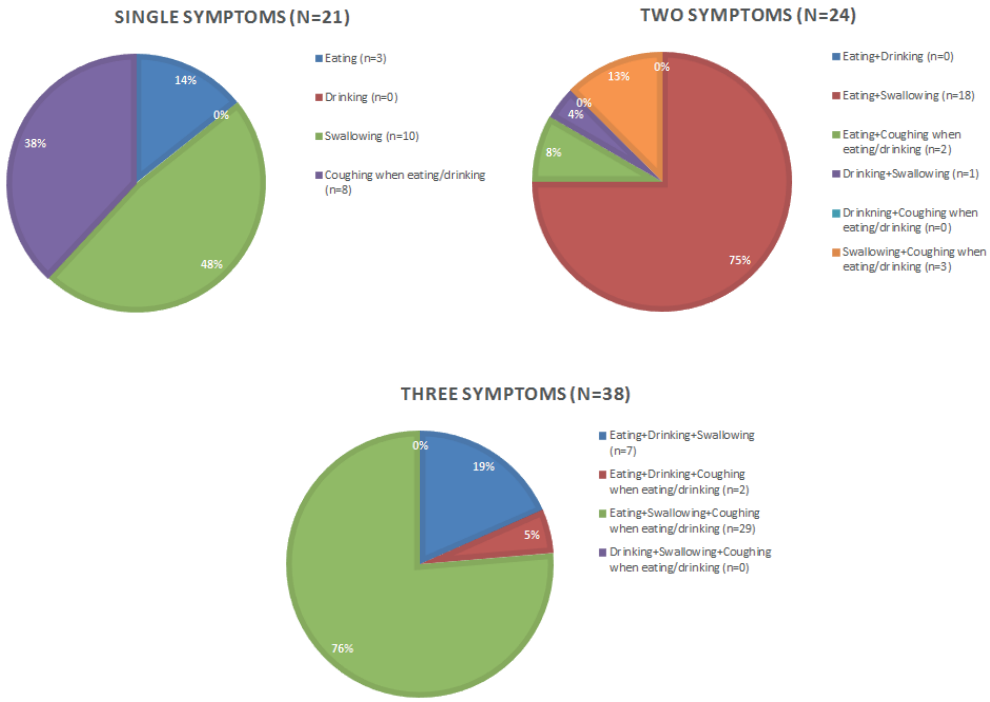

Figure 11. *Distribution of dysphagia symptoms*

Abbreviation: n=number of patients

4.3 STUDY III

The aim of this study was to explore organs-at-risk for radiation-induced late dysphagia. The median assessment time for the 90 patients in the cohort was seven months post (chemo-)RT (range 5-34 months). The mean absorbed radiation dose of the contralateral parotid gland as well as supraglottic larynx and maximum absorbed dose of the contralateral anterior digastric muscle predicted patient-reported late dysphagia (DESdC≥3) (AUC=0.64-0.67). Mean dose of the larynx and the maximum dose of the contralateral submandibular gland predicted moderate dysphagia (PAS≥4) by VFS (AUC=0.76 for both). Last, mean dose to the epiglottis as well as the maximum dose to the contralateral submandibular gland predicted severe dysphagia (PAS≥6) (AUC=0.80 and AUC=0.76, respectively).

In MVA with forward selection, each of the best-performing dose predictors in UVA remained as single strongest predictors for the investigated endpoints, i.e. there were no MVA models including combinations of neither mean nor maximum structure doses. However, in MVA with backward selection, a combination of mean doses of the contralateral parotid gland and supraglottic larynx resulted in a model with an improved discrimination power for DESdC≥3 (OR[95%CI]=1.38-1.58 [1.09-2.11]; p=0.007/0.002; AUC=0.73) than each of the two dose predictors separately (OR[95%CI]=1.23-1.37 [1.00-1.75]; p=0.049/0.013; AUC≤0.67).

Correlations between doses to the epiglottis and the larynx were moderate (mean doses: $\rho<0.6$) whilst doses between the epiglottis and the submandibular glands/pharyngeal constrictor muscle were strongly correlated (mean doses: $\rho=0.8/0.7$). There were also strong correlations between dose to the pharyngeal constrictor muscle and the larynx/submandibular glands (mean doses: $\rho=0.9/0.8$).

Smoking status (current and never smoked) predicted one dysphagia endpoint in UVA (PAS≥4), but its inclusion in the corresponding MVA model did not affect the overall results. The other three clinical variables (age, BMI, comorbidity) did not predict any dysphagia endpoint in UVA and their inclusion in the MVA had no impact on the final result.

The model with the best discrimination power included epiglottis mean dose as predictor of dysphagia evaluated by VFS. DVH thresholds at V60= 60% separated patients with dysphagia from patients without dysphagia.

4.4 STUDY IV

In study IV the SWAL-CARE questionnaire was translated and validated into Swedish. In the field testing, the S-SWAL-CARE demonstrated sufficient reliability, with Cronbach's alpha values ≥0.90 for all domains. All items correlated strongly to their own domain, with weaker correlations to the other domains, indicating proper domain structure. Furthermore, the results also indicate sufficient divergent and discriminant validity when tested for association to the QPP domains and the SWAL-QOL Total score. The test-retest reliability of the S-SWAL-CARE demonstrated sufficient ICC for the General advice domain (0.73) and Clinical advice domain (0.82). The ICC for the Patient satisfaction domain was lower (0.44). This indicates good reproducibility for the General and Clinical advice domain, but somewhat less for the Patient satisfaction domain. The vast majority of the items in the S-SWAL-CARE showed good variability, where the response range spanned mostly all possible values, except for the Patient Satisfaction domain where ceiling effects were shown.

5 DISCUSSION

5.1 ASSESSMENT OF SWALLOWING FUNCTION

Instrumental assessment of the swallowing function plays a key role in dysphagia diagnostics, where VFS and FEES are considered diagnostic gold standard [3]. An accurate estimation of penetration or aspiration in HNC patients is an important objective given that aspiration pneumonia occurs in up to one in four HNC patients following concurrent chemoradiotherapy [20, 124]. A common measure of penetration and aspiration events during swallowing is the PAS [7, 8], which has been found to successfully differentiate between normal and abnormal airway protection in healthy and dysphagia patients in multiple studies [8, 16, 42, 44, 64]. The PAS can be applied in both VFS and FEES. In the assessment protocols for both of these instrumental methods, a series of different bolus volumes and consistencies is tested. Protocols and number of swallowing attempts per bolus differ between studies. Often, but not always, two or more swallowing attempts are performed for each bolus volume and consistency [53, 56, 63].

To this day, there is no consensus on whether to use the mean value from several swallowing attempts, to choose one particular swallow or analyze all swallows [52-56, 63]. For example, *Frowen et al.* [56] indicate that data taken from the mean of several swallows may not be an accurate representation of swallowing function, due to within-bolus variability. Reporting the mean of several swallows is only valid when there are no or small differences between the swallowing attempts [56]. Studies on the variance in PAS score between two consecutive boluses of the same volume and consistency in HNC patients with dysphagia is therefore needed, which was why Study I was conducted. We found that there were no statistically significant differences in PAS score between the first and second swallowing attempt for any of the boluses on a group level. However, the data show differences in PAS score between two subsequent boluses on an individual level and between different volumes and consistencies. For the 20 ml thin liquid, 5 ml mildly thick liquid and 3 ml extremely thick liquid, low ICC and high CV indicated that significant variability exist between the swallowing attempts of these boluses. When assessing the safety of the patient's swallowing function, any tendency to aspirate is important to detect and therefore the "worst" PAS score, regardless of swallowing attempt, should be the most relevant to report.

Identifying a comprehensive measure of dysphagia is challenging due to the complexity of swallowing physiology. There is a dual relationship where there are situations when the patients perceive normal swallowing ability but the instrumental assessment shows severe swallowing dysfunction, but it can also be the opposite that the patients experience severe swallowing impairment but the instrumental assessment show normal or only mild swallowing dysfunction [18, 40-42]. Given that it is known that instrumental assessment of the swallowing function may show weak correlations with patient-reported outcomes on swallowing, it is important to evaluate both aspects in order to perform an as accurate understanding of the swallowing function as possible [18, 42, 121].

Despite this general discrepancy of patients' perception of swallowing and clinically measured swallowing function, a study by *Pauloski et al.* [47] suggests that complaints of dysphagia may act as a reliable indicator of aspiration. The results of Study II in this thesis support this very important aspect. We found that the large majority of the patients with severe swallowing dysfunction according to PAS (≥6), with high risk of aspiration pneumonia as a consequence, reported at least three dysphagia-related symptoms, where very few patients reported difficulties drinking. One probable explanation for fewer patients reporting four symptoms than three symptoms is the occurrence of silent aspiration when consuming liquids. Previous studies demonstrate that liquid consistencies generally result in more penetration/aspiration (higher PAS scores), in patients following HNC-treatment [47, 164]. Furthermore, a study by *Rogus-Pulia et al.* [43] showed that, in their patient cohort, all occurrences of penetration and 83% of aspiration occurrences were "silent". They also showed that higher amounts of pharyngeal residue were found post-treatment compared to pre-treatment, but the patients did not report higher occurrence of food sticking in the throat. For that reason, patients are not always aware of all dysphagia-related symptoms and accordingly do not report them.

Having an easily accessible and reliable screening tool based on patient-reported dysphagia, to use in the everyday clinician-patient encounters, and that indicates if the patient needs further evaluation or treatment would be of great use in clinical practice.

5.2 IMPACT OF RADIATION THERAPY ON SWALLOWING FUNCTION

Dysphagia is a common, severe, dose-limiting toxicity after oncological treatment of HNC. Many HNC patients also experience dysphagia before treatment, due to the tumor's localization, which has to be taken into account when investigating radiation-induced toxicities. Identifying and refining tolerance doses for OARs involved in radiation-induced dysphagia is of great importance since the occurrence can be decreased by reducing the dose below "safe" dose thresholds to involved structures during RT [134, 143, 165]. Previous studies in the field have often only investigated a limited number of swallowing structures (Table 5). In addition, we investigated the impact of laterality and interrelations between dose to different structures, which is not generally done. This is an important aspect for bilateral structures, where it may be important to consider both lateralities for the overall function (c.f. the temporomandibular joint where both sides need to function to enable mouth opening) as well as the possibility to manage by having preserved function on one side (c.f. the salivary glands where functionality of one parotid gland can enable sufficient salivary production).

In study III, the fourteen main anatomical structures involved in normal swallowing and potentially radiation-induced dysphagia, were investigated. Our data showed that the mean dose to the epiglottis, and maximum dose to the contralateral submandibular gland were the statistically strongest predictors for severe dysphagia (PAS≥6) with DVH thresholds at 60Gy and 70Gy to either of them separating patients with and without dysphagia. Models for patient-reported dysphagia, as determined by a study-specific scale, were inferior to models based on the clinical measure (AUC≤0.73 vs. AUC=0.76-0.80). The results add to the current knowledge about OARs for radiation-induced dysphagia in HNC by identifying structures not previously being acknowledged and also underline the importance of taking into account the correlation between dose to different dysphagia risk structures. Our data also stress the importance of keeping a low radiation dose to xerostomia-related risk structures in this context. Previous research has identified the pharyngeal constrictor muscle [15, 113, 115, 124, 132-141], the larynx [14, 15, 133, 134, 136, 138, 140] and the upper esophageal sphincter [14, 134, 142] as OARs for dysphagia in radiation therapy for HNC. Radiation dose to these anatomical structures have been shown to relate to different aspects of swallowing impairment, both clinically determined as well as patient-reported dysphagia.

Our strongest model included mean epiglottis dose as a predictor for severe dysphagia (PAS≥6). However, multiple correlations between investigated dose predictors existed, as did correlations with dose to other previously reported OARs. These correlations also make it difficult to draw any certain conclusion about the role of each individual swallowing structure for the development for radiation-induced dysphagia. In summary, moderate correlations between doses to the epiglottis and the larynx were found, whilst doses between the epiglottis and the submandibular glands/pharyngeal constrictor muscle were strongly correlated. There were also strong correlations between dose to the pharyngeal constrictor muscle and the larynx/submandibular glands. These findings suggest that the interplay between dose to the previously established dysphagia OARs, in particular the pharyngeal constrictor muscle and the larynx, and dose to other less investigated DARS may be more complex than previously reported.

Our results on submandibular gland doses and radiation-induced dysphagia also add to previous data. Since dysphagia is reported to worsen with xerostomia [114, 129, 130] our findings likely capture an indirect negative effect on dysphagia by reduced salivary production as a result of injured submandibular as well as parotid glands. Several studies have demonstrated a correlation between dose to the submandibular gland and xerostomia [166-168], and submandibular doses exceeding 35Gy have been identified as critical in this context [169]. Although, this is a lower threshold than what we identified as critical for separating patients with and without dysphagia at submandibular gland doses of ≥60Gy, our data clearly suggests that this OAR is of importance also for this endpoint.

5.3 PATIENT-REPORTED OUTCOMES AND VALIDATION OF PATIENT-REPORTED INSTRUMENTS

As mentioned previously patient-reported outcomes are important to incorporate as outcome in clinical studies as well as in the everyday patient care. In addition to the QOL aspect, it has become important to evaluate the quality of care from the patient's perspective in order to understand what aspects of the care that the patients consider important as well as their satisfaction with the care given [75]. If patients are not content and do not have confidence in the provided care, there is a great risk that they will not be compliant with the given advice and the risk for dysphagia complications could increase. For the oropharyngeal dysphagia population there is one validated PREM instrument evaluating the quality of care, the SWAL-CARE [72]. The SWAL-CARE was originally developed in English and has not previously been translated and validated into another language. Hence is study IV the first translation and validation study of the SWAL-CARE.

As part of the validation of the S-SWAL-CARE evaluation of the psychometric properties of the instrument was performed. Just as the original SWAL-CARE [72], the S-SWAL-CARE showed high reliability for all domains, with Cronbach's alpha ≥0.90. The validity assessment showed high convergent and discriminant validity of the instrument, as in the original instrument. The S-SWAL-CARE was well accepted by the study participants with high compliance, missing-item values were low and few items were found difficult or disturbing, supporting the feasibility in clinical settings. In two of the three domains, the responses covered the full range of scores and floor and ceiling effects were acceptable. However, for the third domain, the Patient satisfaction domain, ceiling effects were found for all items. This result is similar to the results in the original validation of the SWAL-CARE, where ceiling effects were found in 42% of the Patient satisfaction domain [72]. The explanation in this Swedish population might in part be that when we are to give feedback we are prone to give positive feedback to show that we are content, hence a ceiling effect is shown. Previous research by *Jackson et al.* [170] and *Agoritsas et al.* [171] have shown that patients older than 65 years and those with better functional status are more likely to be satisfied with the given care. Given that the median age in the patient cohort of the present study is 70 years, this could partly explain the ceiling effect. Top scores in this domain show that the patients are content with the given care. However, if a

patient is dissatisfied it would be shown in the Patient satisfaction domain, and therefore this domain is important to take into consideration. Perhaps these patients might need an extra visit, in order for them to properly understand and be given the opportunity to receive answers to any questions or uncertainties they have regarding the given care.

5.4 LIMITATIONS

Generally, it is important with an adequate sample size in research studies. Study I is limited by the sample size, where a larger sample possibly might have yielded statistically significant differences between some of the consecutive swallows. However, the sample size in this study is in the same range as previous studies in the field [54, 56, 63, 164].

For study I-III, the data was collected as patients were followed-up post treatment at different time points, which might be considered a limitation. Effects by assessment time were only investigated in study II (median split analysis) and proved there to have negligible impact on the overall results albeit with a trend of stronger correlations for longer follow-up. The number of individuals in the patient cohorts for study I and III limit how to handle the variable assessment time in the statistical analysis.

In the evaluation of PAS in VFS, if the patient demonstrated a high degree of aspiration (PAS 7-8) on the first swallowing attempt of the bolus, no second attempt was made for the safety of the patient. This means that in study I, boluses where only one swallowing attempt was made were excluded from the analysis, which may have introduced bias towards less variation in PAS within bolus types. Increased reliability of the VFS examinations could be obtained by performing blinded analysis at a separate occasion from the respective examinations, as in study I, as well as by having two radiologists evaluating each examination in order to assess inter-judge reliability. However, the assessments of the VFS examinations in study II and III were performed in collaboration by two professionals, hence the assessments should be reliable.

A limitation in study II and III is that we did not use a validated PRO instrument to evaluate patient-reported dysphagia, but developed and used a study-specific categorized symptom score. However, effects by individual items in commonly used instruments may be hard to identify since items typically are to be summarized according to certain strategies. Using individual questions was of importance for the purpose of study II. One aspect of swallowing, which the study-specific symptom questions do not fully cover, is the aspect of silent aspiration. In a set of questions on dysphagia symptoms, questions on previous pneumonia events and presence of airway discomfort should be included [4, 5].

Study III is an explorative study and the aim was foremost to perform an extensive investigation of radiation dose to all possible OARs for

dysphagia, and to explore the interaction between the OAR doses. More detailed dose-volume response analyses were outside the scope of this thesis.

In the validation of the S-SWAL-CARE we added a response alternative not present in the original instrument. It was requested by the patients to have a response alternative corresponding to "Did not receive any advice" if the question was not applicable to their situation. This response alternative was not included in the scoring and was treated as missing value. It could be considered a limitation to add a response alternative since it may affect the results, given that this leaves room for greater variance of the responses. However, the added response alternative "Did not receive any advice" is not a part of the response scale per se, but accommodates the patient to opt out from answering the item in question. Therefore, the patients who, for example, did not receive advice about "Liquids I should drink" may answer "Did not receive any advice" instead of choosing a response at random, and might therefore result in less variance for this specific instrument.

Study I-III are based on a relatively homogenous patient cohort without multiple comorbidities, which might affect the generalizability of the results. It must be kept in mind that in these studies patients were treated with curative intent for HNC, which would not have been the case if their general health had been severely impaired. Hence, limited comorbidities are to expect in this patient cohort.

5.5 CLINICAL IMPLICATIONS

The results of study I support that in instrumental assessment of swallowing function, i.e. VFS and FEES, it is important to report the worst PAS score to ensure safe swallowing.

The results of study II highlight the importance of incorporating both instrumental assessment and patient-reported information in evaluation of dysphagia. Especially since the occurrence of severe dysphagia as defined as PAS ≥6 is found in 50% of patients reporting three or more dysphagia symptom (Drinking, Eating, Swallowing difficulties, Coughing when eating/drinking).

The results of study III reveal that there is still more to learn about OARs for radiation-induced dysphagia and the complex interactions between them. In particular, the combined effect of doses to salivary glands and different DARS needs to be further explored to decrease the risk of radiation-induced dysphagia in the future. Applying a combined dysphagia- and xerostomia-sparing radiation therapy technique instead of assessing these conditions in isolation may be one strategy.

The SWAL-CARE now is available in Swedish, which provides the possibility for this instrument to be distributed nationally and implemented in clinical practice.

6 CONCLUSION

This thesis highlights the complexity of evaluating swallowing function. It is also demonstrated that a large portion of HNC patients experience swallowing difficulties after completion of (chemo-)RT. Identifying OARs for radiation-induced dysphagia is important in order to, if possible, decrease the radiation dose to these structures and possibly be able to prevent late dysphagia toxicity.

- ◊ In order of testing swallowing safety, the highest PAS score should be reported in VFS.

- ◊ If a patient reports difficulties eating, drinking and swallowing when asked a direct question it is likely that the patient will present with moderate to severe dysphagia according to PAS.

- ◊ In addition to established dysphagia OARs, our data suggest that epiglottis, submandibular and parotid gland doses are important for swallowing function post-RT.

- ◊ Keeping DVH thresholds below V60= 60% and V60=17% for epiglottis and submandibular glands respectively, may increase chances to reduce occurrence of severe late dysphagia.

- ◊ The S-SWAL-CARE can be considered a reliable and valid tool to assess the dysphagia-related quality of care and can be used in clinical practice.

7 FUTURE PERSPECTIVES

This thesis highlights the importance, and the issues of correctly identifying patients developing dysphagia. A simple and correct evaluation needs to be performed to provide the accurate advice and dysphagia treatment, in order to ensure that the patient receives the right care. Further methodological studies, based on larger patient cohorts, are needed in order to determine which types of bolus sizes and consistencies that are most useful in VFS and FEES studies in HNC patients. Today, in dysphagia toxicity studies, it is most often not reported which bolus protocol used and which swallowing attempt the analysis is based on. As this thesis shows, different bolus sizes/consistencies and swallowing attempts can affect the reported swallowing outcome, e.g. PAS, and including this information also when modelling of dysphagia post-RT would improve the data quality.

The usefulness of the four questions on dysphagia-related symptoms (Drinking, Eating, Swallowing difficulties and Coughing when eating/drinking) as a screening tool for swallowing impairment needs to be further investigated. Including questions on previous pneumonia events and presence of airway discomfort in a screening tool could be considered. The categorized symptom score DESdC used in Study II and III for patient-reported dysphagia, needs to be validated and this is a planned project. However, it is our strong belief that questions on drinking difficulties in this context will be of minor importance, while the remaining three questions investigated in this study, will prove to be useful in detecting dysphagia in HNC patients in both outpatient-care and inpatient-care facilities.

To reach a consensus in what anatomical structures are to be considered OARs for late radiation-induced dysphagia, further research is needed to fully understand these complex multi-organ effects and dependencies. Our data indicate that in addition to the established dysphagia OARs, dose to the submandibular gland can be a key player given that xerostomia may be as important for the swallowing function post-RT as dose to the swallowing apparatus itself. We plan to conduct a study focusing on the radiation dose to the submandibular and parotid glands in relation to xerostomia (dry mouth) and dysphagia.

The SWAL-CARE instrument is now available in Swedish to evaluate quality of care in dysphagia patients. Given that quality of care is an important aspect to evaluate, additional translation and validation studies

of the SWAL-CARE should be performed, making the SWAL-CARE questionnaire accessible in more languages than English and Swedish. It is important to look at the Patient satisfaction domain, where many patients score high (i.e. they are satisfied with the given care), and specifically identify the patients who score a lower score, to be able to provide these patients additional care and also be aware of the specified areas where we as health care professionals can improve.

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APPENDIX

Appendix 1

The Swallowing Quality of Care Questionnaire, Swedish version (S-SWAL-CARE)

SWAL-CARE

Att undersöka vårdkvalitet vid sväljningssvårigheter

Instruktioner

Detta frågeformulär är utformat för att ta reda på hur du upplever den vård du får/har fått för dina sväljningssvårigheter.

Även om vissa frågor kan verka lika så skiljer de sig åt och vi ber dig besvara samtliga frågor.

Här är ett <u>exempel</u> på hur en fråga i enkäten ser ut.

Hur skulle du betygsätta de råd du fått inom följande områden?

(Ringa in en siffra på varje rad)

	Råden var						
Råd jag fått av sväljningsspecialist om	**Dåliga**	**Rimliga**	**Bra**	**Mycket bra**	**Utmärkta**	**Enastående**	**Fick inga råd**
1. mat jag borde äta	1	2	3	4	5	6	7

Tack för att du deltar i denna enkätundersökning!

Sväljningsspecialister (logoped eller läkare) är den vårdpersonal du träffar och som undersöker samt behandlar dina sväljningsproblem. Sväljningsspecialisten observerar hur du äter samt dricker och ger dig därefter råd om hur du lättare och mer säkert kan svälja. Sväljningsfunktionen kan även undersökas med röntgen eller genom att filma ditt svalg samtidigt som du sväljer mat och dryck.

Tänk på de eventuella råd du fått av dina sväljningsspecialister.
Hur skulle du betygsätta de råd du fått inom följande områden:

(Ringa in en siffra på varje rad)

	Råden var						
Råd jag fått av sväljningsspecialist om	**Dåliga**	**Rimliga**	**Bra**	**Mycket bra**	**Utmärkta**	**Enastående**	**Fick inga råd**
1. mat jag borde äta	1	2	3	4	5	6	7
2. mat jag borde undvika	1	2	3	4	5	6	7
3. drycker jag borde dricka	1	2	3	4	5	6	7
4. drycker jag borde undvika	1	2	3	4	5	6	7
5. tekniker för att hjälpa mig svälja mat	1	2	3	4	5	6	7
6. tekniker för att undvika att sätta i halsen	1	2	3	4	5	6	7
7. när jag borde kontakta en sväljningsspecialist	1	2	3	4	5	6	7
8. målsättning med behandlingen för mina sväljningsproblem	1	2	3	4	5	6	7
9. mina behandlingsalternativ	1	2	3	4	5	6	7
10. vad jag ska göra om jag sätter i halsen	1	2	3	4	5	6	7
11. tecken på att jag inte får i mig tillräckligt att äta eller dricka	1	2	3	4	5	6	7

Vi är intresserade av dina upplevelser, såväl positiva som negativa, av den vård du fått gällande din sväljning.

(Ringa in en siffra på varje rad)

Under de senaste **3 månaderna** hur ofta har du känt att*:	**Aldrig**	**Ibland**	**Ofta**	**Alltid**
12. du har haft förtroende för dina sväljningsspecialister	1	2	3	4
13. dina sväljningsspecialister förklarade allt om din behandling för dig	1	2	3	4
14. dina sväljningsspecialister hade tillräckligt med tid för dig	1	2	3	4
15. dina sväljningsspecialister satte dina behov först	1	2	3	4

***** *Om du endast träffat sväljningsspecialist vid ett tillfälle tänk utifrån det tillfället.*

Allmänna frågor om dig

När är du född?
Vänligen skriv ditt födelsedatum här: _____/_____/_____
år månad dag

Hur gammal är du idag? _____ år

Är du - (*Ringa in en siffra)*

Man 0
Kvinna 1

Vilken är den högsta utbildningsnivå du avslutat?

Grundskola (1-9 år) 1
Gymnasium (10-12 år) 2
Eftergymnasial utbildning upp till 4 år (13-16 år) 3
Eftergymnasial utbildning mer än 4 år (16+) 4

Hur många år har du gått i skola/studerat? ..... år

Vilket är ditt nuvarande civilstånd? *(Ringa in en siffra)*

Ensamstående..... 1
Gift/sambo..... 2
Särbo 3

Yrkesarbete: *Arbetar du?*

Ja, heltid 2
Ja, deltid ..... 1 Hur många %? _____ %
Nej ..... 0 Arbetssökande ☐₁ Pensionär ☐₂

Rökning

Aldrig rökt..... 0
Tidigare rökt, slutat för mer än 12 månader sedan 1
Tidigare rökt, slutat för mindre än 12 månader sedan 2
Röker 3

Vikt idag: _____ (kg)

Längd: _____ (cm)

Hjälpte någon dig att fylla i detta formulär?

(*Ringa in en siffra)*

Nej, jag gjorde det själv 0
Ja, jag fick hjälp att fylla i det 1

Om någon hjälpte dig att fylla i undersökningen, hur hjälpte den personen dig?

(*Ringa in en siffra)*

Läste frågorna för dig och/eller skrev ner dina svar 1
Besvarade frågorna åt dig 2
Hjälpte till på något annat sätt 3

Har du problem med att:

Äta: ☐1 Ja ☐0 Nej

Dricka: ☐1 Ja ☐0 Nej

Svälja: ☐1 Ja ☐0 Nej

Hostar du i samband med måltid?

☐1 Ja ☐0 Nej

Har du haft lunginflammation under de senaste 6 månaderna?

☐1 Ja ☐0 Nej

Om du svarat ja, hur många lunginflammationer som krävt antibiotika har du haft under de senaste 3 månaderna?

Det vill säga som behandlats med penicillin eller annan antibiotika.

Antal lunginflammationer _____

Har du problem med att gapa? ☐1 Ja ☐0 Nej

Om du vet hur många millimeter (mm) du kan gapa, skriv det här: _____

Vänligen skriv dagens datum här: _____/_____/_____

år månad dag

Här följer några frågor för att utvärdera enkäten, tack för att du hjälper till med detta!

1. Hur lång tid tog det ungefär att fylla i frågeformuläret?

mindre än 10 min ☐$_1$ 10-20 min ☐$_2$ mer än 20 min ☐$_3$

2. Tyckte Du att några av frågorna var oklara eller svåra att besvara? Nej ☐$_0$ Ja ☐$_1$

Om Ja, vilken/vilka gällde det? (Ange frågans/frågornas nummer)

_____

_____

Om Ja, vad var oklart eller varför var det svårt att svara?

_____

_____

_____

3. Tycker du att någon fråga saknades? Nej ☐$_0$ Ja ☐$_1$

Om ja, vilken/vilka frågor saknade Du?

_____

_____

_____

4. Gjorde någon av frågorna Dig orolig? Nej ☐$_0$ Ja ☐$_1$

Om Ja, vilken/vilka gällde det?

_____

_____

_____

5. Saknades det några symtom/besvär som Du har? Nej ☐$_0$ Ja ☐$_1$

Om Ja, i så fall vilka?

_____

_____

_____

Övriga kommentarer:

_____

_____

_____

Tack för ditt deltagande i denna enkätundersökning!

Appendix 2

Quality from the patient's perspective (QPP)

Markera svar i både **A** (☐) och **B** (❍) för varje fråga.	**A** SÅ HÄR VAR DET FÖR MIG					**B** SÅ HÄR BETYDELSEFULLT VAR DET FÖR MIG				
	Instämmer helt	Instämmer till stor del	Instämmer delvis	Instämmer inte alls	Ej aktuellt	Av allra största betydelse	Av stor betydelse	Av ganska stor betydelse	Av liten eller ingen betydelse	Ej aktuellt
1. Jag fick bra information om hur undersökningar och behandlingar skulle gå till	☐	☐	☐	☐	☐	❍	❍	❍	❍	❍
2. Jag fick bra information om resultatet av undersökningar och behandlingar	☐	☐	☐	☐	☐	❍	❍	❍	❍	❍
3. Jag fick bra information om egenvård; "hur jag bäst bör sköta mig"	☐	☐	☐	☐	☐	❍	❍	❍	❍	❍
4. Jag fick bra information om vilken sväljningsspecialist som var ansvarig för min vård	☐	☐	☐	☐	☐	❍	❍	❍	❍	❍
5. Jag fick bästa möjliga medicinska vård (undersökningar och behandlingar) så gott som jag själv kan bedöma	☐	☐	☐	☐	☐	❍	❍	❍	❍	❍
6. Jag fick undersökningar och behandlingar genomförda inom acceptabel väntetid	☐	☐	☐	☐	☐	❍	❍	❍	❍	❍
7. Sväljningsspecialisten verkade förstå hur jag upplevde min situation	☐	☐	☐	☐	☐	❍	❍	❍	❍	❍
8. Sväljningsspecialisten bemötte mig med respekt	☐	☐	☐	☐	☐	❍	❍	❍	❍	❍
9. Sväljningsspecialisten visade engagemang; ”brydde sig om mig”	☐	☐	☐	☐	☐	❍	❍	❍	❍	❍
10. Övrig personal på mottagningen bemötte mig med respekt	☐	☐	☐	☐	☐	❍	❍	❍	❍	❍
11. Jag fick tala med sväljningsspecialisten i enrum vid de tillfällen som jag önskade	☐	☐	☐	☐	☐	❍	❍	❍	❍	❍
12. Jag hade bra möjlighet att delta i beslut när det gällde min behandling	☐	☐	☐	☐	☐	❍	❍	❍	❍	❍

Markera svar i både **A** (☐) och **B** (❍) för varje fråga.	**A** SÅ HÄR VAR DET FÖR MIG					**B** SÅ HÄR BETYDELSEFULLT VAR DET FÖR MIG				
	Instämmer helt	Instämmer till stor del	Instämmer delvis	Instämmer inte alls	Ej aktuellt	Av allra största betydelse	Av stor betydelse	Av ganska stor betydelse	Av liten eller ingen betydelse	Ej aktuellt
13. Det var en trivsam atmosfär på mottagningen	☐	☐	☐	☐	☐	❍	❍	❍	❍	❍
14. Min vård styrdes av mina behov snarare än av personalens rutiner	☐	☐	☐	☐	☐	❍	❍	❍	❍	❍
15. Mina närstående bemöttes på ett bra sätt	☐	☐	☐	☐	☐	❍	❍	❍	❍	❍
16. Jag hade tillgång till den apparatur och utrustning som var nödvändig för min vård (så gott jag själv kan bedöma)	☐	☐	☐	☐	☐	❍	❍	❍	❍	❍

17. Följer du råd och anvisningar du fick av sväljningsspecialisten?

- ☐ Ja, helt och hållet
- ☐ Ja, delvis
- ☐ Nej
- ☐ Vet ej
- ☐ Har inte fått råd och anvisningar av sväljningsspecialisten

18. Hur lätt är det att komma fram på telefon till sväljningsmottagningen?

- ☐ Mycket lätt
- ☐ Lätt
- ☐ Varken lätt eller svårt
- ☐ Svårt
- ☐ Mycket svårt
- ☐ Vet ej

19. Känner du någon tveksamhet när det gäller att på nytt söka denna sväljningsmottagning/motsvarande vid framtida vårdbehov?

- ☐ Ja, stor tveksamhet
- ☐ Ja, ganska stor tveksamhet
- ☐ Ja, viss tveksamhet
- ☐ Nej, ingen tveksamhet
- ☐ Vet ej

Appendix 3

The Swallowing Quality of Life Questionnaire (SWAL-QOL)

Instructions for Completing the SWAL-QOL Survey

This questionnaire is designed to find out how your swallowing problem has been affecting your day-to-day quality of life.

Please take the time to carefully read and answer each question. Some questions may look like others, but each one is different.

Here's an <u>example</u> of how the questions in the survey will look.

1. In the last month how often have you experiences each of the symptoms below.

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
Feel weak	1	2	3	4	5

Thank you for your help in taking part in this survey!

IMPORTANT NOTE: We understand that you may have a number of physical problems. Sometimes it is hard to separate these from swallowing difficulties, but we hope that you can do your best to concentrate ***only*** on your ***swallowing problem.*** Thank you for your efforts in completing this questionnaire.

1. Below are some general statements that people with ***swallowing problems*** might mention. In the last month, **how true** have the following statements been for you.

(circle one number on each line)

	Very much true	**Quite a bit true**	**Somewhat true**	**A little true**	**Not at all true**
Dealing with my swallowing problem is very difficult.	1	2	3	4	5
My swallowing problem is a major distraction in my life.	1	2	3	4	5

2. Below are aspects of day-to-day eating that people with ***swallowing problems*** sometimes talk about. In the last month, **how true** have the following statements been for you?

(circle one number on each line)

	Very much true	**Quite a bit true**	**Somewhat true**	**A little true**	**Not at all true**
Most days, I don't care if I eat or not.	1	2	3	4	5
It takes me longer to eat than other people.	1	2	3	4	5
I'm rarely hungry anymore.	1	2	3	4	5
It takes me forever to eat a meal.	1	2	3	4	5
I don't enjoy eating anymore.	1	2	3	4	5

3. Below are some physical problems that people with ***swallowing problems*** sometimes experience. In the last month, **how often** you have experienced each problem as a result of your swallowing problem?

(circle one number on each line)

	Almost always	**Often**	**Sometimes**	**Hardly ever**	**Never**
Coughing	1	2	3	4	5
Choking when you eat food	1	2	3	4	5
Choking when you take liquids	1	2	3	4	5
Having thick saliva or phlegm	1	2	3	4	5
Gagging	1	2	3	4	5
Drooling	1	2	3	4	5
Problems chewing	1	2	3	4	5
Having excess saliva or phlegm	1	2	3	4	5
Having to clear your throat	1	2	3	4	5
Food sticking in your throat	1	2	3	4	5
Food sticking in your mouth	1	2	3	4	5
Food or liquid dribbling out of your mouth	1	2	3	4	5
Food or liquid coming out your nose	1	2	3	4	5
Coughing food or liquid out of your mouth when it gets stuck	1	2	3	4	5

4. Next, please answer a few questions about how your ***swallowing problem*** has affected your diet and eating in the last month.

(circle one number on each line)

	Strongly agree	**Agree**	**Uncertain**	**Disagree**	**Strongly disagree**
Figuring out what I can and can't eat is a problem for me.	1	2	3	4	5
It is difficult to find foods that I both like and can eat.	1	2	3	4	5

5. In the last month, **how often** have the following statements about communication applied to you because of your ***swallowing problem***?

(circle one number on each line)

	All of the time	**Most of the time**	**Some of the time**	**A little of the time**	**None of the time**
People have a hard time understanding me.	1	2	3	4	5
It's been difficult for me to speak clearly.	1	2	3	4	5

6. Below are some concerns that people with ***swallowing problems*** sometimes mention. In the last month, **how often** have you experienced each feeling?

(circle one number on each line)

	Almost always	**Often**	**Sometimes**	**Hardly ever**	**Never**
I fear I may start choking when I eat food.	1	2	3	4	5
I worry about getting pneumonia.	1	2	3	4	5
I am afraid of choking when I drink liquids.	1	2	3	4	5
I never know when I am going to choke.	1	2	3	4	5

7. In the last month, how often have the following statements **been true** for you because of your ***swallowing problem***?

(circle one number on each line)

	Always true	**Often true**	**Sometimes true**	**Hardly ever true**	**Never true**
My swallowing problem depresses me.	1	2	3	4	5
Having to be so careful when I eat or drink annoys me.	1	2	3	4	5
I've been discouraged by my swallowing problem.	1	2	3	4	5
My swallowing problem frustrates me.	1	2	3	4	5
I get impatient dealing with my swallowing problem.	1	2	3	4	5

8. Think about your social life in the last month. How strongly would you agree or disagree with the following statements?

(circle one number on each line)

	Strongly agree	**Agree**	**Uncertain**	**Disagree**	**Strongly disagree**
I do not go out to eat because of my swallowing problem.	1	2	3	4	5
My swallowing problem makes it hard to have a social life.	1	2	3	4	5
My usual work or leisure activities have changed because of my swallowing problem.	1	2	3	4	5
Social gatherings (like holidays or get-togethers) are not enjoyable because of my swallowing problem.	1	2	3	4	5
My role with family and friends has changed because of my swallowing problem.	1	2	3	4	5

9. In the last month, **how often** have you experienced each of the following physical symptoms?

(circle one number on each line)

	All of the time	**Most of the time**	**Some of the time**	**A little of the time**	**None of the time**
Feel weak?	1	2	3	4	5
Have trouble falling asleep?	1	2	3	4	5
Feel tired?	1	2	3	4	5
Have trouble staying asleep?	1	2	3	4	5
Feel exhausted?	1	2	3	4	5

10. Do you now take any food or liquid through a feeding tube?

(circle one)

No 1

Yes..... 2

11. Please circle the letter of the one description below that best describes the consistency or texture of the food you have been eating most often in the last week.

Circle one:

A. Circle this one if you are eating a full normal diet, which would include a wide variety of foods, including hard to chew items like steak, carrots, bread, salad, and popcorn.

B. Circle this one if you are eating soft, easy to chew foods like casseroles, canned fruits, soft cooked vegetables, ground meat, or cream soups.

C. Circle this one if you are eating food that is put through a blender or food processor or anything that is like pudding or pureed foods.

D. Circle this one if you take most of your nutrition by tube, but sometimes eat ice cream, pudding, apple sauce, or other pleasure foods.

E. Circle this one if you take all of your nourishment through a tube.

12. **Please circle the letter** of the one description below that best describes the consistency of liquids you have been drinking most often in the last week.

Circle one:

A. Circle this if you drink liquids such as water, milk, tea, fruit juice, and coffee.

B. Circle this if the majority of liquids you drink are thick, like tomato juice or apricot nectar. Such thick liquids drip off your spoon in a slow steady stream when you turn it upside down.

C. Circle this if your liquids are moderately thick, like a thick milkshake or smoothie. Such moderately thick liquids are difficult to suck through a straw, like a very thick milkshake, or drip off your spoon slowly drop by drop when you turn it upside down, such as honey.

D. Circle this if your liquids are very thick, like pudding. Such very thick liquids will stick to a spoon when you turn it upside down, such as pudding.

E. Circle this if you did not take any liquids by mouth or if you have been limited to ice chips.

13. In general, would you say your health is:

(circle one)

Poor 1

Fair 2

Good 3

Very Good 4

Excellent 5

Appendix 4

Anatomical boundaries for the delineated dysphagia-aspiration-related structures (DARS)

Appendix 4. Anatomical boundaries for the delineated dysphagia-aspiration-related structures (DARS)

DARS	Anatomical boundaries					
	Cranial	Caudal	Anterior	Posterior	Lateral	Medial
PCM (total)	Pterygoid plates (C1)	Lower edge of the cricoid cartilage	Pharyngeal lumen; Posterior wall of hypopharynx	Retropharyngeal fat (space), anterior to the spine	Medial pterygoid muscle; hyoid bone; thyroid cartilage	
Superior PCM	Pterygoid plates (C1)	Lower edge of C2	Pharyngeal lumen	Retropharyngeal fat (space), anterior to the spine	Medial pterygoid muscle	
Middle PCM	Upper edge of the hyoid bone (upper C3)	Lower edge of the hyoid bone (upper C4)	Pharyngeal lumen	Retropharyngeal fat (space), anterior to the spine	Hyoid bone	
Inferior PCM	Lower edge of the hyoid bone (upper C4)	Lower edge of the cricoid cartilage	Posterior wall of hypopharynx	Retropharyngeal fat (space), anterior to the spine	Superior horn of thyroid cartilage	
Base of tongue	Lower edge of C1	Upper edge of the hyoid bone/floor of mouth	Anterior two thirds of the tongue	Pharyngeal lumen	Medial pterygoid muscle; mylohyoid muscle	
Epiglottis	Varies depending on position of the larynx	Varies depending on position of the larynx, mostly inferior C4.	Hyoid bone	Pharyngeal lumen		
Submandibular gland	Inferior C2	C4	The mandible	Sternocleidomastoid muscle	The mandible; Medial pterygoid muscle	Floor of mouth; base of tongue
Parotid gland	Base of skull	C3	The mandible; masseter muscle	Neck musculature		
Larynx total	Upper edge of the hypoid bone; tip of the epiglottis	Lower edge of the cricoid cartilage	Hyoid bone; pre-epiglottic space; thyroid cartilage	Pharyngeal lumen	Thyroid cartilage	
Supraglottic larynx	Upper edge of the hypoid bone; tip of the epiglottis	Upper edge of the cricoid cartilage	Hyoid bone	Pharyngeal lumen	Thyroid cartilage	
Hyoglossus muscle	Intrinsic tongue musculature	Hyoid bone	Genioglossus muscle		Mylohyoid muscle	Mylohyoid muscle
Mylohyoid muscle	Genioglossus muscle	Digastric muscle	Interior surface of the mandible	Masseter muscle		
Geniohyoid muscle	Genioglossus muscle	Floor of mouth/mylohyoid muscle	Interior surface of the mandible; mylohyoid muscle	Genioglossus muscle; interior surface of the hyoid bone		
Digastric muscle	Floor of mouth/mylohyoid muscle	Platysma muscle	Interior surface of the mandible	Hyoid bone		
Genioglossus muscle (tongue)	Lower edge of C1	Floor of mouth	Mandible	Base of tongue		
Soft palate	Base of scull; pharyngeal lumen	C1; pharyngeal lumen	Hard palate	Anterior pharyngeal wall; uvula		
Upper esophageal sphincter	Lower edge of the cricoid cartilage	Lower edge of the third tracheal ring.	Tracheal lumen	Retropharyngeal fat (space), anterior to the spine		

Abbreviations: CX=cervical vertebra X; DARS=dysphagia-aspiration-related structures; PCM=pharyngeal constrictor muscle

Study I

Study II

Study III

Study IV