New insights into the diagnostic workup of oropharyngeal dysphagia in head and neck cancer patients

NEW INSIGHTS INTO THE DIAGNOSTIC WORKUP OF OROPHARYNGEAL DYSPHAGIA IN HEAD AND NECK CANCER PATIENTS

Integration of fiberoptic endoscopic evaluation of swallowing and patient-reported outcome measures for clinical decision making

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Colofon

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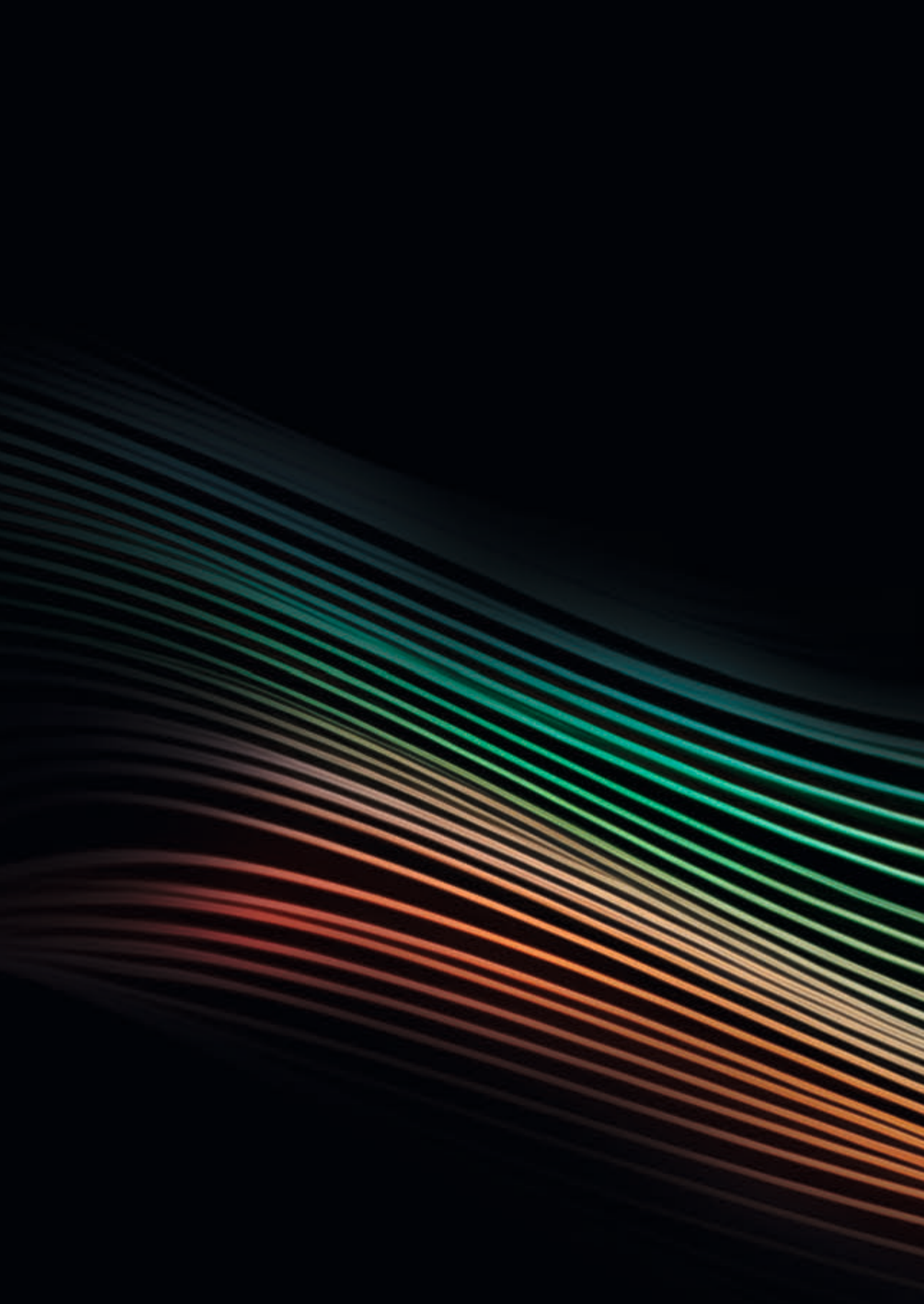
CHAPTER OVERVIEW



CHAPTER 1

GENERAL INTRODUCTION

Head and neck cancer and oropharyngeal dysphagia

Head and neck cancer (HNC) accounts for nearly 4.9% of all new cancer diagnoses worldwide [1]. In the Netherlands, approximately 3000 patients are diagnosed with HNC each year [2]. Alcohol and tobacco consumption are well-known risk factors for the development of HNC [3]. In addition, infection with human papillomavirus (HPV) is associated with HNC, in particular with the development of oropharyngeal squamous cell carcinoma [4]. Oncological treatment may comprise surgery, radiation, chemo/bioradiation, or combinations thereof referred to as multimodality treatment. The type of oncological treatment (single versus multimodality) is based on, among others, tumor site, tumor size (early versus advanced tumor stage), overall stage grouping of the cancer, individual patient characteristics, etc. Despite recent advances in oncological treatment such as transoral robotic surgery, intensity-modulated radiation therapy, life-extending targeted therapy, and prehabilitation strategies, morbidity and mortality rates remain substantial among HNC patients [5]. HNC patients are frequently confronted with multiple short- and long-term sequelae of their locoregional disease and its treatment. Loss of upper aerodigestive tract function such as swallowing impairment, dysphonia, airway obstruction, and dysarthria can lead to a poor health-related quality of life (HRQoL) [6]. This function loss emphasizes the need for continuous improvement of pre- and rehabilitation strategies [7]. Increased recognition of the complex needs for rehabilitation of HNC survivors is crucial [8], especially as the prevalence of HNC is expected to rise due to an increasing incidence of HPV-positive HNC [9] and an ageing population. Patients with HPV-positive oropharyngeal carcinoma, which is considered a distinct disease entity [10], tend to be younger and healthier compared to patients with HPV-negative HNC [4, 9]. HPV-positive HNC patients also have a better prognosis [5], contributing to improved long-term survival. Although HPV vaccines have been available for girls since 2010 in the Netherlands and for boys since 2022, the impact of HPV vaccines on the prevention of HPV-positive HNC will probably remain unknown for decades to come [9, 11]. Among HNC survivors, the needs for rehabilitation may differ across various health domains including the physical, emotional, and social domain. HNC survivors may face different challenges as they try to reintegrate into society or return to work. This underlines the importance of providing and optimizing person-centered rehabilitation of HNC survivors [12].

HNC affects the most important basic needs in life such as the ability to eat, to communicate verbally, and to interact socially, which can have detrimental effects on patients' HRQoL [13, 14]. In addition to the uncertainty about one's chances of survival after oncological treatment, patients may have major concerns regarding all these aspects of function loss. Swallowing impairment is one of the most prevalent forms of function loss in HNC patients and it deeply affects one's life. Swallowing is essential to everyday life: it plays a key role in achieving nutritional requirements and eating is also an important social activity as patients who eat together with others are expected to have a wider social network [15].

Swallowing is a complex neurologically driven sensory-motor function. It is historically arbitrary divided into an oral preparatory, oral transport, pharyngeal, and esophageal phase,

and all these phases of swallowing can be affected by HNC and/or its oncological treatment [16]. HNC-related oropharyngeal dysphagia (OD) can result from abnormalities of muscles, nerves or other structures of the oral cavity, pharynx, larynx, and upper esophagus. OD or impaired swallowing refers to difficulty or the inability to swallow liquids and/or foods in a safe and efficient manner [17]. OD is common among HNC patients, as up to 64% of the patients experience OD following oncological treatment [18]. Patients may also present OD prior to oncological treatment due to the primary tumor and/or cancer cachexia, and pre-treatment OD in HNC patients can predict impaired swallowing function after treatment completion [19, 20]. In addition, patients presenting with locoregionally advanced tumor stages with extensive lymph node metastases often demonstrate invasion of important swallowing structures such as cranial nerves and muscles [21]. These patients may also have higher levels of cancer metabolism, including cytokine production, thereby increasing the risk of cancer cachexia and loss of skeletal muscle mass, thus contributing to OD [22, 23].

Moreover, dental health problems and dental extractions prior to radiation may result in impaired mastication, further aggravating swallowing dysfunction [24]. Next to tumor-induced OD, oncological treatment can cause various acute and late adverse effects on swallowing function due to, for example, surgical sacrifice of important swallowing structures and/or chemo/bioradiation-induced alterations of tissue such as mucositis, xerostomia, radioneuropathy, fibrosis, and trismus [21]. Furthermore, masticatory and swallowing difficulties can cause dietary restrictions, which may contribute to an impaired nutritional status, increased risk of malnutrition, and loss of skeletal muscle mass [18, 25].

Among cancer patients, the HNC population is a distinct subgroup of individuals with a high prevalence of psychosocial vulnerability [26]. Increased levels of affective symptoms have been reported in HNC patients [14, 27]. Psychological distress, including depression and anxiety disorders, is related to alcohol and tobacco consumption [28, 29]. Alcohol and tobacco are in turn well-established risk factors for the development of HNC, closing the vicious circle [3]. Previous research also found an association between affective symptoms and OD in HNC patients [30, 31] emphasizing the importance of integrating information on psychosocial status into OD rehabilitation.

In summary, there are several factors that may influence the presentation and consequently the management of OD in HNC patients. The biophysiological features of OD can be measured using instrumental imaging techniques such as fiberoptic endoscopic evaluation of swallowing (FEES) or videofluoroscopic swallowing study (VFSS) [32]. However, dynamic imaging does not provide any information on other dimensions of swallowing impairment such as the patient's perception and burden of OD nor on other important issues such as a status of underlying malnutrition or psychological distress. This underlines the need for a multidimensional diagnostic workup of OD including the use of clinician-reported outcome measures (CROMs) such as measurements performed during FEES, and patient-reported outcome measures (PROMs) on swallowing, symptom burden, malnutrition, etc.

The studies in this thesis focus on new insights into the diagnostic workup of OD in HNC patients which can be applied in daily practice. Multiple aspects of the diagnostic workup of OD are explored in this thesis including the safety of methylene blue as food dye during FEES, the association between and the mutual effect of symptoms of impaired swallowing safety and efficiency using visuoperceptual variables to measure aspiration and pharyngeal residue during FEES, and the reproducibility of a frequently used HNC-specific overall pharyngeal dysphagia severity scale for FEES.

As mentioned previously, OD can be described as a biophysiological phenomenon which can be expressed in outcomes using FEES or VFSS, or expressed in terms of severity of OD sequelae such as the number of aspiration pneumonias, the presence of malnutrition, etc. Yet OD can also be evaluated using another dimension namely the patient's the perspective using PROMs. The five main domains of health are physical, mental, emotional, spiritual, and social health [33, 34], and OD can have an impact on all of these domains. PROMs can be used to determine a patient's perception on health [35], and PROMs can capture the disease characteristics, issues, and outcomes that matter to the patient [36]. PROMs on symptoms and symptom burden may identify symptoms not otherwise captured by history taking and instrumental imaging during diagnostic workup, and these outcomes are best assessed through self-report [35] and subsequently integrated into OD rehabilitation. This thesis explores and integrates different dimensions of OD namely patient's perspective on swallowing impairment and on OD-related consequences, and measures on the actual nature and severity of OD.

New insights into the diagnostic workup of oropharyngeal dysphagia in head and neck cancer patients

A comprehensive diagnostic workup of OD is often carried out using an instrumental imaging technique such as FEES and/or VFSS [37]. Both are considered gold standard imaging techniques to evaluate swallowing function including the nature and severity of OD. FEES and VFSS provide complimentary information as both imaging techniques visualize completely different aspects of swallowing function [37-39]. Both imaging techniques have their pros and cons. Patients swallow different bolus consistencies during the transnasal flexible pharyngolaryngoscopy of the FEES procedure. FEES provides an excellent visualization of the anatomical and physiological changes of the pharynx and larynx in HNC patients and allows a comprehensive evaluation of swallowing safety and efficiency during the pharyngeal phase of deglutition [38, 40]. Furthermore, minor abnormalities of the surface mucosa of the pharynx and larynx that may be consistent with new malignant lesions or recurrent disease can be visualized with FEES [41]. Another positive aspect of FEES is the assessment of pharyngolaryngeal sensibility, the location and severity of, and response to saliva residue in the pharynx and larynx. Compared to VFSS, FEES is an imaging technique without radiation exposure, which is of added value as the majority of HNC patients already has significant exposure to ionizing radiation during the oncological workup, oncological treatment, and/or follow-up period [42-44]. VFSS is another widely used imaging technique to evaluate swallowing function based on a dynamic x-ray procedure. Swallowing anatomy

and physiology are visualized using high-frequency pulsed fluoroscopy. The field of imaging must cover the oral cavity, pharynx, and (upper) esophagus at least in lateral position but, if possible, also in anteroposterior position [39, 45]. Unlike FEES, VFSS also visualizes the preparation of solid foods during mastication and bolus transport in the oral and esophageal phase of swallowing [39].

Use of methylene blue during fiberoptic endoscopic evaluation of swallowing

As previously described, FEES is a particularly suitable imaging technique to evaluate swallowing function in HNC patients. Despite the wide use of FEES, there is no consensus on the use of any type of medical or commercial food dye [46, 47]. In our search of optimizing swallowing evaluation, a medical blue dye, i.e., methylene blue was chosen to enhance visualization of bolus transit in the pharynx during FEES. Methylene blue is an officially authorized drug in the European Union and it can be stored without refrigeration in contrast to natural-colored products such as yellow pudding or milk [48]. However, according to the United States Food & Drug Administration (FDA) and the European Medicines Agency (EMA), the only registered indication for methylene blue is the intravenous treatment of acute methemoglobinemia under certain conditions [49-51]. Off-label use of methylene blue leading to repeated critical comments from peer reviewers during the review process of previously published studies by our group [52, 53] underlined the need for evidence on the safety of using certain amounts of methylene blue as food dye during FEES.

Visuoperceptual measures during fiberoptic endoscopic evaluation of swallowing

In the context of accuracy and reproducibility of measures during FEES, our attention was not only focused on the use of methylene blue as food dye during the FEES procedure. Specific attention was also paid to the FEES interpretation protocol focusing in particular on psychometric properties of visuoperceptual measures. In daily practice, the interpretation of visuoperceptual FEES measures is usually done by a clinician [37]. Several visuoperceptual measures can be carried out during FEES such as measures of impaired swallowing safety, i.e., penetration and aspiration, and measures of impaired swallowing efficiency, i.e., pharyngeal residue or pooling [38, 40]. Aspiration, also described as unsafe swallowing, refers to entry of liquid and/or food into the airway below the level of the true vocal folds, and this is a major concern in dysphagic HNC patients with a reported incidence ranging from 36 to 94% [54]. Factors associated with aspiration in HNC patients are advanced age and tumor stage, a previous history of head and neck surgery, and/or chemotherapy [54]. Pharyngeal residue is commonly used as an outcome of OD during FEES and it refers to the amount of bolus remaining in the pharynx after swallowing. For many years, aspiration has been considered the most critical sign of OD due to its potentially severe consequences, including aspiration pneumonia, sepsis, and death [55]. Only recently pharyngeal residue has gained more attention in the literature as an important sign of OD due to its impact on patients' HRQoL [56-58]. The interpretation of FEES using visuoperceptual measures guides the choices for OD rehabilitation. Thickened liquids are often recommended as a therapeutic strategy to reduce the risk of aspiration. Thickened liquids are thought to slow bolus flow,

yet the understanding of the effects of thickened liquids on aspiration in HNC patients is limited [59]. The question arises as to whether thickened liquids with a higher viscosity give rise to more severe pharyngeal residue, thus increasing the risk of secondary aspiration. This is a clinically relevant question as commercially available thickeners, which are added to drinks, are designed to reduce the risk of aspiration. However, we do not know all the consequences of natural-thicker liquids let alone of commercially available thickeners for the swallowing function [60]. This emphasizes the need for a better understanding of the underlying swallowing pathophysiology of different symptoms or signs of OD in HNC patients. Identifying aspiration is one thing, but knowing what causes it is no less important. The risks of thickened liquids, including the potential synergistic relationship between pharyngeal residue and aspiration, deserve further investigation. Exploring the association between pharyngeal residue and aspiration as signs of OD will further improve the understanding of the underlying pathophysiology of pharyngeal residue in light of OD treatment strategies such as the use of thickened liquids.

Additionally, visuoperceptual FEES measures including aspiration and pharyngeal residue can be used to determine overall OD severity. In turn, overall OD severity plays an important role in determining the content of OD rehabilitation and in determining the effectiveness of OD rehabilitation over time [41]. At baseline, prior to oncological treatment, overall OD severity can also help in selecting the most appropriate oncological treatment modality or a combination of modalities, i.e., the treatment modality with an equivalent oncological outcome but estimated to have the lowest risk of disruption of upper aerodigestive tract functions. FEES plays an important role in the evaluation of OD severity, as FEES can help determine the underlying pathophysiology of OD [41]. At present, few scales that measure specific aspects of swallowing function have been validated for FEES such as the Penetration-Aspiration Scale (PAS) [61, 62], Yale Pharyngeal Residue Severity Rating Scale [63], and Boston Residue and Clearance Scale [64]. There are even fewer validated measurement scales that determine overall pharyngeal dysphagia severity based on FEES [65]. The Dynamic Imaging Grade of Swallowing Toxicity (DIGEST) was developed for grading the overall severity of pharyngeal dysphagia in HNC patients before or after oncological treatment [66]. The DIGEST was initially developed and validated for VFSS. Currently, it has also been validated for FEES [65]. A visuoperceptual measurement scale for OD should not only be valid, but also reproducible. Reproducibility concerns the degree to which repeated measurements provide similar results, and reproducibility parameters can be divided in agreement and reliability parameters [67]. Agreement addresses how close the scores of repeated measurements are by estimating the measurement error in repeated measurements, which is independent of the variability between patients [67]. Reliability addresses how well patients can be distinguished from each other despite measurement errors, in which case the measurement error is related to the variability between patients [67]. Reliability is highly dependent on the heterogeneity of a study sample. In turn, observer agreement is more a characteristic of the measurement instrument and observer agreement is preferable in case the measurement instrument is used for evaluation purposes [67]. A reproducible measurement scale for the severity of

pharyngeal dysphagia using FEES is valuable in clinical practice, as it may contribute to clinical decision making on both the content of OD rehabilitation as well as on the selection of oncological treatment modalities. FEES can also be useful to monitor swallowing in HNC patients following oncological treatment especially since FEES can be performed safely as often as necessary because it is not accompanied by radiation exposure. Reaching observer agreement on visuoperceptual FEES measures is important but can also be challenging [68]. Currently, there is little to no evidence in the literature with regard to the reproducibility and external validity of the DIGEST in FEES, as only one study investigated these methodological aspects [65]. Additional research is required to assess the methodological robustness of the DIGEST measurements in FEES, and studies among different study populations can also contribute to improve external validity. Therefore, in order to increase the body of evidence in the literature, the challenges of reaching agreement among observers on the DIGEST in FEES are explored in this thesis.

Patient-reported outcome measures of great significance in the diagnostic workup of oropharyngeal dysphagia

As mentioned before, OD can have an impact on different domains of health. Therefore, the diagnostic workup of OD is preferably carried out using a combination of CROMs, for example, measurements performed during FEES or VFSS, and PROMs. PROMs are usually self-report questionnaires that measure patient-reported outcomes [69, 70]. A PROM can cover any aspect of a patient's health domain, directly assessed by the patient himself, without the interpretation of the patient's response by anyone else [69]. PROMs are valuable in the diagnostic workup of OD in HNC patients, as they provide unique data and reflect patients' own view on swallowing impairment and/or on consequences of OD such as OD-specific HRQoL, symptoms of OD, symptoms of malnutrition, affective symptoms, etc.

The use of PROMs can facilitate and improve communication between patients and clinicians. More specific, PROMs can increase the clinicians' awareness of patients' functioning, helping to identify patients with concerns and needs, and subsequently aid in referral to consultants [71, 72]. Furthermore, PROMs may facilitate shared decision making due to enhanced patient participation [72]. PROMs can also be used to assess changes over time within and between patients. In person-centered care, there is an increasing recognition of the importance of investigating the patient's perspective using PROMs as a healthcare outcome [70].

The integration of CROMs and PROMs unravels different dimensions of swallowing impairment that may not necessarily correlate with one another [6]. For example, a patient may present severe OD and aspiration during instrumental imaging techniques, yet may simultaneously have poor symptom perception and, subsequently, may present poor adherence to OD rehabilitation. On the other hand, some patients may experience a high symptom burden that makes them socially isolated despite the lack of signs of severe OD during FEES or VFSS. These patients may express a strong desire to participate in OD rehabilitation. These examples from clinical practice underline the importance of integrating different types of

outcome measures into the multidimensional diagnostic workup of OD. The integration of information on the actual nature and severity of OD and the patient's perspective on swallowing and on OD-related consequences will lead to a more holistic view of the extent and impact of swallowing impairment. Finally, this integration of information forms the foundation for developing person-centered OD (p)rehabilitation.

The use of PROMs in HNC patients to monitor HRQoL and/or health status is feasible and acceptable [72], and commonly used OD-specific HRQoL PROMs include the MD Anderson Dysphagia Inventory (MDADI) [73, 74] and the Swallowing Quality of Life (SWAL-QOL) questionnaire [75], etc. Different PROMs can be used for the assessment of symptoms of anxiety and/or depression in HNC patients [74, 76] such as the Hospital Anxiety and Depression Scale (HADS) [77], the Beck depression inventory fast screen (BDI-FS) [78], etc. Furthermore, risks and major consequences of OD such as the risk of malnutrition can also be captured using PROMs, as described in the next paragraph.

Risk of malnutrition

As nutritional status in dysphagic HNC patients is often compromised, the diagnosis and treatment of malnutrition is of critical importance in this population. Due to different causes, HNC patients have a high risk of malnutrition prior to, during, and after oncological treatment during their survivorship [25, 79-81]. They often present a pre-existing compromised nutritional status due to an unhealthy diet and lifestyle with excessive use of alcohol and tobacco [82, 83]. Moreover, tumor-induced OD, cancer metabolism, and oncological treatment can further compromise HNC patients' nutritional status [23, 82-84]. In a previous systematic review on the nutritional status of HNC patients, OD was the most commonly reported symptom affecting oral intake besides nausea, decreased appetite, and pain [85].

Few studies have investigated the relationship between swallowing function and malnutrition in HNC patients [79, 86]. Currently, there aren't any studies on screening for risk of malnutrition in dysphagic HNC patients. However, screening for risk of malnutrition in dysphagic HNC patients is crucial, as it is hypothesized that the presence of OD may increase the risk of malnutrition in HNC patients. Screening is an important step prior to the final diagnostic workup and treatment of malnutrition in this patient population. Screening can be performed using PROMs such as the Short Nutritional Assessment Questionnaire (SNAQ) [87, 88]. This thesis explores the risk of malnutrition in dysphagic HNC patients using the SNAQ and it also studies the association between visuoperceptual FEES measures and the risk of malnutrition.

Affective symptoms

Much like malnutrition, psychological distress is also a common phenomenon among HNC patients. A cancer diagnosis is likely to cause uncertainty and anxiety, which can be psychologically debilitating for patients. Compared to other cancer populations, the HNC population suffers from a higher prevalence of psychological distress including anxiety and depression [89]. Subsequently, OD can further negatively impact a patient's affective state

and HRQoL, as OD severity has been associated with clinically relevant affective symptoms and a compromised HRQoL [30, 74, 90]. For example, social isolation due to OD may further increase the level of affective symptoms [31]. A compromised affective state may even affect the chance of success of OD rehabilitation, suggesting a potential bidirectional synergetic relationship between OD and affective symptoms [31]. Symptoms of anxiety and depression are frequently underdiagnosed and undertreated in HNC patients [89], yet the identification of psychological distress in HNC patients is important as distress may interfere with the ability to cope with the disease and oncological treatment. In oncological healthcare settings, PROMs such as the HADS can be used as screening tools to help identify HNC patients at risk for clinically relevant affective symptoms [77]. The HADS is one of the most commonly used screening tools for affective symptoms [77] and it has been extensively tested against criterion standards [89, 91].

As previously stated, OD can physically manifest in many different symptoms and signs including aspiration and pharyngeal residue. Yet the question arises as to whether HNC patients experience more psychological distress in case they aspirate. Aspiration is considered one of the most critical signs of OD due to its potentially severe consequences, and aspiration can further negatively impact a patient's affective state. However, to date no studies have been published exploring the association between aspiration during FEES and affective symptoms including anxiety and depression in a heterogeneous HNC population in terms of various tumor sites, disease stages, and length of survival. More knowledge about the prevalence and consequences of clinically relevant affective symptoms in dysphagic HNC patients is needed.

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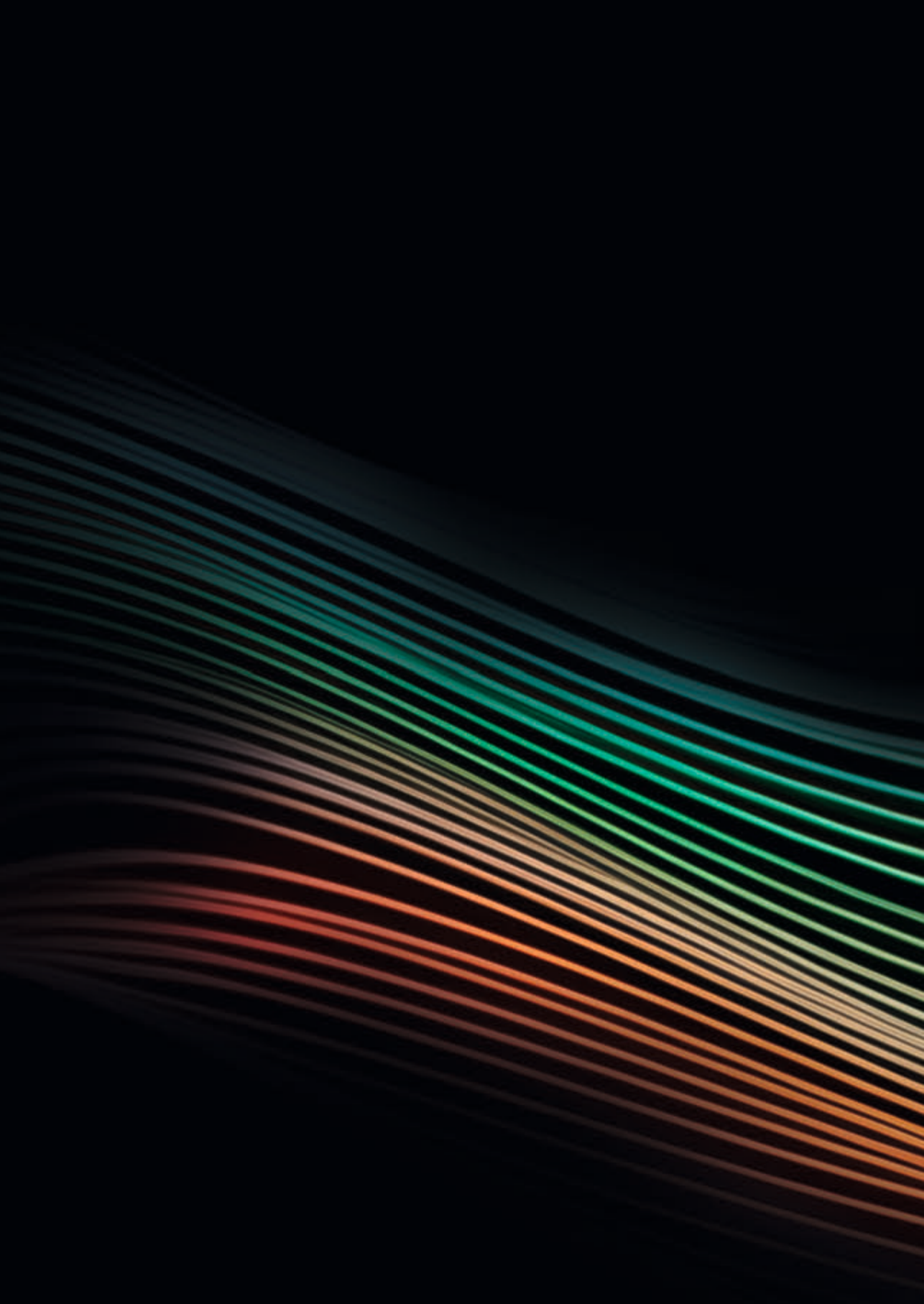
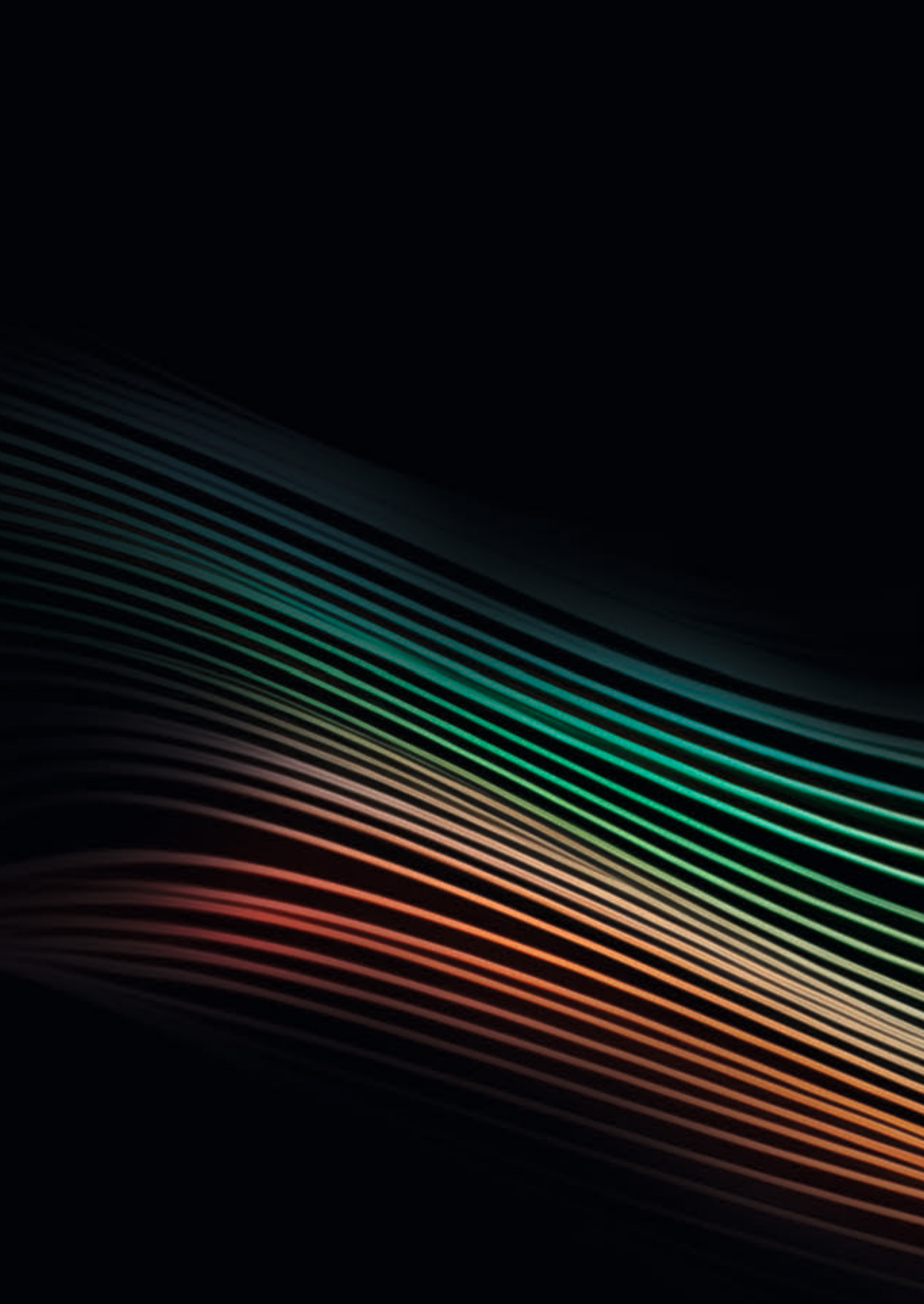


CHAPTER 2

AIMS AND OUTLINE OF THE THESIS

This thesis provides new insights into the diagnostic workup of oropharyngeal dysphagia (OD) in head and neck cancer (HNC) patients by exploring and integrating different dimensions of OD namely patient-reported outcome measures (PROMs) on swallowing impairment and on OD-related consequences and clinician-reported outcome measures (CROMs) on swallowing using instrumental imaging techniques.

Despite the wide use of fiberoptic endoscopic evaluation of swallowing (FEES), there is no consensus on the use of any type of medical or commercial food dye including methylene blue. Off-label use of methylene blue in conjunction with critical comments from peer reviewers indicated an urgent need for evidence on the safety of using certain amounts of methylene blue as food dye during FEES. In that light, a systematic review to investigate the evidence on the safety of using certain amounts of methylene blue as food dye during FEES is presented in **chapter 3**. The interpretation of FEES using visuoperceptual measures such as aspiration and pharyngeal residue or pooling guides the choices for OD rehabilitation. The study presented in **chapter 4** explores the association between pharyngeal residue and aspiration using FEES in dysphagic HNC patients, which will improve the understanding of the underlying swallowing pathophysiology of different signs of OD. A reproducible measurement scale for the severity of pharyngeal dysphagia using FEES is valuable in clinical practice, as it may contribute to clinical decision making on both the content of OD rehabilitation as well as on the selection of oncological treatment modalities. The Dynamic Imaging Grade of Swallowing Toxicity (DIGEST) was developed for grading the overall severity of pharyngeal dysphagia in HNC patients, yet there is little to no evidence in the literature with regard to the reproducibility and external validity of the DIGEST in FEES. In order to increase the body of evidence in the literature, the challenges of reaching agreement among observers on the DIGEST in FEES are explored in **chapter 5**. Screening for risk of malnutrition in dysphagic HNC patients is crucial, as it is hypothesized that the presence of OD may increase the risk of malnutrition in HNC patients. The risk of malnutrition in dysphagic HNC patients using the Short Nutritional Assessment Questionnaire (SNAQ) is investigated in **chapter 6**. This chapter also investigates the association between the risk of malnutrition versus tumor and patient characteristics including oncological treatment modality, visuoperceptual FEES measures such as aspiration and pharyngeal residue, and OD-specific quality of life. Among HNC patients, psychological distress is a common phenomenon, and OD can further negatively impact a patient's affective state and health-related quality of life (HRQoL). As aspiration is considered one of the most critical signs of OD due to its potentially severe consequences, the study in **chapter 7** explores the association between aspiration during FEES and affective symptoms including anxiety and depression in HNC patients. This thesis is completed with a discussion and reflection on the findings, implications for clinical practice, education, and future research in **chapters 8** and **9.**



CHAPTER 3

EVALUATING THE SAFETY OF ORAL METHYLENE BLUE DURING SWALLOWING ASSESSMENT: A SYSTEMATIC REVIEW

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**Bina Tariq and Sorina R. Simon contributed equally to the work*

Abstract

Objective

Methylene blue (MB) is frequently administered during fiberoptic endoscopic evaluation of swallowing (FEES) to enhance visualization of pharyngeal bolus transit. However, the safety of MB is being questioned since serious adverse events (AEs) such as hemodynamic instability, hemolysis, and serotonin syndrome were reported. The aim of this study is a systematic analysis of the literature to obtain an evidence-based overview of AEs due to oral administration of MB and to determine its safety as a food dye during swallowing assessment.

Methods

A systematic literature search was carried out in PubMed, Embase, and Cochrane Library. Two reviewers independently selected articles describing oral administration of MB as a main diagnostic/therapeutic intervention, dosage, and AEs. Expert opinions, conference papers, sample size < 10, and animal studies were excluded. Level of evidence of the included studies was determined.

Results

A total of 2264 unduplicated articles were obtained. Seventeen studies met the inclusion criteria with 100% agreement between the two reviewers. Among these, twelve studies were randomized controlled trials. In a pooled population of 1902 patients receiving oral MB, three serious AEs were reported related to MB. Non-serious AEs showed a dose-related trend and were usually mild and self-limiting. A meta-analysis could not be performed as studies were methodologically too heterogeneous.

Conclusion

Serious AEs due to oral administration of MB are rare (n = 3, 0.16%). MB-related non-serious AEs are mild, self-limiting, and show a dose-related trend. These findings indicate that it is safe to use small amounts of MB as a food dye during swallowing examinations.

Introduction

Methylene blue (MB) is a chemically active synthetic dye that has been used in the medical field for more than a century [1]. It has a multitude of pharmacological properties, being an antioxidant, monoamine oxidase inhibitor, cholinesterase inhibitor, memory-improving agent, neuroprotective agent, antimicrobial agent, and guanylate cyclase inhibitor [2, 3]. The United States Food & Drug Administration (FDA) and the European Medicines Agency (EMA) granted authorization in 2016 and 2017 respectively, to use methylthioninium chloride (Proveblue®) 5 mg/mL as an intravenous solution to treat acute methemoglobinemia in adults and children older than 3 months of age, with a recommended dose of 1-2 mg/kg body weight. This is the only registered indication for use of MB according to the FDA and EMA [4-6]. Nevertheless, MB has been used intravenously and orally to treat many more conditions. Studies have shown a positive effect of the oral administration of MB as a treatment for malaria, some psychiatric disorders, Alzheimer's disease, and urinary tract infections [2, 3, 7-10].

Additionally, MB has also been used widely as a medical dye. It is widely used in surgical procedures to visualize structures (e.g. parathyroid glands, lymph nodes, pulmonary nodules), leakage following surgical anastomoses in gastrointestinal procedures, and bladder defects [1, 11-13]. Within the field of otorhinolaryngology MB is used non-pharmacologically to enhance visualization of pharyngeal bolus transit during fiberoptic/flexible endoscopic evaluation of swallowing (FEES), to detect fistulas and anastomotic leakages following head and neck cancer surgery, and to identify aspiration in tracheostomized patients (Evan's Blue Dye Test (EBDT)) or patients receiving tube feeding [14-22]. The amount of MB used during a FEES examination varies per clinician and seems to be based on experience and preference. Usually, a few drops of MB, corresponding to approximately 16 mg MB [14, 16, 20, 21], are sufficient to obtain the desired color effect. However, the exact amount of MB used is often not reported [22-29]. It is striking that there is no consensus document on the use of MB as a medical dye or food dye for oral administration [22, 25, 26, 28].

The safety of MB as a food dye has been questioned after reports of serious adverse events (AEs) and life-threatening consequences in the early 2000s [22, 25, 26, 30]. At high doses MB can induce methemoglobinemia [2, 4, 6-31]. It might also cause discoloration and necrosis of skin and fat tissue, hemodynamic instability, hemolytic anemia, serotonin syndrome, and even death [22, 26, 30, 32-35]. MB-induced serotonin syndrome is a rare, but potentially life-threatening condition resulting from the concomitant use of MB and serotonergic drugs (e.g. selective serotonin reuptake inhibitors, tricyclic antidepressants, and monoamine oxidase inhibitors) [35].

Nonetheless, in several European countries small amounts of MB are used as food dye during FEES examinations [14, 23, 24, 27-29], while this method is discouraged by the FDA in the United States [1, 22, 30].

Considering the clinical relevance of this topic, the aim of the current systematic review is a thorough analysis of AEs of MB following oral administration either in the context of its use as a food dye or in the context of treatment for a specific medical condition. The following broad PICOS question was applied: what are the adverse events in any patients receiving oral MB as compared to not receiving oral MB?

Methods

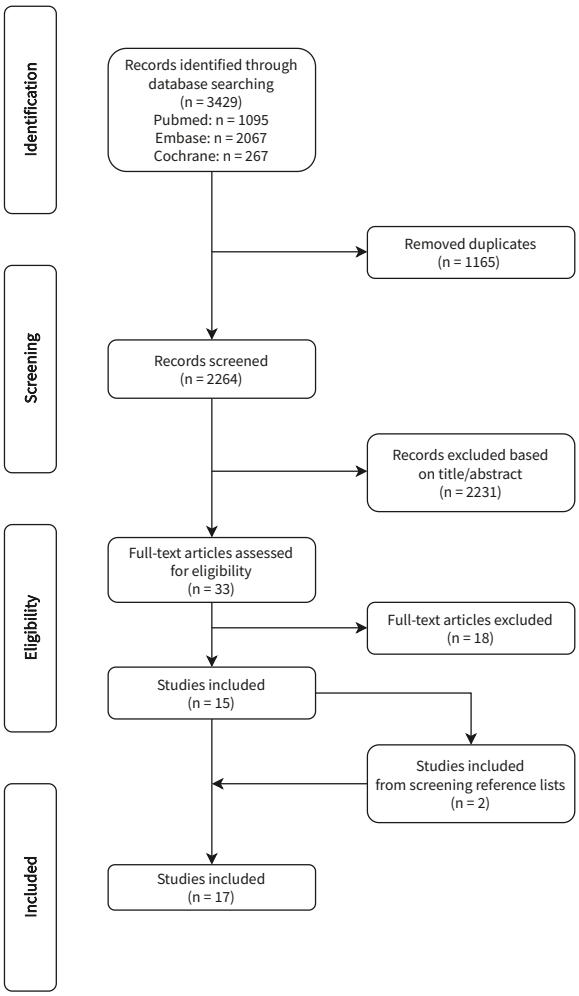
Identification and selection of studies

A systematic literature search was carried out in June 2020 using three electronic databases PubMed, Embase, and the Cochrane Library. The search strategy is presented in Table 1. Articles in English, Dutch, German, French, Spanish, or Portuguese published until June 2020 were eligible for selection. Two reviewers independently searched, selected, and analyzed the studies based on inclusion and exclusion criteria. Studies were included if they: (1) were published in a peer-reviewed journal; (2) described the oral administration of MB as main diagnostic or therapeutic intervention; (3) reported the MB dosage; (4) reported side effects or AEs; (5) included ≥10 participants. The Good Clinical Practice definition of adverse event (AE) and serious AE is used [36]. Expert opinions, conference papers, descriptive reviews, case reports, experiments on animals or cadavers, and in vitro studies were excluded. Reference lists of the included articles were searched for additional articles. Interobserver agreement on study inclusion based on full-text review was calculated. Figure 1 comprises a flow diagram showing the article selection according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [37].

Table 1 Search strategy

PubMed	((((((Methylene Blue) OR Methylthion* Chloride*) OR Tetramethylthionin* chloride) OR Swiss Blue) OR Methylene Blue[MeSH])) AND (((((Safe*[Title/Abstract]) OR Toxic*[Title/Abstract]) OR Side effect*[Title/Abstract]) OR Adverse effect*[Title/Abstract]) OR Complicat*[Title/Abstract]))
Embase	((Methylene blue OR Methylene blue mp OR Methylthion* Chloride* mp OR Swiss Blue mp OR Tetramethylthionin* chloride mp).af. AND (toxic* OR safe* OR side effect* OR adverse effect* OR complicat*)).ab.
Cochrane	((Methylene blue) OR (Methylthion* Chloride*) OR (Swiss Blue) OR (Tetramethylthionin* chloride) OR [Methylene Blue] (MeSH)) AND ((Safe*):ti,ab,kw OR (Toxic*):ti,ab,kw OR (Side effect*):ti,ab,kw OR (Adverse effect*):ti,ab,kw OR (Complicat*):ti,ab,kw))

Fig. 1 PRISMA flow diagram



Level of evidence

The level of evidence of the included articles was determined based on the Oxford Centre for Evidence-Based Medicine (CEBM) [38]. Level 1a refers to a systematic review of randomized controlled trials (RCT(s)), level 1b to an individual RCT, level 2a to a systematic review of cohort studies, level 2b to an individual cohort study/ low quality RCT, level 3a to a systematic review of case control studies, level 3b to an individual case-control study, level 4 to a case-series or poor quality cohort/case-control study, level 5 to a case report or expert opinion. This assessment was carried out independently by two reviewers blinded for each other's results. A third reviewer was consulted in case of disagreement.

Results

General results

Fifteen articles met all inclusion criteria. The selection process of the articles is presented in Figure 1. The majority of the studies were excluded because no information was provided on the absence/presence of AEs and/or on MB dosage. Searching the reference lists of the included articles two additional studies were found resulting in a total of 17 articles being included. No AEs were described in studies using MB as a food dye during a swallowing assessment [14, 16, 20, 21, 23, 24, 27-29]. The final selection of eligible studies was reached in full consensus with an interobserver agreement of 100%. A meta-analysis could not be performed because the included studies were of insufficient methodological quality and the heterogeneous study designs made comparability and statistical pooling impossible. The variables for data extraction are reported in Tables 2, 3, 4, 5 and 6.

Table 2 Overview of the included studies – ADULTS

Author	Study design MB indication Age	Treatment group(s) Total dose of MB per day[b]	Duration of MB treatment[b]	Method of assessment of AEs and follow-up	Authors' conclusion on safety and tolerability of MB[b]
Rengelshausen et al. [39]	• RCT • Malaria • Mean±SD: 25.0±3.93 years	Total: n=24 • Group 1: CQ (*n*=12) • Group 2: CQ + MB 260 mg (*n*=12)	3 days	Physical examination, laboratory blood, and urine test during the 3-day hospitalization and weekly follow-up till 28 days after treatment.	MB was well tolerated.
Walter-Sack et al. [40]	• Part I Cross-over, Part II RCT • Malaria • Mean±SD: 26.3±4.9 years	Total: *n*=16 Part I: • Group 1: MB 500 mg • Group 2 (IV): MB 50 mg Part II: • Group 1: CQ (*n*=8) • Group 2: CQ + MB 500 mg (*n*=8)	Single oral dose + single iv dose Single oral dose	Blood pressure measurements and electrocardiography during drug administrations. Blood samples during the study period (15 days). Follow-up examination 2 weeks after treatment.	No relevant safety concerns arose during the study. AEs were mild and self-limiting.
Bountogo et al. [41]	• Non-randomized controlled trial • Malaria • Median [range] Group 1: 26.5 years [18-55] Group 2: 24 years [18-43] Group 3: 25.5 years [18-53]	Total: *n*=60 • Group 1: MB 780 mg 3 days (*n*=20) • Group 2: MB 780 mg 5 days (*n*=20) • Group 3: MB 780 mg 7 days (*n*=20)	3 or 5 or 7 days	Self-reported complaints, temperature, blood samples at follow-up (days 1–7, 14, and 28)[a].	There were no major differences in the number of AEs and their duration among the three groups (3, 5, and 7 days MB) with p-values >0.05.
Mandi et al. [42]	• Cohort study • Malaria • Mean±SD: 31±12 years	Total: *n*=81 • Group: CQ + MB 260 mg	3 days	Self-reported complaints and physical examination twice daily during the study period.	No serious AEs were observed during exposure of healthy adult West African men with G6PD deficiency to the combination of MB + CQ. In particular, the risk of life-threatening hemolysis (Hb ≤5 g/dl) was low (<5% in the G6PD-deficient population and <0.7% in the total population). Furthermore, only a few AEs were associated with the study medication and most of them were mild.

Table 2 Continued

Author	Study design MB indication Age	Treatment group(s) Total dose of MB per day[b]	Duration of MB treatment[b]	Method of assessment of AEs and follow-up	Authors' conclusion on safety and tolerability of MB[b]
Telch et al. [10]	• RCT • Claustrophobia • Mean±SD: 19.04±1.46 years	Total: *n*=42 • Group 1: psychotherapy + placebo (*n*=19) • Group 2: psychotherapy + MB 260 mg (*n*=23)	1 day	Telephone interview at 24h post-intervention and interview during the follow-up visit, one month after treatment.	Minor AEs such as urine discoloration, increased frequency of urination, and dizziness were reported in both groups and they were generally mild. No serious AEs were reported.
Zoellner et al. [43]	• RCT • Chronic PTSD • Mean±SD: 37.5±12.4 years	Total: *n*=42 • Group 1: psychotherapy + MB 260 mg (*n*=15) • Group 2: psychotherapy + placebo (*n*=16) • Group 3: waitlist, no interventions (n=11)	5 days	Self-reported complaints, blood pressure, heart rate during 6 consultations. Self-reported complaints at the follow-up visits (2 weeks, 1 month, and 3 months post-intervention).	MB was generally well tolerated. Few and minor AEs occurred. AEs did not differ significantly across treatment groups.
Alda et al. [7]	• Cross-over • Bipolar disorder • Mean±SD: 48.3±9.2 years	Total: *n*=37 • Group 1: placebo dose MB 15 mg • Group 2: MB 195 mg (Both groups received MB with concurrent lamotrigine (or other mood-stabilizers))	26 weeks (placebo + intervention)	Blood samples at baseline, crossover, and termination. Self-reported complaints, vital signs (blood pressure, heart rate) during follow-up visits (0-27 weeks, every two weeks).	MB was generally well tolerated with no severe AEs. Only transient and mild AEs were present in both groups. None of the patients showed any signs of serotonergic toxicity.
Repici et al. (2019) [44]	• RCT • Colonoscopy • Mean±SD: 61.3± 6.7 years	Total: *n*=1249 • Group 1: MB 100 mg (*n*=241) • Group 2: MB 200 mg (*n*=488) (Both groups received MB with concurrent polyethylene glycol (bowel preparation))	Single dose	Self-reported complaints, physical exam, vital signs, blood samples before, during, and one week after treatment.	MB was well tolerated. The proportion of patients with AEs was higher in the 200 mg MB group (mainly chromaturia and discolored feces) compared to the placebo group (64.3% vs. 29.2%). Few participants, four (0.8%) in the 200 mg MB group and two (0.4%) in the placebo group, had severe AEs leading to discontinuation of the study (not further specified). No serotonin toxicity occurred in the few patients who made concomitant use of SSRIs and MB.

Table 2 Continued

Author	Study design MB indication Age	Treatment group(s) Total dose of MB per day[b]	Duration of MB treatment[b]	Method of assessment of AEs and follow-up	Authors' conclusion on safety and tolerability of MB[b]
Repici et al. (2012) [45]	• Part I cross-over, Part II single group, non-randomized, uncontrolled trial • Colonoscopy • Mean±SD: 46.0±12.4 years	Total: *n*=22 Part I: total *n*=10 • Group 1: MB 200 mg • Group 2 (IV): MB 100 mg Part II: total *n*=12 • Group 1: MB 400 mg (All groups received MB with concurrent Moviprep® (bowel preparation))	Single dose Single dose	Self-reported complaints, physical exams, blood pressure, heart rate, body weight measurements, and electrocardiography at pre- and 5 days post-intervention. Blood and urine samples after each dose. Self-reported complaints at 2 weeks after treatment.	The majority of the reported AEs seemed related to MB intake and were of mild severity. All AEs resolved spontaneously.
Repici et al. (2018) [46]	• Prospective cohort • Colonoscopy • Mean: 63.1 years	Total: *n*=10 • Group 1: MB 200 mg (All groups received MB with concurrent polyethylene glycol (bowel preparation))	Single dose	After the treatment H2AX biomarker was applied to the biopsies taken during colonoscopy to detect DNA damage of the intestinal mucosa. Self-reported complaints at 2 weeks follow-up.	The risk of MB having genotoxic potential is probably negligible.
DiStefano et al. [47]	• Prospective cohort • Colonoscopy • Mean±SD: 33.7±8.4 years	Total: *n*=23 • Group 1: MB 100 mg (*n*=5) • Group 2: MB 200 mg (*n*=18) (Both groups received MB with laxative (bowel preparation))	Single dose	Self-reported complaints, physical exams, blood pressure, heart rate, and body weight measurements, electrocardiography pre- and post-intervention. Blood and urine samples after each dose.	The majority of the reported AEs were not considered to be related to MB. The results confirmed the favorable tolerability profile of the MB-MMX tablets.

AEs adverse events; *CQ* chloroquine; *G6PD* glucose-6-phosphate dehydrogenase; *IV* intravenous(ly); *MB* methylene blue; *MB-MMX* methylene blue multi-matrix modified-release tablet; *PTSD* post-traumatic stress disorder; *RCT* randomized controlled trial; *SD* standard deviation; *SSRI* selective serotonin reuptake inhibitor.
[a]The follow-up schedule is based on the World Health Organization protocol "Assessment and monitoring of antimalarial drug efficacy for the treatment of uncomplicated falciparum malaria" [48].
[b]MB was administered orally unless specified otherwise.

Table 3 Overview of the included studies – CHILDREN

Author	Study design MB indication Age	Treatment group(s) Total dose of MB per day	Duration of MB treatment[b]	Method of assessment of AEs and follow-up	Authors' conclusion on safety and tolerability of MB[b]
Coulibaly et al. [49]	• RCT • Malaria • Median [range]: 49.0 months [7.0–59.0]	Total: *n*=193 • Group 1: AS + AQ (*n*=101) • Group 2: AS + AQ + MB 15 mg/kg (median: 200 mg) (*n*=92)	3 days	Self-reported complaints and blood samples on days 1- 3 of treatment and at follow-up (days 7, 14, and 28).	There were no differences in the number and pattern of AEs between the two groups. However, 25 (13%) children vomited after the first and second dose of the study medication and they were either excluded from the study or judged as early treatment failure. Of these 25 children, significantly more children had been allocated to group 2 than to group 1 (24% and 3% respectively; $p<0.001$).
Dicko et al. [50]	• RCT • Malaria • Median [IQR]: 11 years [8.0–14.5]	Total: n=80 • Group 1: SP + AQ (*n*=20) • Group 2: SP + AQ +PMQ (*n*=20) • Group 3: DA + PQ (*n*=20) • Group 4: DA + PQ +MB 15 mg/kg (median: 400 mg) (*n*=20)	3 days	Self-reported complaints and blood samples on days 1- 3 of treatment and at follow-up (days 7, 14, 28, and 42).	The number of participants who reported an AE was higher in the DA+PQ+MB group vs. the DA+PQ group ($p=0.031$). After the exclusion of chromaturia, no differences in the number of AEs or hemolysis were observed across the four groups, suggesting that MB is safe in G6PD-normal male participants with uncomplicated falciparum malaria.
Meissner et al. (2005) [51]	• RCT • Malaria • Mean±SD: 29.6±14.5 months	Total: *n*=226 • Group 1: CQ (*n*=45) • Group 2: CQ + MB 4 mg/kg (median: 40 mg) (*n*=181)	3 days	Physical examination twice daily, blood, and urine samples during 4-day hospitalization. Self-reported complaints, physical exam, and blood samples at follow-up (day 14).	No differences in the incidence of serious AEs and other AEs were observed between the two groups, even though there were 24 cases of children with G6PD deficiency in group 2. There was no case of severe hemolysis and no significant difference in the mean values of hemoglobin between study groups. MB appears to be safe at an oral dose of up to 4 mg/kg/day over three days in a population of young children with a high prevalence of G6PD deficiency.

Table 3 Continued

Author	Study design MB indication Age	Treatment group(s) Total dose of MB per day	Duration of MB treatment[b]	Method of assessment of AEs and follow-up	Authors' conclusion on safety and tolerability of MB[b]
Mendes Jorge et al. [52]	• RCT • Malaria • Mean±SD: 40.3 ±13.3 months	Total: *n*=100 • Group 1: AS + AQ + PQ (*n*=50) • Group 2: AS + AQ + MB 15 mg/kg (median: 200 mg) (*n*=50)	3 days	Self-reported complaints, physical examination, vital signs, temperature, blood samples on days 0 - 2 of treatment and at follow-up (days 3, 7, 14, and 28).	Malaria treatment with MB mini-tablets was considered safe in very young children. There were no significant differences in the occurrence of AEs between the two groups, except for vomiting, which was more frequent in group 2 as compared to group 1 (40% versus 14%, *p*=0.003). As a result, six children (12%) discontinued treatment after repeated vomiting. Nevertheless, there was no difference in the number of AEs during follow-up.
Zoungrana et al. [53]	• RCT • Malaria • Median [range]: 6 years [6–10]	Total: *n*=180 • Group 1: AS + AQ (*n*=61) • Group 2: AS + MB 20 mg/kg (median: 400 mg) (*n*=61) • Group 3: AQ + MB 20 mg/kg (median: 380 mg) (*n*=58)	3 days	Self-reported complaints, temperature, blood samples on days 1- 3 of treatment and at follow-up (days 7, 14, and 28)[a].	Group 2 and 3 presented significantly more AEs compared to group 1. The majority of the AEs reported in group 2 and 3 included vomiting and dysuria. These events were always mild and self-resolving. The occurrence of vomiting was reduced when MB was administered together with food.
Meissner et al. (2006) [54]	• Randomized, uncontrolled trial • Malaria • Mean: 33.3 months	Total: *n*=412 • Group 1: CQ + MB 12 mg/kg (*n*=147) • Group 2: CQ + MB 18 mg/kg (*n*=150) • Group 3: CQ + MB 24 mg/kg (*n*=115)	3 days	Self-reported complaints, physical exam, temperature, blood samples during hospitalization (days 0-3) and at follow-up (days 4 and 14)[a].	One G6PD deficient child had an episode of life-threatening hemolysis (Hb ≤5 g/dl) that could be attributed to MB. Seven children presented with a mild drop in Hb value, of which three were G6PD deficient. There were no major differences in the incidence of other AEs between study groups.

AE adverse event; *AEs* adverse events; *AS* artesunate; *AQ* amodiaquine; *CQ* chloroquine; *DA* dihydroartemisinin; *G6PD* glucose-6-phosphate dehydrogenase; *Hb* hemoglobin; *IQR* interquartile range; *PMQ* primaquine; *PQ* piperaquine; *MB* methylene blue; *RCT* randomized controlled trial; *SD* standard deviation; *SP* sulfadoxine-pyrimethamine.
[a]The follow-up schedule is based on the World Health Organization protocol "Assessment and monitoring of antimalarial drug efficacy for the treatment of uncomplicated falciparum malaria" [48].
[b]MB is administered orally unless specified otherwise.

Table 4 Summary of serious adverse events related to orally administered methylene blue

Author	Study population (*N*) Age	Dosage MB[a]	Serious AE
Mendes Jorge et al. [52]	*n*=100 Mean±SD: 40.3 ±13.3 months	15 mg/kg/day for 3 days	(1) A 15-month-old child developed repeated vomiting after the first dose of the study medication. She had severe malaria and became very weak being unable to take medication or hydrate orally. She recovered after intravenous artesunate.
			(2) A 22-month-old child (G6PD normal) developed severe anemia on day 3 (Hb value dropped 7.1 g/dl to 5.8 g/dl). The child fully recovered after a blood transfusion.
Meissner et al. (2006) [54]	*n*=412 Mean: 33.3 months	24 mg/kg/day for 3 days	A child with G6PD deficiency presented a severe drop in Hb value (8.7 g/dl to 4.7 g/dl) 2 days after end of treatment (total dose of 72 mg/kg MB). This was considered a case of hemolysis. Hb value improved after iron supplementation.

AE adverse event; *G6PD* glucose-6-phosphate dehydrogenase; *Hb* hemoglobin; *MB* methylene blue; *SD* standard deviation.
[a]MB is administered orally unless specified otherwise.

Table 5 Number of adverse events in relation to orally administered methylene blue dose level – ADULTS

					AEs *N* (%) of participants						
		Studies using the dose	Participants receiving the dose (N)	Total reported AEs	Chromaturia	Dysuria, polyuria	Fecal discoloration	Abdominal pain, nausea, vomiting, diarrhea	Headache, dizziness, fatigue	Mild increase transaminases AST/ALT	Other AEs[a]
Dose of MB (mg/day)	100	2	246	165	102 (41.5)	-	43 (17.5)	11 (4.5)	9 (3.7)	-	-
	200	5	563[b]	423[c]	242 (43.0)	4 (0.7)	99 (17.6)	60 (10.7)	16 (2.8)	2 (0.4)	-
	260	4	131	73[d]	34 (26.0)	8 (6.1)	1 (0.8)	9 (6.9)	16 (12.2)	-	Heartracing: 1 (0.8)
	400	1	12	10	-	3 (25.0)	-	2 (16.7)	2 (16.7)	2 (16.7)	Back pain: 1 (8.3)
	500	1	16	40	16 (100.0)	2 (12.5)	-	22 (137.5)	-	-	-
	780	1	60	72	-	47 (78.3)	-	13 (21.7)	12 (20.0)	-	-

AEs adverse events; *AST/ALT* aspartate transaminase and alanine transaminase; *MB* methylene blue.
[a]Not clearly associated with the use of MB.
[b]Including the participants from the study by Alda et al. [7]. This study reported that AEs such as dysuria, nausea, diarrhea, and headache were present among the participants who received MB via oral administration. However, they did not report the number of AEs.
[c]Therefore, the total reported AEs is excluding the AEs from Alda et al. [7].
[d]Zoellner et al. reported the presence of four AEs without specifying what the AEs were [43]. The total reported AEs is including the number of AEs from Zoellner et al. However, the columns of specific AEs are excluding the AEs from Zoellner et al.

Table 6 Number of adverse events in relation to orally administered methylene blue dose level – CHILDREN

					AEs *N* (%) of participants					
		Studies using the dose	**Participants receiving the dose (N)**	**Total reported AEs**	**Chromaturia**	**Dysuria**	**Nausea, vomiting, diarrhea**	**Headache, dizziness, weakness**	**Drop Hb value**	**Other AEs[a]**
Dose of MB (mg/kg/day)	4	1	181	93	-	-	93 (51.0)	-	-	Respiratory symptoms: 78 Infections[b]: 38 Skin symptoms: 9
	12	1	147	Not reported	-	-	-	-	-	-
	15	3	162	60	19 (11.7)	-	35 (22.0)	6 (3.7)	-	Respiratory symptoms: 25 Respiratory infection: 7 Skin/eye infection: 10 Fever: 3 Mild bradycardia: 1
	18	1	150	Not reported	-	-	-	-	-	-
	20	1	119	160	-	66 (55.5)	85 (71.0)	9 (7.6)	-	Pruritus: 6 Bronchitis: 10
	24	1	115	7	-	-	-	-	7 (6.1)[c]	-

AEs adverse events; *G6PD* glucose-6-phosphate dehydrogenase; *Hb* hemoglobin; *MB* methylene blue.
[a]Not clearly associated with the use of MB.
[b]Not further specified.
[c]Three of these seven participants had a G6PD deficiency.

Level of evidence

Twelve studies met the criteria of level 1b; nine randomized controlled trials (RCTs) [10, 39, 43, 44, 49-53] and three randomized cross-over trials [7, 40, 45]. Five studies met the criteria of level 2b; one non-randomized controlled trial [41] and four prospective cohort studies [42, 46, 47, 54]. The interobserver agreement for the level of evidence of the included studies was 88%. A third reviewer was consulted who judged the studies independently. After consensus discussion, 100% agreement was reached on the level of evidence.

Study characteristics

The total patient population of the seventeen studies consisted of 1606 adults and 1191 children aged 0.5-15 years. Among this population, 1028 adults and 874 children received orally administered MB. Most of the children who received MB were under the age of 5 (N=735, 84%).

Four studies [41, 42, 47, 50] included only male participants and two studies [46, 51] had a relatively high amount of male participants, 80% and 70% respectively. Seven studies [39, 40, 44, 45, 49, 52, 53] had a gender-balanced population. Three studies [7, 10, 43] had a small number of male patients, ranging from 24% to 35%. One study [54] did not provide any data on gender distribution. Information on the relationship between AEs and gender was lacking in all the included studies.

In the majority of the studies (N=14) MB was administered in combination with other medication(s). Even though articles using MB intravenously were excluded, two included studies [40, 45] also administered MB intravenously in addition to the oral administration. AEs for oral and intravenous administration of MB were reported separately in both studies. Since intravenous use of MB was not within the scope of this systematic review, only the data regarding the oral use of MB were used for this systematic review.

Detailed information on the study population, MB dosage, method of assessment of AEs, and the authors' conclusion is summarized in Tables 2 and 3. To facilitate the interpretation of the results the data were divided into two categories: adults versus children.

Indication of orally administered MB

The majority of the studies used MB as a treatment for falciparum malaria (*N*=10), either combined with antimalarial drugs [39, 40, 42, 49-54] or without any co-medication [41]. In three studies MB was used in combination with psychotropic drugs [7] or with a certain form of psychotherapy to treat bipolar disorder [7], claustrophobia [10], and chronic posttraumatic stress disorder [43]. MB was used in four studies [44-47] to aid visualization of mucosal abnormalities during colonoscopy.

Dosage forms of orally administered MB

The most frequently used oral dosage forms of MB in adults were gelatin capsules [7, 10, 39, 42, 43], MB multi-matrix (MMX®) modified-release tablets [44-47], solutions [40], and regular

tablets [41]. In children, MB was presented as mini-tablets [49, 50, 52], solutions [51, 54], and regular tablets [53]. The concentration of orally administered MB solutions for adults and children ranged from 0.5 % to 2.5% [40, 51, 54]. The dose of MB administered was reported in mg for adults and in mg per kilogram body weight (mg/kg) for children. To facilitate comparison of doses between adults and children the absolute dose given to children was calculated using their mean/median weight as presented in Table 3 [49-53].

Adverse events

Assessment of AEs was mainly based on patients' or parents' self-report. AEs were reported as either the number of events that occurred or as the number of patients experiencing one or more events. One serious AE, being a gastrointestinal hemorrhage, occurred in an adult and was deemed unrelated to MB [47]. Eight serious AEs were reported in children [47, 49, 51-54]. Among these, three AEs were attributed to MB, being repeated vomiting, anemia, and hemolysis [52, 54]. Serious AEs related to MB were summarized in Table 4.

The most frequently reported non-serious AEs were urinary and gastrointestinal symptoms. These AEs were well tolerated, mainly of mild intensity, self-resolving, and showed a dose-related trend. When looking at the number of AEs in relation to the dose of orally administered MB a positive trend was observed. The number of AEs increased as a function of higher MB dosage.

Non-serious AEs in children showed a similar dose-related pattern as in adults, with the most frequently reported AEs being gastrointestinal symptoms. However, children seemed to experience gastrointestinal symptoms more intensively compared to adults. Especially younger children experienced more severe nausea and vomiting. All non-serious AEs were pooled per dose level and presented in Table 5 and 6.

Discussion

To summarize, this systematic review shows that oral administration of MB has been used up to a dose of 780 mg/day in adults and 24 mg/kg/day in children with no major concerns regarding AEs, even in a population with a high prevalence of G6PD deficiency [49-54]. Since usually a few drops of MB are used during swallowing examinations, only a low dose (approximately 16mg) is ingested as compared to the doses described in the included studies [14, 16, 20, 21]. Hence, the use of small amounts of MB as a food dye during FEES examinations seems to be safe.

Within the field of otorhinolaryngology, MB is frequently administered orally in different procedures such as FEES examination, EBDT to identify aspiration in tracheostomized patients, and as a bedside test to detect fistulas and anastomotic leakages following head and neck cancer surgery [14-22]. While it has been reported that MB can cause serious health issues, at present, there are no consensus guidelines for the use of MB as a medical dye or food dye. Therefore, the current systematic review provides a thorough analysis of AEs of MB

following oral administration in order to estimate its safety as a food dye during swallowing assessment. A systematic literature search yielded seventeen relevant studies, none of which concerned AEs of the oral use of MB during swallowing assessment. It is unclear whether this is due to the non-occurrence of AEs during swallowing assessment or whether this is due to underreporting [28]. The included studies either used MB via oral administration as a treatment (e.g. malaria, bipolar disorder) or as a medical dye (colonoscopy). The safety of MB was rarely the primary outcome of these studies. Consequently, some studies provided extensive data on AEs, while other studies reported poorly on AEs. This made statistical data-pooling and a meta-analysis impossible. Nevertheless, some interesting findings can be observed in the results.

Firstly, serious AEs due to oral administration of MB are rare since only two MB-related serious AEs were reported in a large pooled sample of 1902 adults and children. It should also be taken into account that both participants who experienced serious AEs were very young children, had a frail health status, received a high dose of MB, and one of them was glucose-6-phosphate dehydrogenase (G6PD) deficient. MB belongs to a group of drugs considered to potentially cause hemolysis when given to patients with G6PD deficiency [51].

Non-serious MB-related AEs were not a concern as they were mild and self-resolving. Although chromaturia is known to occur very frequently [5, 6], it was not possible to determine its frequency in this systematic review as it was inconsistently reported. In some studies, urine and fecal discoloration were considered a physiological consequence merely due to the staining effect of the dye, while other studies considered it as an AE.

In the majority of studies (N=14) MB was administered concomitantly with medication(s) or intervention(s). This may have introduced bias since antimalarial drugs (e.g. amodiaquine, chloroquine, artesunate, etc.), laxatives (e.g. Moviprep®), and colonoscopy are known to cause gastrointestinal complaints as well. It is therefore impossible to distinguish whether some of the AEs were due to MB, the co-medication, the colonoscopy, or interaction between MB and these co-interventions.

Additionally, the dosage form is also a point of consideration when comparing the studies. Mini-tablets dissolve rapidly in the oral cavity and have a diameter of <3 mm, making them suitable for small children and toddlers [49, 55]. It has been suggested that children receiving mini-tablets might show a lower number of gastrointestinal AEs compared to children receiving regular tablets [49, 50, 52]. Another special dosage form is the MB multi-matrix modified-release tablet (MB-MMX®), which is a coated multi-matrix structure ensuring colonic delivery of MB [44-47]. This leads to a high bioavailability of MB which might increase the number of AEs compared to regular tablets. Concerning bioavailability, the average maximum blood concentration of a single intravenous dose of e.g. 100 mg MB is higher than a single oral dose of 200-400 mg MB [45]. Therefore, ingesting a low dose of MB during swallowing examination is less likely to cause complications as compared to the same dose being

administered intravenously. A systematic review by Zuschlag et al. showed that serotonin syndrome is far more likely to happen during intravenous administration of MB and is extremely rare during oral ingestion of MB [35]. This is consistent with the findings of the present systematic review, i.e. serotonin syndrome has not been reported during concurrent use of orally administered MB and psychotropic medication [7, 44].

Alternatives to MB enhancing the visualization of pharyngeal bolus transit during FEES have been suggested such as milk and yellow pudding [56-58] or blue and green commercially available food dyes [26, 59, 60]. Yet, these alternatives are not necessarily a superior substitute for MB. First of all, dairy products are not suitable for patients having lactose intolerance or allergy to milk. Secondly, food dyes are commercially available without any information on safety for medical purposes. There is no scientific evidence to justify patient safety of food dyes [61]. FD&C no. 1 (blue) and FD&C no. 2 (green) have also been associated with serious AEs such as severe allergic reactions and even death [22, 26, 30, 62]. Additionally, dairy products spoil if not refrigerated and food dyes are usually manufactured in non-sterile, multi-use bottles posing a risk of bacterial contamination. Adjusting to dietary intolerances, providing refrigerated storage facilities, labeling bottles, keeping track of expiration dates, etc. are logistical challenges in a highly regulated environment such as a hospital. In this context, where patient-safety and evidence-based healthcare are important points of attention, MB has an added value as it is an authorized drug only available on prescription and manufactured in sterile single-use ampules.

Limitations of the study

This systematic review has some limitations. Despite the broad systematic search strategy, the number of studies reporting on AEs due to oral administration of MB was low. It is unclear if this was the result of a low prevalence of MB-related AEs or of underreporting of AEs in the literature. Furthermore, the first round of selection of the articles was based on reviewing the title and abstract. Some studies might not have included safety/complications of MB in the primary and/or secondary outcome and therefore did not report MB or AEs in their abstract. Consequently, it is possible that some eligible studies were missed. Also, grey literature was not included because it generally lacks strict bibliographic control, meaning that basic information such as author, publication date, or publishing body may not be easily discerned. Publication bias cannot be ruled out as it is likely that unpublished studies did not find any effects of MB, consequently also missing information on severe AEs.

Conclusion

Serious AEs due to the oral administration of MB are rare (n=3, 0.16%). MB-related non-serious AEs are mild, self-limiting, and show a dose-related trend. These findings indicate that it is safe to use small amounts of MB as a food dye during swallowing examinations.

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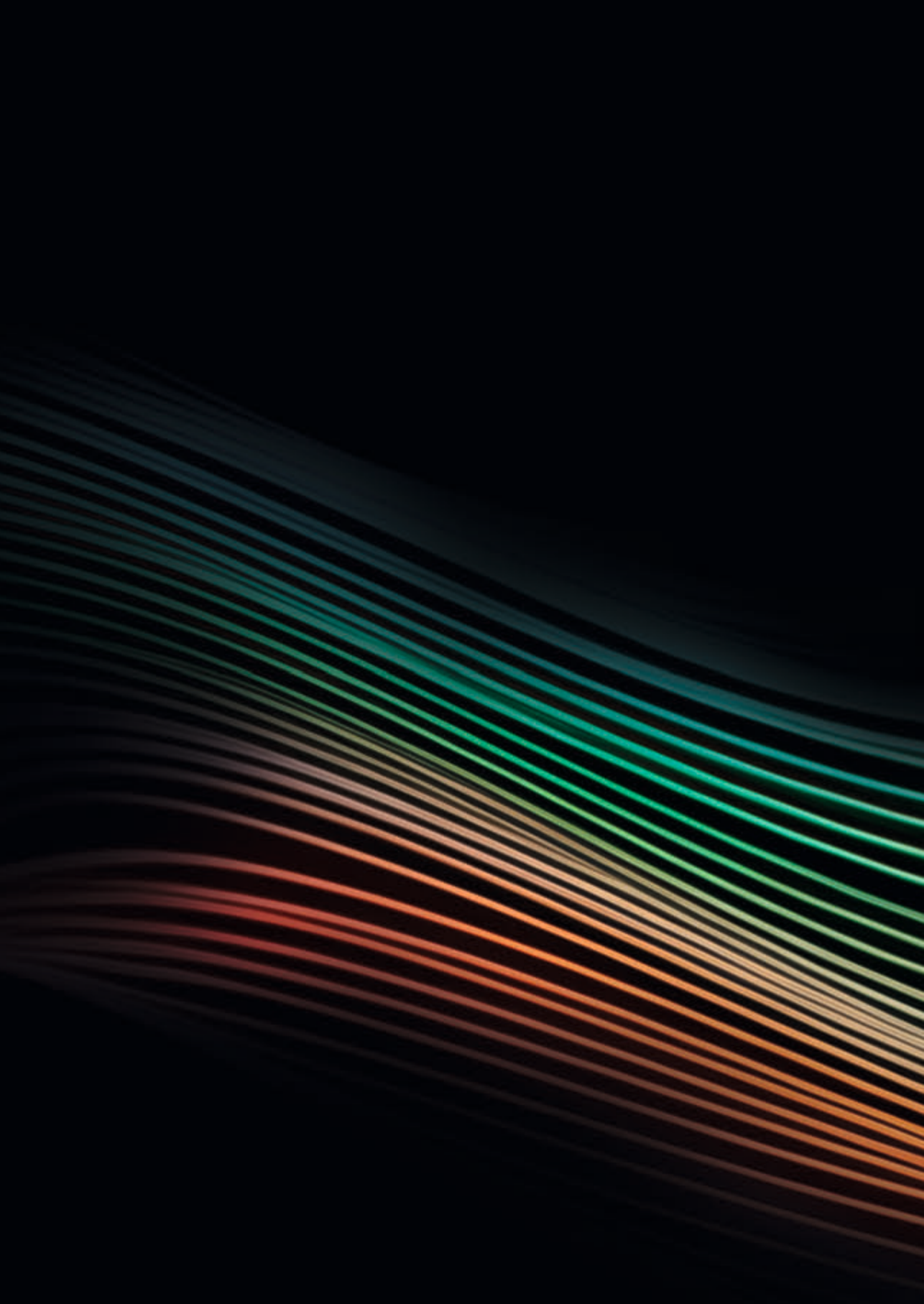

CHAPTER 4

ASSOCIATION BETWEEN PHARYNGEAL POOLING AND ASPIRATION USING FIBEROPTIC ENDOSCOPIC EVALUATION OF SWALLOWING IN HEAD AND NECK CANCER PATIENTS WITH DYSPHAGIA

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Abstract

Postswallow pharyngeal pooling may be a risk factor for tracheal aspiration. However, limited literature shows the potential association between pharyngeal pooling and aspiration in head and neck cancer (HNC) patients. This study investigates the relationship between postswallow pharyngeal pooling and aspiration in HNC patients with oropharyngeal dysphagia. Furthermore, the effects of tumor stage, tumor location, and cancer treatment on aspiration were examined.

Ninety dysphagic HNC patients underwent a standardized fiberoptic endoscopic evaluation of swallowing (FEES) using thin and thick liquid boluses. For each swallow, three visuoperceptual ordinal variables were scored: postswallow vallecular pooling, postswallow pyriform sinus pooling, and aspiration. Logistic regression analyses with correction for the location of pooling, tumor stage, tumor location, and cancer treatment were performed to explore the association between pooling and aspiration.

No significant association was found between postswallow vallecular pooling and aspiration for thin liquid. However, severe versus mild-to-moderate postswallow vallecular pooling of thick liquid was significantly associated to aspiration. Similar results were seen after correction for the presence of pyriform sinus pooling, tumor stage, tumor location, or type of cancer treatment. This study showed a significant association between severe postswallow pyriform sinus pooling of thick liquid and aspiration, independent of the presence of vallecular pooling, tumor stage, tumor location, or cancer treatment.

Concluding, location (valleculae versus pyriform sinuses), liquid bolus consistency (thin versus thick liquid), and amount of postswallow pharyngeal pooling (no pooling, mild/moderate pooling, severe pooling) have an influence on the probability of aspiration in dysphagic HNC patients, and they should be carefully considered during FEES, even in the absence of aspiration during the examination.

Introduction

Oropharyngeal dysphagia (OD) is common among patients with head and neck cancer (HNC) with a prevalence of 60-75% [1]. In this population OD can be a result of the disease itself or its treatment. Treatment-induced alterations that contribute to OD include xerostomia, lymphedema, fibrosis, and damage to neuromuscular structures. Furthermore, chemoradiotherapy and the presence of hypopharyngeal carcinoma are associated with an increased risk for late OD [2]. Common symptoms of swallowing impairment in HNC patients while eating include complaints of food 'sticking' in the throat, nasal regurgitation, coughing, or choking [3]. OD following oncologic treatment can lead to dietary restrictions, dehydration, malnutrition, aspiration pneumonia, and death [4-6]. Therefore, an evaluation of swallowing complaints in patients with OD of oncological origin is highly recommended. To evaluate the pharyngeal phase of swallowing fiberoptic endoscopic evaluation of swallowing (FEES) is deemed a reliable, safe, and well tolerated tool. It provides a direct, two-dimensional view of the pharyngeal surface anatomy with a clear visualization of the bolus path [7]. Using FEES, the safety (aspiration) and efficacy (pooling) of swallowing can be evaluated [8-10]. Several studies used FEES to evaluate the swallowing function but few used this method to assess OD in the HNC population [11, 12]. The visualization of aspiration during swallowing assessment in HNC patients has received much attention due to its potentially severe consequences, including aspiration pneumonia, sepsis, and death. Therefore, aspiration of food or liquids in patients with HNC is a major concern, with a reported incidence ranging from 36–94% [13]. Factors associated with aspiration are advanced age and tumor stage, previous history of head and neck surgery and/or chemotherapy [13]. As postswallow pharyngeal pooling is assumed to pose a risk for tracheal aspiration on the subsequent swallow, the detection of pooling during swallowing assessment is also becoming increasingly important [14]. Postswallow pharyngeal pooling is defined as any portion of the bolus remaining in the valleculae and/or pyriform sinuses after the swallow, and it is considered to be a sign of impairment of deglutition [15, 16]. Reduced base-of-tongue retraction with loss of contact to the posterior pharyngeal wall and incomplete cricopharyngeal relaxation can result in pharyngeal pooling. This in turn may lead to postswallow aspiration, as observed during a videofluoroscopic swallow study (VFSS) in HNC patients [15]. Yet there is limited literature regarding the possible association between postswallow pharyngeal pooling and aspiration in patients with HNC. Previous studies demonstrated that postswallow pharyngeal pooling is associated with aspiration during FEES examination in patients with nasopharyngeal carcinoma treated with definitive radiotherapy [11, 12]. However, these studies only included patients with nasopharyngeal carcinoma and therefore their findings cannot be generalized to the overall HNC population. Although, Jung et al. found an association between the presence of vallecular pooling and aspiration in patients with HNC [13]. During their retrospective analysis a different swallowing assessment tool (VFSS) without standardized bolus consistencies was used, and not all patients suffered from OD. To our knowledge no studies have explored the potential association between postswallow pharyngeal pooling and aspiration in a more general HNC population using FEES. The purpose of this study was

to determine the association between postswallow pharyngeal pooling and aspiration in HNC patients with OD, using a standardized FEES protocol. The influence of tumor stage, tumor location, and cancer treatment on the association was also investigated.

Methods

Participants

HNC patients with complaints of OD who underwent a FEES examination at the Maastricht University Medical Center outpatient clinic between 2009 and 2016 were enrolled in the study. The study sample comprised patients drawn from a routine outpatient clinic and they were invited to participate if the inclusion/exclusion criteria were met. Patients were included if HNC treatment (surgery, radiotherapy, chemoradiotherapy, or combinations - multimodality treatment) was completed at least six months before the data collection and FEES examination, and if the disease was in a stable period (total remission, absence of radiation mucositis, or severe odynophagia). None of the patients was receiving palliative care. The following exclusion criteria were applied: HNC and a concurrent neurological disease; a Mini Mental State Examination score below 23; older than 85 years; having undergone a total laryngectomy; having recurrent HNC or a second primary tumor, and osteoradionecrosis of the maxilla or mandible. Cancer staging according to the tumor, nodes, and metastasis (TNM) classification system was performed [17]. Informed consent was obtained from all patients in the outpatient clinic. The study protocol is classified as non-WMO dutiful according to the Dutch Medical Research Human Subjects Act (http://www.ccmo.nl/en/non-wmo-research).

Swallowing Protocol

A standardized examination protocol used in the dysphagia outpatient clinic for regular health care was applied. The protocol included a clinical ear, nose, and throat examination comprising integrity of cranial nerves performed by a laryngologist, the Functional Oral Intake Scale (FOIS) [7], and a standardized FEES examination [18]. The FOIS is used as a standardized measurement in daily clinical practice in the outpatient clinic for OD (heterogeneous etiologies of OD are present, not only HNC). It is used as part of a structured interview (descriptive variable) to assess the level of oral (or non-oral) intake. FOIS scores range from one ('nothing by mouth') to seven ('total oral diet with no restrictions') [7]. The FOIS provides an overall picture of which patients use a modified texture diet or tube feeding, and which patients have a total oral diet without any restrictions. Thus, the FOIS was used as a descriptive diet variable in this study. During the FEES examination, two liquid bolus consistencies were administered. Patients were offered three trials of thin liquid followed by three trials of thick liquid. Each trial contained 10 cc of water (thin liquid) or applesauce (One 2 fruit®) (hereafter 'thick liquid') dyed with five percent methylene blue as described in previous papers [19-21]. The viscosity (measured at 25 degrees Celsius 50 s-1 of shear rate) of the thin and thick liquid boluses was 1 mPa·s and 1200 mPa·s respectively. Furthermore, during the flow test thick liquid met the descriptive criteria for 'moderately thick' according to the International Dysphagia Diet Standardisation Initiative (IDDSI) [22]. For safety concerns (risk of severe aspiration), some

liquid bolus consistencies were not administered to all patients. Therefore, only subjects who had at least one trial thin liquid or thick liquid were included in the study. The tip of the flexible fiberoptic endoscope Pentax FNL-10RP3 (Pentax Canada, Mississauga, Ontario, Canada) was positioned just above the epiglottis in the 'high position' [18]. FEES images were obtained with a Xion SD camera, XionEndoSTROBE camera control unit (PAL 25 fps), and Matrix DS datastation with DIVAS software (Xion Medical, Berlin, Germany). The images were recorded on a DVD at 30 frames per second. Neither a nasal vasoconstrictor nor a topical anesthetic was administered to the nasal mucosa.

FEES Outcome Variables

For each FEES swallow trial three visuoperceptual ordinal variables were scored: postswallow vallecular pooling, postswallow pyriform sinus pooling, and aspiration [20, 21]. The term 'pooling' was defined as the amount of bolus remaining in the valleculae and/or pyriform sinuses after spontaneous clearing swallows. No distinction was made between right and left sided pooling. Postswallow pooling was evaluated after the last swallowing of the same bolus, i.e. after the last piecemeal deglutition swallow. Three-point ordinal scales (range 0-2) were used to capture pooling severity. The categorical rating scale comprises three levels of pooling severity: no pooling (0), mild to moderate pooling (1), and severe pooling (2). The description of each ordinal level of the severity of pooling is based on the perceptual judgment of the amount of bolus in relation to the size of the valleculae and/or pyriform sinuses. Postswallow vallecular pooling was scored as no pooling ('0'), mild to moderate pooling ('1': filling of less than 50 % of the valleculae), or severe pooling ('2': filling of more than 50 % of the valleculae up to complete filling). Postswallow pyriform sinus pooling was scored as no pooling ('0'), mild to moderate pooling ('1': filling of less than 50 % of the pyriform sinuses), or severe pooling ('2': filling of more than 50 % of the pyriform sinuses up to complete filling). Severe pooling in the valleculae means pooling up to the free edge of the epiglottis. For pyriform sinus pooling severe pooling was up to the level of the arytenoids. Aspiration was defined as bolus passing below the level of the vocal folds entering the trachea. Bolus on the true vocal folds secondarily leaking in the trachea was also classified as aspiration. Therefore, bolus in and below the anterior commissure was scored as aspiration. These FEES outcome variables were described in previous studies and are presented in the supplementary material (Table S1) [20, 21]. Prior to data collection, two experts received consensus training on the interpretation of the ordinal FEES variables. This is a standardized procedure for each new study containing visuoperceptual assessment tools for OD. The protocol of this training has been described in previous studies [19, 21]. Both observers were blinded to the identity and medical history of the patient and to each other's ratings (independent rating). The swallow trials were scored in randomized order at varying speed (slow motion, normal, and up to frame-by-frame). To obtain intraobserver agreement, each observer performed repeated measurements of all visuoperceptual FEES variables. Moreover, observers were advised to limit the duration of the measurement sessions (maximum of two hours per session) to avoid fatigue-related bias.

Statistical Analysis

Descriptive statistics were reported in terms of means with standard deviations (SDs) for numerical variables and number (percentage) for categorical variables. The score indicating more severe impairment of each FEES variable, dependent of liquid bolus consistency (thin or thick liquid), was used for statistical analysis. Where appropriate a Chi-square test or Fisher's exact test was used to analyze whether the proportions of events (aspiration) were different for various amounts of pooling. Logistic regression analysis was performed to further explore the association between pooling and aspiration. Correction for pooling in the other location (pyriform sinuses versus valleculae) was performed to determine whether pooling location was associated with aspiration, independent of pooling in the other location. The analysis was also adjusted for the influence of tumor stage (T3-4 versus T1-2), tumor location (pharynx tumor versus non pharynx tumor), and cancer treatment (only radiotherapy, only surgery, or multimodality treatment). Multimodality treatment refers to a combination of (primary or salvage) surgery, (neo)adjuvant radiotherapy and/or chemotherapy [23]. Due to the limited number of events (aspiration) and non-events (no aspiration), it was not possible to adjust for all three factors simultaneously, thus these factors were included in the analysis separately. Furthermore, the effect of tumor stage, tumor location, or cancer treatment on aspiration was determined. A two-sided p value ≤ 0.05 was considered statistically significant. For each visuoperceptual ordinal FEES variable, the inter- and intraobserver agreement was calculated using linear weighted kappa coefficient [24]. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 23.0 (IBM, Armonk, NY).

Results

Participants

Ninety patients (81.1% men) were included in the study. The mean age of the patients was 65.9 years (SD 10.8). All patients reported OD complaints. Patients' characteristics including TNM classification, tumor location, oncologic treatment, and FOIS score are presented in Table 1. Pharynx (51.1%) and larynx (26.1%) were the most common tumor sites. Within the group of patients with pharyngeal cancer, oropharynx was the most common tumor location (60%). Squamous cell carcinoma of the head and neck was the most frequent type of cancer (76.7%). The majority of the patients (88.8%) underwent radiotherapy as single modality or part of multimodality treatment (Table 1). Fourteen patients (16.1%) underwent a tracheotomy. The mean score of the FOIS was 4.7 (SD 1.8). Seventy-six patients underwent the entire FEES examination protocol. For safety concerns (risk of severe aspiration) fourteen patients did not receive the entire FEES protocol (3 x 10 cc thin, 3 x 10 cc thick liquid): three patients only received thin liquid, and eleven patients only received thick liquid.

Table 1 Frequency distribution of HNC patient characteristics (total number of patients = 90)

Characteristics	Number of patients (%)
Age distribution (*N* = 90)	
< 60 years	22 (24.4)
≥ 60 years	68 (75.6)
Length of time since completion of HNC treatment (*N* = 89)	
< than 5 years after treatment	62 (69.7)
> than 5 years after treatment	27 (30.3)
T classification (*N* = 75)	
T1	17 (22.7)
T2	25 (33.3)
T3	13 (17.3)
T4	20 (26.7)
N classification (*N* = 75)	
N0	37 (49.3)
N1	11 (14.7)
N2	25 (33.3)
N3	2 (2.7)
M classification (*N* = 75)	
M0	75 (100)
Tumor location (*N* = 88)	
Pharynx	45 (51.1)
Larynx	23 (26.1)
Oral cavity	11 (12.5)
Other location[a]	9 (10.2)
Treatment (*N* = 89)	
Definitive radiotherapy	37 (41.6)
Surgery	10 (11.2)
Surgery and adjuvant radio(chemo)therapy	26 (29.2)
Definitive radiochemotherapy	16 (18)
Tracheotomy (*N* = 87)	
Tracheotomy	14 (16.1)
No tracheotomy	73 (83.9)
FOIS (*N* = 88)	
Level 1	8 (9.1)
Level 2	9 (10.2)
Level 3	1 (1.1)
Level 4	5 (5.7)
Level 5	38 (43.1)
Level 6	14 (15.9)
Level 7	13 (14.8)

HNC head and neck cancer; *FOIS* Functional Oral Intake Scale.
[a]Tumor sites including the nasal cavity or paranasal sinuses are reported as 'Other location'.

Observer Agreement

The interobserver and intraobserver agreement levels were sufficient for all FEES variables (all Kappa coefficients ≥ 0.71, indicating substantial to almost perfect agreement) (Table S2 in supplementary material).

Postswallow vallecular pooling

Thin liquid bolus consistency

Postswallow vallecular pooling of thin liquid bolus consistency occurred in 39 (51.3%) patients: mild to moderate and severe vallecular pooling were observed in 24 (31.6%) and 15 (19.7%) patients, respectively (Table 2). Twenty-four (61.5%) of the patients showing postswallow vallecular pooling aspirated. 'Mild to moderate vallecular pooling' compared to 'no pooling', was not significantly associated with aspiration (OR 1.94, 95% CI 0.69, 5.51, $p = 0.212$) (Table 3). However, 'severe vallecular pooling' compared to 'no pooling' was significantly associated with aspiration (OR 4.52, 95% CI 1.20, 16.97, $p = 0.026$). The effect of 'severe vallecular pooling' compared to 'mild to moderate pooling' on aspiration was not significant (OR 2.33, 95% CI 0.58, 9.43, $p = 0.236$). Correction for pooling in the other location was performed to determine whether a certain pooling location was associated with aspiration, independent of pooling in the other location. The effect of 'severe vallecular pooling' compared to 'no pooling' on aspiration appeared not significant (OR 2.58, 95% CI 0.56, 11.91, $p = 0.226$) after this correction (pooling in pyriform sinuses). Similar results were seen after correction for tumor stage, tumor location, or type of cancer treatment.

Thick liquid bolus consistency

In 69 (87.3%) patients postswallow vallecular pooling of thick liquid bolus consistency was observed and was scored as mild to moderate and severe pooling in 32 (40.5%) and 37 (46.8%) patients, respectively (Table 2). Aspiration occurred in 22 (31.9%) of the patients showing postswallow vallecular pooling. The analysis regarding amount of pooling in the valleculae showed that, when compared to 'no vallecular pooling', both 'mild to moderate pooling' (OR 0.21, 95% CI 0.04, 1.11, $p = 0.066$) and 'severe pooling' (OR 1.42, 95% CI 0.34, 5.88, $p = 0.628$) were not significantly associated with aspiration (Table 3). However, the effect of 'severe vallecular pooling' compared to 'mild to moderate pooling' on aspiration was significant (OR 6.62, 95% CI 1.94, 22.73, $p = 0.003$). Similar results were seen after correction for pooling location, and after additional correction for tumor stage, tumor location, or type of cancer treatment.

Table 2 Frequency distribution of the occurrence of postswallow pharyngeal pooling and aspiration (total number of patients = 90)

Pooling location and liquid bolus consistency	Presence of pooling[a] *N* (%)	Aspiration in patients who presented pooling *N* (%)	Aspiration in patients who did not present pooling *N* (%)
Valleculae			
Thin liquid (*N* = 76)	39 (51.3)	24 (61.5)	14 (37.8)
Thick liquid (*N* = 79)	69 (87.3)	22 (31.9)	4 (40.0)
Pyriform sinuses			
Thin liquid (*N* = 77)	26 (33.8)	17 (65.4)	22 (43.1)
Thick liquid (*N* = 80)	38 (47.5)	20 (52.6)	8 (19.0)

N Number of patients.
[a]Presence of postswallow pooling is defined as the presence of mild to moderate pooling and/or severe pooling.

Table 3 Association between aspiration and postswallow vallecular or pyriform sinus pooling

	Unadjusted[a]				Adjusted for location of pooling[b]			
	Thin liquid		Thick liquid		Thin liquid		Thick liquid	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Postswallow vallecular pooling								
Mild to moderate pooling versus no pooling	1.94 (0.69, 5.51)	0.212	0.21 (0.04, 1.11)	0.066	1.39 (0.44, 4.35)	0.572	0.18 (0.03, 1.05)	0.056
Severe pooling versus no pooling	4.52 (1.20, 16.97)	0.026*	1.42 (0.34, 5.88)	0.628	2.58 (0.56, 11.91)	0.226	0.80 (0.17, 3.78)	0.781
Severe pooling versus mild-moderate pooling	2.33 (0.58, 9.43)	0.236	6.62 (1.94, 22.73)	0.003*	1.86 (0.41, 8.33)	0.420	4.51 (1.17, 17.54)	0.029*
Postswallow pyriform sinus pooling								
Mild to moderate pooling versus no pooling	1.13 (0.33, 3.84)	0.845	4.25 (0.87, 20.75)	0.074	0.92 (0.25, 3.42)	0.895	5.87 (1.00, 34.41)	0.05004
Severe pooling versus no pooling	7.25 (1.46, 36.10)	0.016*	4.86 (1.70, 13.91)	0.003*	4.78 (0.80, 28.35)	0.086	3.44 (1.03, 11.47)	0.044*
Severe pooling versus mild-moderate pooling	6.41 (0.99, 41.67)	0.0501	1.14 (0.24, 5.44)	0.867	5.21 (0.78, 34.48)	0.089	0.59 (0.10, 3.34)	0.548

OR odds ratio; *CI* confidence interval.
[a]Logistic regression analysis, without adjustment for other variables.
[b]Logistic regression analysis, with adjustment for pooling in the other location.
*Significance at $p \leq 0.05$.

Postswallow pyriform sinus pooling

Thin liquid bolus consistency

Postswallow pyriform sinus pooling of thin liquid bolus consistency occurred in 26 (33.8%) patients: mild to moderate and severe pyriform sinus pooling were observed in 13 (16.9%) and 13 (16.9%) patients, respectively (Table 2). Seventeen (65.4%) of the patients showing postswallow pyriform sinus pooling aspirated. 'Mild to moderate pyriform sinus pooling' compared to 'no pooling', was not significantly associated with aspiration (OR 1.13, 95% CI 0.33, 3.84, $p = 0.845$) (Table 3). However, 'severe pyriform sinus pooling' compared to 'no pooling' was significantly associated with aspiration (OR 7.25, 95% CI 1.46, 36.10, $p = 0.016$). Although a trend towards significance was seen, the effect of 'severe pyriform sinus pooling' compared to 'mild to moderate pooling' on aspiration was not significant (OR 6.41, 95% CI 0.99, 41.67, $p = 0.0501$). After correction for pooling in the other location (valleculae), the effect of 'severe pyriform sinus pooling' compared to both 'no pooling' (OR 4.78, 95% CI 0.80, 28.35, $p = 0.086$) and 'mild to moderate pooling' (OR 5.21, 95% CI 0.78, 34.48, $p = 0.089$) on aspiration was not found to be significant. Similar results were seen following additional correction for tumor stage or tumor location. An exception was found after correction for type of cancer treatment. The effect of 'severe pyriform sinus pooling, compared to both 'no pooling' (OR 9.99, 95% CI 1.44, 64.47, $p = 0.020$) and 'mild to moderate pooling' (OR 11.24, 95% CI 1.37, 90.91, $p = 0.024$), on aspiration was found to be significant.

Thick liquid bolus consistency

Postswallow pyriform sinus pooling of thick liquid bolus consistency was observed in 38 (47.5%) patients, which was scored as 'mild to moderate' and 'severe pooling' in 8 (10%) and 30 (37.5%) patients, respectively (Table 2). Aspiration occurred in 20 (52.6%) of the patients showing pyriform sinus pooling. 'Mild to moderate pyriform sinus pooling' compared to 'no pooling' was not significantly associated with aspiration (OR 4.25, 95% CI 0.87, 20.75, $p = 0.074$) (Table 3). However, the effect of 'severe pyriform sinus pooling' compared to 'no pooling' on aspiration was significant (OR 4.86, 95% CI 1.70, 13.91, $p = 0.003$). The effect of 'severe pyriform sinus pooling' compared to 'mild to moderate pooling' on aspiration was not significant (OR 1.14, 95% CI 0.24, 5.44, $p = 0.867$). Similar results were seen after correction for pooling in the other location, and after additional correction for tumor stage, tumor location, or type of cancer treatment.

Effect of tumor stage, tumor location, or cancer treatment on aspiration after correction for postswallow pooling in both locations

After correction for postswallow pooling in valleculae and pyriform sinuses location, the effect of tumor stage, tumor location, or cancer treatment on aspiration was determined.

Both tumor stage ($p = 0.764$) and tumor location ($p = 0.470$) had no significant effect on aspiration in swallows of thin liquid bolus consistency. However, cancer treatment showed a significant effect on aspiration (overall $p = 0.003$). The proportion of patients with aspiration

was significantly higher for the group of patients who only underwent definitive radiotherapy, compared to the group of patients who received multimodality treatment (OR 7.86, 95 % CI 2.19, 28.23, $p = 0.002$). The group of patients who underwent surgery exclusively, did not have a significantly increased proportion of patients with aspiration, compared to the group of patients who received multimodality treatment (OR 0.79, 95 % CI 0.12, 5.07, $p = 0.800$). Finally, tumor stage, tumor location, and cancer treatment had no significant effect on aspiration in swallows of thick liquid bolus consistency (all p-values ≥ 0.209).

Discussion

In this study we investigated the relationship between postswallow pharyngeal pooling and aspiration in dysphagic HNC patients using FEES. Furthermore, we analyzed the association between tumor stage, tumor location, and cancer treatment on the one hand, and aspiration on the other hand.

The results of our study showed that location, liquid bolus consistency, and amount of postswallow pharyngeal pooling have an influence on the probability of aspiration. 'Severe vallecular pooling' of thick liquid, compared to 'mild to moderate pooling', showed a significant association with aspiration, independent of the presence of pooling in the pyriform sinuses. However, no significant association was found between 'severe vallecular pooling' of thick liquid versus absence of pooling and aspiration. This outcome is not what would be expected in clinical practice and no clear explanation was found for it. It would be interesting to replicate this study with a larger sample size to verify if the association might change. Whereas, severe vallecular pooling of thin liquid, compared to the absence of pooling, was only significantly associated with aspiration if there was also pooling in the pyriform sinuses. This finding may be explained by the greater distance between the valleculae and laryngeal vestibule, compared to the anatomical position of the pyriform sinuses relative to the laryngeal vestibule [25]. As the bolus may spill from the lateral parts of the valleculae, the overflow of the bolus from the valleculae directly into the laryngeal vestibule seems less likely to happen. The epiglottis might play an additional role as a barrier between the valleculae and laryngeal vestibule, even though oncologic treatment or tumor location (oropharynx, supraglottis) in HNC patients may impair the epiglottic function due to fibrosis, malformation, and tissue destruction [26]. Consequently, in the case of severe vallecular pooling, this epiglottis barrier function may fail. Also the phenomena of pooling in both locations (pyriform sinuses and valleculae) probably indicate a more severe swallowing impairment with an increased risk of aspiration [27]. Previous studies by other authors demonstrated a significant association between vallecular pooling and aspiration [13, 16, 27], however most studies included mainly non-oncological patients [16, 27]. Considerable heterogeneity exists across studies making comparisons difficult, especially regarding the methodology and study population, as the majority of patients showed neurogenic OD [16, 27]. Only one study included patients with HNC [13]. Moreover, in previous studies the swallowing function was evaluated with a different assessment tool (VFSS), which may

influence the results, considering that FEES may yield more severe scores for both pooling and penetration/aspiration, when compared to VFSS [28, 29]. Furthermore, non-standardized bolus consistencies and/or varying volumes were administered across these studies [13, 16] and diverse rating scales for pharyngeal pooling were applied [16, 30].

In our current study we found a significant association between severe pyriform sinus pooling versus absence of pooling and aspiration of thin liquid, without correction for vallecular pooling in the statistical model. This finding may be related to the thin and watery nature of the boluses which can very quickly flow, but may not apply for thicker or solid boluses that stick and clump. However, after correction for vallecular pooling in the regression model no significant association was found between severe pyriform sinus pooling versus absence of pooling and aspiration of thin liquid. In the current study, the presence of severe versus no pyriform sinus pooling of thick liquid was significantly associated with aspiration, independent of the presence of vallecular pooling. This association may be explained by the proximity of the pyriform sinuses to the laryngeal vestibule, facilitating the overflow of the bolus from the pyriform sinuses into the laryngeal vestibule [25]. Decreased opening of the UES, which has been previously observed in patients with HNC treated with (chemo)radiotherapy, impairs the passage of food or liquids from the (hypo)pharynx into the esophagus and may contribute to the occurrence of bolus overflow from the pyriform sinuses into the laryngeal vestibule [31]. More than 80% of the patients in our study received radiotherapy (single or multimodality treatment). Ku et al. also found a significant association between postswallow pyriform sinus pooling and aspiration assessed during FEES in dysphagic patients with nasopharyngeal carcinoma [11]. Other studies using VFSS mainly in patients with neurogenic OD did not show any association between pyriform sinus pooling and aspiration [16, 27]. However, some studies reported that the risk of aspiration increased with increasing amounts of pharyngeal pooling [27, 32]. Likewise, our results showed that an increasing amount of postswallow pooling in the pyriform sinuses significantly increased the incidence of aspiration in HNC patients.

It was hypothesized that the type of treatment may contribute to the occurrence of postswallow pharyngeal pooling and/or aspiration as oncologic treatment can cause impaired pharyngeal contraction and laryngopharyngeal motorsensory deficits due to fibrosis and post-radiation neuropathy [6]. Other factors, including an advanced tumor stage, were thought to strengthen the association between postswallow pharyngeal pooling and aspiration. However, in the present study the association between postswallow pharyngeal pooling and aspiration did not change after correcting for tumor stage, tumor location, or type of cancer treatment, with the exception of a significant association between 'severe pyriform sinus pooling' of thin liquid and aspiration after correction for type of cancer treatment. The fact that an association between tumor stage and pooling or aspiration was not found, might be a result of the small sample size: perhaps an association would have been found if more patients were included in the study. The distribution of tumor stage among the included patients (i.e. 42 patients with T1 or T2 stage versus 33 patients with T3 or T4 stage) is considered fairly equal. A more elaborate statistical analysis, including detailed group

stratification for all (separate) tumor stages, might have led to different results. However, the present sample size was too small to allow statistical pooling.

Additionally, our results indicated that the occurrence of aspiration of thin liquid is influenced by cancer treatment, whereby patients who underwent definitive radiotherapy as a single modality treatment demonstrate significantly higher aspiration rates, compared to patients who received multimodality treatment, which comprises a combination of (primary or salvage) surgery, (neo)adjuvant radiotherapy and/or chemotherapy. According to the report of Pearson et al., HNC patients treated with radiotherapy demonstrated poor swallowing outcomes, including increased aspiration and pharyngeal pooling [33]. However, discordant results on aspiration have been reported in HNC patients too. Several studies found that aspiration was significantly associated with either tumor stage [4, 13, 34], tumor location [34, 35], or cancer treatment [13]. In contrast other studies could not demonstrate a significant relation between either tumor stage [35], tumor location [4, 13], or cancer treatment [4] on the one hand, and aspiration on the other hand. It has also been suggested that the presence of aspiration in HNC patients is affected by the type of cancer treatment (surgery, chemotherapy, or radiotherapy), rather than by tumor location [13].

Our study investigated the potential association between postswallow pharyngeal pooling and aspiration using FEES in dysphagic HNC patients. However, it is unknown whether the association between postswallow pyriform sinus pooling and aspiration represents a high co-occurrence rate, or a causal association. Patients who showed significant pooling during FEES may not present aspiration during the examination, but they may aspirate after the examination or at any time, when they are eating at home in their daily habitat [19]. In fact, FEES with its standardized protocols is only a short observation of a complex swallowing process and therefore it is not always a realistic representation of daily swallowing. In a non-clinical setting multiple factors may affect the swallowing mechanism such as fatigue, increased complexity of feeding in terms of various bolus consistencies, and diverse eating behaviors and postures. Previous research in patients with OD showed that the risk of aspiration can be underestimated when a limited number of swallow trials is performed during FEES [19]. Based on our results, we assumed that patients presenting severe pyriform sinus pooling of thick liquid are more likely to present aspiration, compared to patients who do not present pooling in the pyriform sinuses. Thus, pyriform sinus pooling in HNC patients is not only a marker of impaired swallow efficiency but was also associated with impaired swallow safety (aspiration). Based on these findings, even when aspiration is not observed during a FEES examination, it is presumed that severe pyriform sinus pooling could be predictive for or associated with aspiration that may or may not have been visualized. On these grounds, we suggest to pay specific attention to the presence of postswallow pharyngeal pooling during the swallowing assessment, in order to estimate the severity of OD and to design an appropriate OD management plan.

Limitations of the study

Our study has some limitations. Solid food boluses were not examined in the present study. In some HNC patients, the pyriform sinuses may be occluded from edema, fibrosis and/or surgical changes. The cavity size of the pyriform sinuses could also be a determining factor in the risk analysis of aspiration, as well as the subjective visuoperceptual assessment of the amount of pooling. Moreover, the sample size was too small to allow detailed group stratification for all tumor locations, TNM classifications, and all single or combined oncologic treatment modalities. Therefore, it was not possible to analyze the potential effect of these parameters on the association between pooling and aspiration. However, the patient population included was a realistic representation of HNC patients consulting the multidisciplinary outpatient clinic for dysphagic complaints, which gives insight in the overall severity of swallowing impairment in this group. We hope to investigate these factors in a larger sample size in the future.

Conclusion

Location (valleculae versus pyriform sinuses), liquid bolus consistency (thin versus thick liquid), and amount of postswallow pharyngeal pooling (no pooling, mild/moderate pooling, severe pooling) seem to have an influence on the probability of aspiration. Severe versus mild-to-moderate postswallow vallecular pooling of thick liquid was significantly associated to aspiration in HNC patients with OD, independent of the presence of pyriform sinus pooling, tumor stage, tumor location or type of cancer treatment. Furthermore, this study showed a significant association between severe postswallow pyriform sinus pooling of thick liquid and aspiration. This association was independent of the presence of vallecular pooling, tumor stage, tumor location, or cancer treatment. Based on these findings, identification of location and amount of pooling during FEES evaluation should be carefully considered, even in the absence of aspiration during the examination.

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Supplementary material

Table S1 Description of the fiberoptic endoscopic evaluation of swallowing outcome variables (as described in previous studies [20,21]

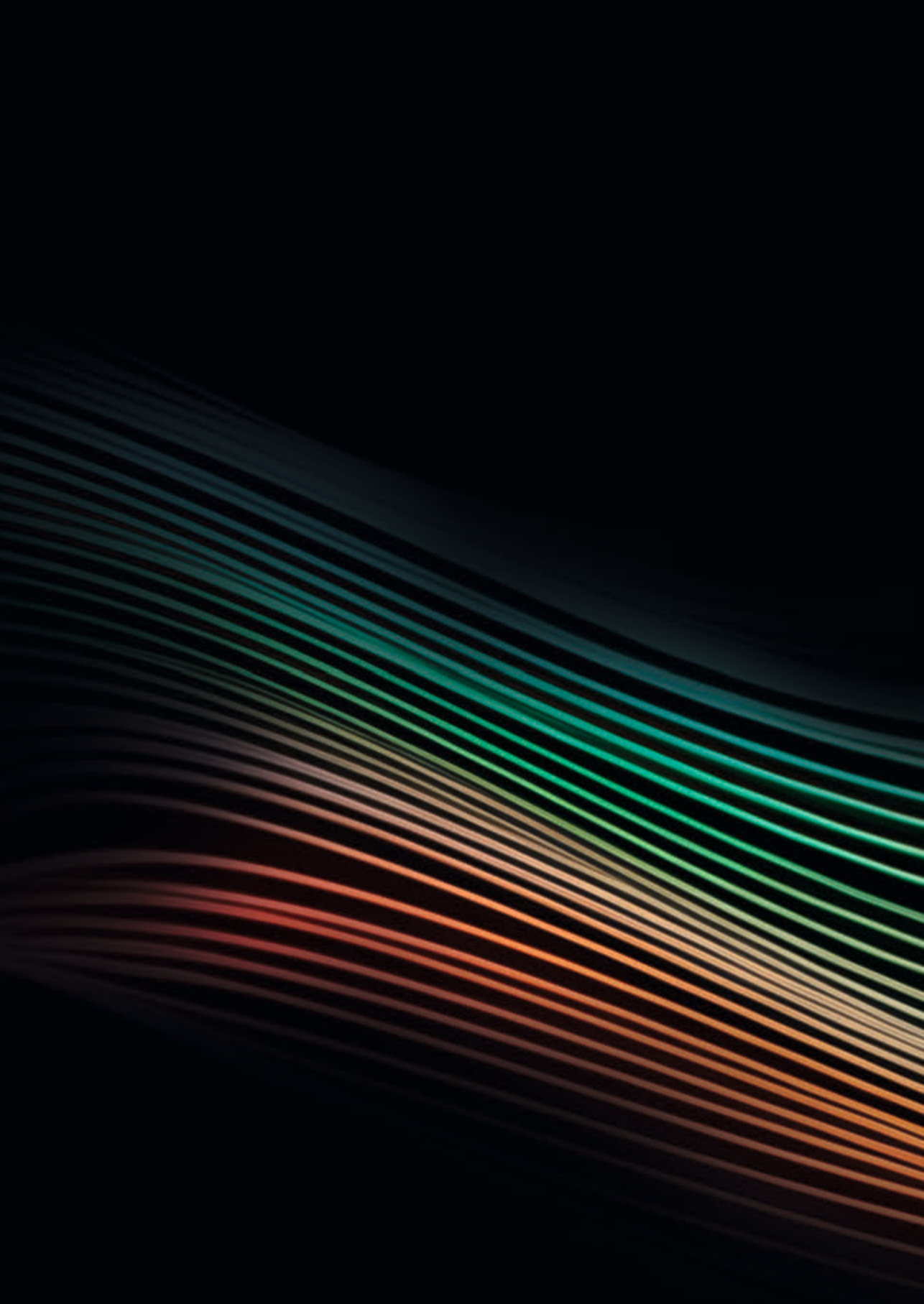
FEES ordinal outcome variable	Description	Scale[a,b]
Postswallow vallecular pooling	Pooling in the valleculae after the swallow	Three-point scale (range 0–2) 0 = no pooling 1 = mild to moderate pooling (filling of less than 50 % of the valleculae) 2 = severe pooling (filling of more than 50 % of the valleculae up to complete filling)
Postswallow pyriform sinus pooling	Pooling in the pyriform sinuses after the swallow	Three-point scale (range 0–2) 0 = no pooling 1 = mild to moderate pooling (filling of less than 50 % of the pyriform sinuses) 2 = severe pooling (filling of more than 50 % of the pyriform sinuses up to complete filling)
Aspiration	Bolus passing below the level of the vocal folds and entering the trachea	Two-point scale (range 0-1) 0 = no aspiration 1 = aspiration

FEES fiberoptic endoscopic evaluation of swallowing.
[a]Lower scores refer to normal functioning; higher scores refer to more severe disability.
[b]A pooling score of 1 indicates mild to moderate pooling; a pooling score of 2 indicates severe pooling.

Table S2 Observer agreement levels (linearly weighted kappa) of the fiberoptic endoscopic evaluation of swallowing (FEES) outcome variables

FEES ordinal outcome variable	Interobserver agreement[a]	Intraobserver agreement[a] (observer 1; observer 2)
Postswallow vallecular pooling	κ = 0.73	κ = 0.76; 0.87
Postswallow pyriform sinus pooling	κ = 0.71	κ = 0.81; 0.84
Aspiration	κ = 0.76	κ = 0.81; 0.71

<0 less than chance agreement
0.01–0.20 slight agreement
0.21–0.40 fair agreement
0.41–0.60 moderate agreement
0.61–0.80 substantial agreement
0.81–0.99 almost perfect agreement
FEES fiberoptic endoscopic evaluation of swallowing.
[a]Kappa agreement (linearly weighted kappa coefficient of agreement).



CHAPTER 5

INTRA AND INTEROBSERVER AGREEMENT OF THE DYNAMIC IMAGING GRADE OF SWALLOWING TOXICITY SCALE (DIGEST) IN FIBEROPTIC ENDOSCOPIC EVALUATION OF SWALLOWING (FEES): THE IMPORTANCE OF OBSERVER-TAILORED TRAINING

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Abstract

Purpose

The Dynamic Imaging Grade of Swallowing Toxicity (DIGEST) is a scale to quantify the severity of pharyngeal dysphagia in head and neck cancer (HNC) patients. This study 1) described the training process of the observers for DIGEST in fiberoptic endoscopic evaluation of swallowing (FEES), 2) determined observer agreement on the DIGEST in FEES, 3) explored the effect of bolus consistency on observer agreement, and 4) explored criterion validity of the DIGEST in FEES.

Methods

Twenty-seven dysphagic HNC patients were enrolled. Two observers completed a training program for DIGEST in FEES. Observer agreement on the Penetration-Aspiration Scale (PAS), percentage of pharyngeal residue (PPR), and DIGEST grades was determined using linearly weighted Cohen's kappa coefficient (κ).

Results

Due to insufficient observer agreement after the first measurement attempt, additional training was organized using an elaborated manual with descriptions of the visuoperceptual variables, thereby improving observer agreement. Intraobserver agreement was almost perfect on the PAS (κ=0.86-0.88) and PPR (κ=0.84-0.86). Interobserver agreement was substantial on the PAS (κ=0.78), almost perfect on the PPR (κ=0.82), substantial on the safety grade (κ=0.64), almost perfect on the efficiency grade (κ=0.85), and substantial on the summary grade (κ=0.71). Bolus consistency had an effect on observer agreement. A significant correlation was found between DIGEST efficiency grade and EAT-10.

Conclusion

The DIGEST showed to be a reproducible measurement for FEES in terms of observer agreement. However, agreement between novice observers on the DIGEST was only reached after specific observer-tailored training. Observer agreement should be analyzed by taking bolus consistency into account during training, as this might affect the interpretation of the outcome. A manual with well-defined descriptions can optimize the reproducibility of DIGEST measurements.

Introduction

Patients with head and neck cancer (HNC) often experience pharyngeal dysphagia, which can be caused by the cancer itself and/or by the oncological treatment [1, 2]. An accurate evaluation of swallowing function is paramount to guide dysphagia management. Videofluoroscopic swallowing study (VFSS) and fiberoptic endoscopic evaluation of swallowing (FEES) are widely considered gold standards for the instrumental assessment of swallowing [3-5]. During VFSS or FEES swallowing safety (penetration or aspiration) [6-9] and swallowing efficiency (pharyngeal residue) [9-12] can be measured. These measurements are carried out by observers and are based on subjective judgement [9, 13, 14]. As VFSS and FEES are completely different imaging techniques, observers have a different perspective when measuring the same variables [6, 10, 15]. To date, only few visuoperceptual measurement scales for VFSS and FEES have been validated [7, 8, 16, 17]. The Dynamic Imaging Grade of Swallowing Toxicity (DIGEST) was developed for grading the overall severity of pharyngeal dysphagia in HNC patients before or after oncological treatment [18]. The DIGEST was initially developed and validated for VFSS. Recently, this scale was validated for FEES by Starmer et al. [19]. Measurement scales such as the Penetration-Aspiration Scale (PAS) and percentage of pharyngeal residue (PPR) measure only one specific aspect of swallowing, thus these scales cannot determine overall dysphagia severity if used as the sole measurement. The DIGEST, however, uses the integration of the aforementioned phenomena of swallowing safety (penetration and/or aspiration) and efficiency (pharyngeal residue) to arrive at a composite severity score for pharyngeal dysphagia [18]. A reproducible measurement scale for the severity of dysphagia is very valuable for clinical practice as decision making on dysphagia treatment is, among others, based on the results of these measurements. However, observer agreement has an impact on reproducibility and on the validity of a test because if the observers who perform the measurements, cannot agree on the values after measuring the same variables, the test results will be of little use. Interobserver agreement refers to the degree to which two or more independent observers report the same observed values after measuring the same variables. An accurate diagnosis, sensitivity, specificity, predictive values, and likelihood ratios are items that address the validity of a test [20]. However, studies on FEES with a detailed description of the training process of observers to obtain sufficient intra and interobserver agreement on visuoperceptual measurements are scarce [11, 21].

Currently, there is very little evidence in the literature with regard to the reproducibility and external validity of the DIGEST in FEES, as only one study investigated these methodological aspects [19]. Additional research is required to assess the methodological robustness of the DIGEST measurements in FEES, and studies among different study populations can also contribute to improve external validity. In Europe, different health professionals often being member of an interdisciplinary dysphagia team may use the DIGEST, including speech–language pathologists, laryngologists, physician assistants, occupational therapists, etc. This wider use by multiple professionals underlines the importance of increasing our understanding of the conditions and restrictions of the reproducibility of the DIGEST in FEES.

The present study investigated how to reach agreement among observers on the DIGEST in FEES in order to increase the body of evidence in the literature.

The study aims to 1) describe the training process of the observers for DIGEST in FEES, 2) determine observer agreement on the DIGEST in FEES, 3) explore the effect of bolus consistency on observer agreement, and 4) explore the criterion validity of the DIGEST in FEES. It is hypothesized that the DIGEST is a reproducible measurement for FEES in terms of observer agreement. Moreover, it is expected that observer agreement of novice observers will improve after completion of a training program.

Methods

Study design and patient selection

For this cross-sectional study, HNC patients who underwent a standardized FEES examination between June 2016 and October 2020 in the interdisciplinary outpatient clinic for dysphagia of the Comprehensive Cancer Center of Maastricht University Medical Center in the Netherlands were included. Exclusion criteria were: a history of total laryngectomy or total glossectomy, a Mini Mental State Examination score below 23, not being able to tolerate or handle more than one bolus consistency during FEES, and any concurrent diagnosis causing dysphagia (stroke, Parkinson's disease, cervical spine surgery, dementia, etc.) [22]. Data on demographic patient characteristics, tumor staging, and oncological treatment were collected according to the Dutch Head and Neck Audit (DHNA) [23] and retrospectively extracted from the electronic health records. Cancer staging was carried out according to the tumor, nodes, and metastasis classification (TNM classification, 8th edition) [24]. The study protocol was approved by the medical ethics committee (METC 2020-1321) and all patients gave their informed consent.

Swallowing Assessment

All patients underwent a standardized swallowing assessment, including a clinical ear, nose, and throat examination, the Functional Oral Intake Scale (FOIS), the Eating Assessment Tool (EAT)-10, the MD Anderson Dysphagia Inventory (MDADI), and a standardized FEES examination.

The FOIS is a clinician-reported scale to determine the level of oral intake of food and liquids in dysphagic patients [25]. This ordinal scale ranges from 1 to 7 where level 1 represents tube feeding dependency and level 7 represents a total oral diet without any restrictions [25].

The EAT-10 is a patient-reported 10-item dysphagia-specific symptom questionnaire and the Dutch version was completed by all the patients [26, 27]. An EAT-10≥3 score is considered abnormal and represents a higher level of self-perceived symptom severity [26].

The Dutch version of the MDADI was also completed [28-30]. The MDADI is a patient-reported 20-item dysphagia-specific quality-of life (QoL) questionnaire that consists of 4 subscales (global, functional, physical, and emotional subscale). Responses are summed to calculate

the total MDADI score (MDADI-T): a minimum score of 20 represents a poor dysphagia-specific QoL whereas a maximum score of 100 represents a high dysphagia-specific QoL.

During the FEES examination, the following standardized protocol was carried out: three boluses of thin liquid (3 x 10 cc water), three boluses of thick liquid (3 x 10 cc applesauce; 'One2fruit'), and one bite-sized cracker (Delhaize mini toast 80 gr). Each liquid bolus was dyed with 5% methylene blue to enhance endoscopical visualization [11, 31, 32]. The viscosities of thin and thick liquid boluses were, respectively, 1 mPa.s for thin liquid and 1200 mPa.s for thick liquid. The viscosities were measured at 25 ^{0}C and 50 s–1 of shear rate as recommended by the National Dysphagia Diet [33]. According to the International Dysphagia Diet Standardisation Initiative (IDDSI), thin liquid was classified as IDDSI level zero 'thin' and thick liquid as IDDSI level 3 'moderately thick' during the flow test [34] . The position of the tip of the flexible endoscope (Pentax FNL-10RP3, Pentax Canada Inc., Mississauga, Ontario, Canada) ensured observation of the pharyngolaryngeal anatomy and physiology during swallowing. Topical anesthetics, which may affect pharyngolaryngeal sensory function, were not applied. FEES videos were recorded on a secured network drive of the hospital at 25 frames per second using a Xion SD camera, XionEndoSTROBE camera control unit and Matrix DS data station with DIVAS software (Xion Medical, Berlin, Germany).

The seven bolus swallows of each patient were split in seven separate video clips. The clips of all the patients were pseudonymized and randomized prior to the measurement process. The observers were blinded to the order of the bolus swallows, patient's identity and clinical data, and to each other's measurements. During the measurement process, the FEES video clips were analyzed at varying speed (normal to frame-by-frame) using Quick Time Media Player (Apple Inc, Cupertina, California, USA) and repeated as often as necessary. Observers were instructed to limit the duration of each session to two hours, in order to avoid attentional bias due to fatigue. To obtain intraobserver agreement, each observer repeated the same measurements again blinded and in randomized order. These measurements were performed with an interval of at least one week to avoid memory bias.

DIGEST

The DIGEST is based on the integration of two primary outcome measurements representing swallowing safety and swallowing efficiency [18]. The DIGEST safety grade is based on the maximum score of the PAS over all bolus swallows [8]. The PAS is a well-known 8-point ordinal scale to measure the severity of airway invasion by the bolus. The maximum PAS score is then transferred into one of the four pooled PAS categories: PAS 1-2, PAS 3-4, PAS 5-6, and PAS 7-8. Thereafter, modifiers are applied to account for the amount and frequency or pattern of penetration/aspiration events. After applying the modifiers, a safety grade is determined (grade 0-4).

The DIGEST efficiency grade is based on the maximum score of the PPR over all bolus swallows. The PPR after the first swallowing movement per bolus (so without clearing

swallows on that single bolus) is measured. The maximum PPR score is then transferred into one of the four residue categories: <10%, 10–49%, 50–90%, and >90%. Thereafter, again modifiers are applied to account for variations across different bolus consistencies. After applying these modifiers, an efficiency grade is determined (grade 0-4) [18].

For each patient, an overall pharyngeal dysphagia severity grade (the summary DIGEST grade, ranging from 0 to 4) is obtained by the integration of the safety and efficiency grade according to the DIGEST safety and efficiency profiles table of the DIGEST study in VFSS [18]. DIGEST grade 0 represents no pharyngeal dysphagia, grade 1 mild, grade 2 moderate, grade 3 severe, and grade 4 life-threatening pharyngeal dysphagia [18].

Training process

Two novice observers (Master of Medicine students) without previous experience in swallowing assessment followed an intensive training on the measurement of the PAS and PPR in FEES videos. Master of Medicine students who participate in the 4-month fulltime mandatory scientific internship and write a scientific master thesis are in their final year of the Master of Medicine. In this final year they also did a 6-month fulltime clinical internship in the department of otorhinolaryngology, working under supervision on the hospitalization ward and in the outpatient clinic having three new patients daily to examine (including flexible endoscopy) under supervision. The reason for selecting novice observers was based on the fact that these observers will pose a bigger challenge in using the DIGEST in terms of reproducibility of measurements compared to experienced clinicians.

The training process is presented in a flowchart in the supplementary information (Online Resource 1). The duration of the training sessions was approximately one hour, interspersed with homework assignments. The training was given by an expert clinician (speech-language pathologist W.P.) with more than 10 years of clinical and scientific experience in performing and interpreting FEES examinations.

During the training, the novice observers were educated about the anatomy and physiology of the pharynx and larynx and about the purpose and protocols of the FEES examination by using FEES sample videos for demo purpose. Thereafter, the observers received instructions on the interpretation of the definitions of the PAS and PPR categories and how to measure these variables. The definitions of the variables were explained verbally using visual depictions of the ordinal categories of both variables. When the observers understood the definition of the ordinal variables, the FEES variables were scored by the expert clinician in the presence of the observers.

Seven joint training sessions were held, in which the PAS and PPR variables were reviewed and scored by the observers under supervision of the expert clinician. After each training session, the observers received a batch of 10 to 40 FEES video clips that should be scored independently as homework assignments. In the next training session, the results of the

homework assignments were reviewed and revised if necessary. Any disagreement in the scores was discussed with the expert clinician and a consensus on the interpretation of the variables was reached.

A written manual containing definitions of the ordinal variables, including points-of-attention from the analysis of disagreements during the training program, was developed. This user manual was available for the observers during the subsequent measurements of the experiment. The training sessions were completed when the observers reached a percentage of agreement >70% and felt confident to start measuring the variables in FEES video clips for the present experiment.

As observer agreement was not sufficient after the first measurement attempt of the experiment, the observers underwent an additional training program. This was done to identify and understand reasons for disagreement and subsequently reach consensus in order to improve observer agreement during the second measurement attempt.

Statistical Analysis

Normally distributed baseline characteristics were represented by means and standard deviation (SD). Median and interquartile range (25^{th} and 75^{th} percentile) were used to describe baseline characteristics when the frequency distribution of the data was skewed. Normality was assessed using histograms and Q-Q plots. Frequencies and proportions were used for ordinal variables. Intra and interobserver agreement were calculated using linearly weighted Cohen's kappa coefficient (κ) and percentage of agreement. The linearly weighted kappa was interpreted as follows: <0 no agreement, 0.01-0.20 slight agreement, 0.21-0.40 fair agreement, 0.41-0.60 moderate agreement, 0.61-0.80 substantial agreement, and 0.81-1.00 almost perfect agreement [35]. An agreement of ≥0.61 was considered sufficient. To explore the criterion validity of the DIGEST in FEES, the correlation between safety grade, efficiency grade, and summary DIGEST grade versus the EAT-10, FOIS, TNM, and MDADI (MDADI-T and subscales, including global, functional, physical, and emotional subscale) was determined using Kendall's Tau-b correlation coefficient. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 25 (IBM, Armonk, NY).

Results

Patient characteristics

Twenty-seven HNC patients were included in this study. The mean age of the patients was 64.1 years (SD 9.1). The majority of the patients were male (N=20) (74.1%). Five patients underwent pre-treatment FEES evaluations (18.5%). The median score (25^{th}-75^{th} percentile) of the FOIS was 5 (5-6). Patient characteristics are presented in Table 1.

Table 1 Frequency distributions of data on tumor staging characteristics, oncological treatment, FOIS, and dysphagia-specific questionnaires (total number of HNC patients = 27)

Variables	**Number of patients = 27**
Tumor site	N(%)
Pharynx	14 (51.9)
Oral cavity	5 (18.5)
Larynx	7 (25.9)
Unknown primary tumor	1 (3.7)
T classification	N(%)
T0-1	7 (25.9)
T2	12 (44.4)
T3	5 (18.5)
T4	3 (11.1)
N classification	N(%)
N0	9 (33.3)
N1	3 (11.1)
N2	13 (48.1)
N3	2 (7.4)
M classification	N(%)
M0	23 (85.2)
M1	4 (14.8)
Treatment modality	N(%)
Surgery	2 (7.4)
Surgery and adjuvant (chemo)radiation	4 (14.8)
Primary (chemo)radiation	21 (77.8)
Radiation characteristics	
Mean total dose in Gray (SD)	67.6 (6.5)
Mean number of fractions (SD)	33.6 (4.2)
FOIS	N(%)
1 (nothing by mouth)	0 (0)
2 (tube dependency with minimal attempts of food or liquid)	0 (0)
3 (tube dependency with consistent oral intake of food or liquid)	1 (3.7)
4 (total oral diet of a single consistency)	0 (0)
5 (total oral diet with multiple consistencies requiring special preparation or compensations)	17 (63.0)
6 (total oral diet with multiple consistencies without special preparation, but with specific food limitation)	3 (11.1)
7 (a total oral diet without any restrictions)	6 (22.2)

Table 1 Continued

Variables	Number of patients = 27
	Median (25th-75th percentile)
BMI	22.8 (20.4-28.9)
Time interval in months between end of oncological treatment and FEES (N=22)	21.1 (4.6-76.2)
	Mean (SD)
EAT-10	14.2 (10.3)
MDADI	
Total score	66.8 (17.5)
Global subscale score	3.0 (1.4)
Functional subscale score	19.5 (4.4)
Physical subscale score	23.1 (9.1)
Emotional subscale score	19.3 (6.6)

HNC Head and Neck Cancer; *N* Number of patients; *SD* Standard Deviation; *FOIS* Functional Oral Intake Scale; *FEES* fiberoptic endoscopic evaluation of swallowing; *EAT-10* The Eating Assessment Tool; *BMI* Body Mass Index; *MDADI* MD Anderson Dysphagia Inventory.

First measurement attempt

During the first measurement attempt of the observers, the PAS and PPR were measured in 78 randomized bolus swallows of 27 HNC patients. To obtain intraobserver agreement, each observer repeated the same measurements in the 78 randomized bolus swallows with an interval of at least one week and again blinded. Observer agreement during the first measurement attempt of the present experiment is presented in Table 2.

Linearly weighted kappa coefficient could not be carried out for all measurements due to a limited number of measurements for some bolus consistencies or a lack of variation of the scores across the PAS or PPR scales. For example, a limited number of measurements for bite-sized cracker was obtained due to the lower number of HNC patients who were able to process this consistency because of severe xerostomia. In case of lack of variation of scores, the kappa may incorrectly conclude that the agreement is low (as the correction for chance is too strict). To check whether this was the case, percentage of agreement as a measure of intra and interobserver agreement was also calculated for all bolus consistencies. This limitation of linearly weighted kappa coefficient as measure of agreement is further explained in the Discussion section.

Table 2 Linearly weighted kappa coefficient and percentage of agreement on the PAS and PPR when considering all bolus consistencies together ('total') and per bolus consistency during the first measurement attempt[a]

First measurement attempt	FEES variable and bolus consistency	*Intraobserver agreement*					*Interobserver agreement*		
		N (%)	*Observer 1*		*Observer 2*		*N (%)*	*Kappa (SE)*	*% of agreement*
			Kappa (SE)	*% of agreement*	*Kappa (SE)*	*% of agreement*			
	PAS								
	Total	78	0.90 (0.04)	87.2	0.87 (0.04)	82.9	78	0.77 (0.08)	71.8
	Thin liquid	33 (42)	0.91 (0.04)	82.4	0.86 (0.05)	69.7	33 (42)	0.72 (0.20)	60.6
	Thick liquid	32 (41)	0.88 (0.07)	90.9	0.84 (0.07)	90.3	32 (41)	0.78 (0.09)	74.2
	Bite-sized cracker	13 (17)	[b]	90.9	1.00 (0.00)	100.0	13 (17)	1.00 (0.00)	100.0
	PPR								
	Total	78	0.85 (0.06)	92.3	0.59 (0.09)	77.0	78	0.62 (0.09)	78.7
	Thin liquid	33 (42)	0.88 (0.12)	96.3	0.67 (0.13)	80.0	33 (42)	0.38 (0.15)	62.5
	Thick liquid	32 (41)	0.82 (0.09)	89.3	0.50 (0.15)	73.1	32 (41)	0.87 (0.09)	96.3
	Bite-sized cracker	13 (17)	0.74 (0.24)	90.0	0.54 (0.26)	80.0	13 (17)	0.58 (0.26)	80.0

PAS Penetration-Aspiration Scale [8]; *PPR* percentage of pharyngeal residue; *FEES* fiberoptic endoscopic evaluation of swallowing; *N* number of bolus swallows; *SE* standard error.
[a]Following the initial training program on the measurement of the PAS and PPR in FEES, a first measurement attempt was made in which the PAS and PPR were measured in 78 bolus swallows of 27 HNC patients (Table 2). Due to unexpectedly low observer agreement (especially regarding PPR), an additional training program was organized. During the second measurement attempt, the PAS and PPR were measured in 184 bolus swallows of 27 HNC patients (Tables 3 and 4).
[b]Linearly weighted kappa could not be carried out for all measurements due to a limited number of measurements for some bolus consistencies, such as for bite-sized cracker, or a lack of variation of the scores across the PAS scales.

Penetration-Aspiration Scale
Intraobserver agreement (overall and per bolus consistency) of both observers on the measurement of the PAS was sufficient (κ≥0.84) (Table 2). Interobserver agreement (overall and per bolus consistency) on the PAS was sufficient too (κ≥0.72).

Percentage of pharyngeal residue
The overall intraobserver agreement of both observers on the measurement of the PPR showed notable variation, when considering all bolus consistencies together (κ=0.59-0.85) (Table 2). Observer 1 presented substantial to almost perfect intraobserver agreement for all measurements. Observer 2 did not reach sufficient intraobserver agreement for both thick liquid and bite-sized cracker when agreement was calculated using linearly weighted kappa coefficient (κ≤0.60). However, the corresponding percentage of agreement was 73.1% for thick liquid and 80% for bite-sized cracker.

The overall interobserver agreement was substantial, when considering all bolus consistencies together (κ=0.62). Interobserver agreement was not sufficient for thin liquid (κ=0.38) and bite-sized cracker (κ=0.58) using linearly weighted kappa coefficient, whereas percentage of agreement was 62.5% for thin liquid and 80% for bite-sized cracker.

Additional training program
In the attempt to improve observer agreement, an additional training program consisting of three training sessions was organized in a period of four weeks. Again, the expert clinician and the observers measured the FEES variables in several FEES sample videos together, exploring the reasons of disagreement between the observers. Specific attention was paid to variables with insufficient interobserver agreement (κ≤0.60) per bolus consistency during the first measurement attempt, in particular PPR. As PPR is based on a continuous scale (0-100%), the categorization of this continuous variable into an ordinal scale variable seems to be based on arbitrary cut-off values, and to distinguish between a PPR of 49% (category 10-49%) and a PPR of 50% (category 50-90%) is not an easy task. During this additional training, the written user manual containing the definitions of the variables was further improved by revising and adjusting the descriptions and range of each level of the PPR measurement scale per bolus consistency. Points-of-attention discussed during this additional training program and corresponding images of severity levels of pharyngeal residue were added to the user manual. Thereafter, the manual was further revised and optimized by two expert clinicians. The procedure of this expert revision consisted of two sessions in which the expert clinicians discussed the corresponding images of the severity levels of the PPR. In between these sessions, the expert clinicians studied the advantages and disadvantages of the descriptions and corresponding images independently, and in the second session the expert clinicians made a final consensus decision on the selection of the corresponding images. This expert opinion was determined as 'gold standard'. This manual with well-defined descriptions was used as a reference to enhance the agreement within and between observers during the second measurement attempt.

Second measurement attempt

During the second measurement attempt, the PAS and PPR were measured in 184 randomized bolus swallows of the same 27 HNC patients. To obtain intraobserver agreement, each observer repeated the same measurements with an interval of at least one week, again blinded in a random selection of 59 out of 184 randomized bolus swallows. Frequency distributions of the scores of the PAS, PPR, DIGEST profile, and summary DIGEST grade given by each observer are presented in Table 3. Observer agreement on the PAS and PPR is presented in Table 4.

Table 3 Frequency distributions of the scores of the PAS, PPR, DIGEST profile, and summary DIGEST grade by each observer during the second measurement attempt (in total 184 bolus swallows of 27 HNC patients)

	Observer 1	**Observer 2**
	N (%)	***N (%)***
PAS scores (N=184 bolus swallows)		
1	87 (48.9)	73 (40.2)
2	36 (20.2)	54 (29.7)
3	23 (12.9)	29 (15.9)
4	5 (2.8)	3 (1.6)
5	6 (3.4)	6 (3.3)
6	8 (4.5)	4 (2.2)
7	8 (4.5)	7 (3.8)
8	5 (2.8)	6 (3.3)
Missing	6	2
PPR scores (N=184 bolus swallows)		
1	83 (54.2)	92 (55.1)
2	57 (37.3)	54 (32.3)
3	11 (7.2)	18 (10.8)
4	2 (1.3)	3 (1.8)
Missing	31	17
DIGEST profile (N=27 patients)		
S0E0	3 (11.1)	3 (11.1)
S1E0	2 (7.4)	3 (11.1)
S0E1	5 (18.5)	5 (18.5)
S1E1	6 (22.2)	6 (22.2)
S0E3	1 (3.7)	1 (3.7)
S1E3	2 (7.4)	6 (22.2)
S2E3	2 (7.4)	0 (0.0)
S3E0	1 (3.7)	1 (3.7)
S3E1	3 (11.1)	0 (0.0)
S3E3	2 (7.4)	2 (7.4)

Table 3 Continued

	Observer 1	Observer 2
	N (%)	***N (%)***
Summary DIGEST grade (N=27 patients)		
0	3 (11.1)	3 (11.1)
1	13 (48.1)	14 (51.9)
2	3 (11.1)	7 (25.9)
3	8 (29.6)	3 (11.1)
4	0 (0.0)	0 (0)

PAS Penetration-Aspiration Scale [8]; *PPR* percentage of pharyngeal residue; *DIGEST* Dynamic Imaging Grade of Swallowing Toxicity; *HNC* head and neck cancer; *N* number of bolus swallows or number of patients (as specified in the table); *S* safety grade; *E* efficiency grade.

Penetration-Aspiration Scale

Intraobserver agreement (overall and per bolus consistency) of both observers on the measurement of the PAS was sufficient (κ≥0.77) (Table 4). The overall interobserver agreement on the PAS was substantial, when considering all bolus consistencies together (κ=0.78), showing improvement compared to the 'first measurement attempt'. The lowest interobserver agreement was obtained for bite-sized cracker (κ=0.44) using linearly weighted kappa coefficient. However, when looking at the percentage of agreement among the different bolus consistencies, the interobserver agreement for bite-sized cracker was 82.1%.

Percentage of pharyngeal residue

The overall intraobserver agreement of both observers on the measurement of the PPR was almost perfect, when considering all bolus consistencies together (κ=0.84-0.86) (Table 4). The lowest intraobserver agreement was obtained for thin liquid for observer 1 (κ=0.78). The overall interobserver agreement on the PPR was almost perfect, when considering all bolus consistencies together (κ=0.82), showing improvement compared to the 'first measurement attempt'. The lowest interobserver agreement was obtained for bite-sized cracker (i.e. moderate agreement) (κ=0.55) using linearly weighted kappa coefficient. However, the corresponding percentage of agreement (88.9%) was similar to the other bolus consistencies

Observer agreement on safety, efficiency, and summary DIGEST grade

Based on the scores of the second measurement attempt, the observers independently determined the safety and efficiency grades, per patient, by applying the modifiers described in the DIGEST validation study for VFSS [18]. Interobserver agreement, presented in Table 5, was substantial to almost perfect (safety grade: κ=0.65 (SE 0.12); efficiency grade: κ=0.85 (SE 0.09)). The interobserver agreement on the summary DIGEST grade was substantial (κ=0.71 (SE 0.09)).

Table 4 Linearly weighted kappa coefficient and percentage of agreement on the PAS and PPR when considering all bolus consistencies together ('total') and per bolus consistency during the second measurement attempt

	FEES variable and bolus consistency	*Intraobserver agreement*					*Interobserver agreement*		
		N (%)	*Observer 1*		*Observer 2*		*N (%)*	*Kappa (SE)*	*% of agreement*
			Kappa (SE)	*% of agreement*	*Kappa (SE)*	*% of agreement*			
Second measurement attempt	PAS								
	Total	59	0.88 (0.05)	86.4	0.86 (0.07)	91.5	184	0.78 (0.04)	78.7
	Thin liquid	26 (44)	0.83 (0.08)	76.9	0.77 (0.12)	84.6	79 (43)	0.82 (0.05)	76.3
	Thick liquid	24 (41)	0.92 (0.06)	91.7	0.97 (0.03)	95.8	77 (42)	0.80 (0.05)	79.7
	Bite-sized cracker	9 (15)	[a]	100.0	1.00 (0.00)	100.0	28 (15)	0.44 (0.13)	82.1
	PPR								
	Total	59	0.84 (0.08)	91.7	0.86 (0.07)	92.3	184	0.82 (0.04)	88.1
	Thin liquid	26 (44)	0.78 (0.14)	89.5	0.92 (0.08)	95.7	79 (43)	0.84 (0.07)	91.9
	Thick liquid	24 (41)	0.84 (0.11)	90.5	0.84 (0.11)	90.5	77 (42)	0.82 (0.06)	83.9
	Bite-sized cracker	9 (15)	[a]	100.0	[a]	87.5	28 (15)	0.55 (0.18)	88.9

PAS Penetration-Aspiration Scale [8]; *PPR* percentage of pharyngeal residue; *FEES* fiberoptic endoscopic evaluation of swallowing; *N* number of bolus swallows; *SE* standard error.
[a] Linearly weighted kappa could not be carried out for all measurements due to a limited number of measurements for some bolus consistencies, such as for bite-sized cracker, or a lack of variation of the scores across the PAS or PPR scales.

Table 5 Interobserver agreement on the safety, efficiency, and summary DIGEST grade

Grade	*Interobserver agreement*	
	Linearly weighted kappa (SE)	***% of agreement***
Safety grade	0.65 (0.12)	74.1
Efficiency grade	0.85 (0.09)	88.9
Summary DIGEST grade	0.71 (0.09)	25.9

DIGEST Dynamic Imaging Grade of Swallowing Toxicity; *SE* Standard Error.

Criterion validity

To further explore the criterion validity of the DIGEST, the correlation between safety, efficiency, and summary DIGEST grade versus the EAT-10, FOIS, TNM, and MDADI (MDADI-T and subscales, including global, functional, physical, and emotional) was analyzed. No significant correlation was found between safety, efficiency, and summary DIGEST grade versus FOIS, TNM, and MDADI. However, the efficiency grade significantly correlated with the EAT-10 for both observers (observer 1: p=0.01; observer 2: p=0.008). Also, a significant correlation was found between the summary DIGEST grade and the EAT-10 only for the scores of observer 1 (p=0.04), but not for the scores of observer 2 (p=0.08). No significant correlation was found between the safety grade and the EAT-10.

Discussion

The present study described the training process of two novice observers in order to obtain observer agreement on the visuoperceptual measurements of the DIGEST in FEES including effects of bolus consistency on agreement and statistical analysis to interpret the results. The development and implementation of a user manual with well-defined descriptions, in combination with a learning curve of the observers due to repeated training, led to a significantly better reproducibility of the DIGEST measurements in the present study. The criterion validity of the DIGEST was also explored using several explanatory variables (the EAT-10, FOIS, TNM, and the MDADI) in order to predict the DIGEST outcome. As our study was conducted in a Dutch Comprehensive Cancer Center certified by the Organisation of European Cancer Institutes (OECI accreditation) [36], the results of our study design also contribute to improving the external validity of the DIGEST in FEES.

Following the initial training program to measure the PAS and PPR in FEES, a first measurement attempt was made. When considering observer agreement of all bolus consistencies together, intraobserver agreement on the PAS was almost perfect and moderate to almost perfect for the PPR, whereas interobserver agreement on both the PAS and PPR was substantial. Interobserver agreement on the PPR per bolus consistency showed lower kappa values for thin liquid and bite-sized cracker (fair and moderate agreement). These lower kappa values were related to the PPR scores of observer 2, who presented a lower intraobserver agreement

for all bolus consistencies than observer 1. After the additional training program, the overall intra and interobserver agreement (all bolus consistencies together) on the PPR improved during the second measurement attempt. Interobserver agreement on the safety, efficiency, and summary DIGEST grades was substantial to almost perfect. This is in line with previous research although the observers in these studies were experienced clinicians as opposed to our novice observers [18, 19].

Previous studies have described sufficient observer agreement on the PAS during FEES [6, 12, 37]. However, a comparison with the present study is not possible as observer agreement in these studies was not determined per bolus consistency and the populations were of mixed etiology also containing neurological patients.

As the pharyngeal residue rating scale used in the DIGEST is a newly described scale, there is no information in the literature on observer agreement on the PPR, with the exception of the DIGEST validation studies [18, 19]. While vallecular and pyriform sinus residue are usually scored separately, the PPR is scored based on the 'overall' pharyngeal residue measuring the percentage of the ingested bolus that remains in the entire pharynx after the first swallow. Furthermore, the PPR cannot be compared to the Yale Pharyngeal Residue Severity Rating Scale, which measures the percentage of site-specific pharyngeal space (vallecula or pyriform sinus) that is filled with bolus after the first swallow on that bolus [7]. Yet, measurement of overall pharyngeal residue may be more appropriate and reproducible compared to site-specific pharyngeal residue in this particular population of HNC patients. Alterations of the pharyngeal and/or laryngeal anatomy due to the tumor itself and/or the oncological treatment, including post-radiation edema and necessary surgical sacrifice of structures, can pose a challenge to precisely determine the anatomical location and estimate the amount of residue. Anatomical changes such as absence of an arytenoid or epiglottis following CO2 laser surgery for supraglottic larynx carcinoma, or post-radiation mucosal edema filling the vallecular and/or pyriform sinus space can make it very difficult to measure the amount of bolus residue at a specific anatomical subsite of the pharynx. Insufficient agreement on some DIGEST measurements, especially the PPR, during the first attempt of this experiment could also be explained by several other factors, such as the initial absence of clear definitions of cut-off values (boundaries) between ordinal categories of a scale and inexperience of the novice observer in determining the percentage of residue based on FEES images. For instance, during VFSS, the bolus volume is visible during all the swallowing phases. Therefore, the amount of bolus residue in the pharynx can be compared to the initial bolus volume in the oral cavity to facilitate the estimation of the proportion of bolus left in the pharynx after swallowing. As during FEES only the pharyngeal phase is shown, this comparison is not possible.

Improved observer agreement after the additional training program and the use of the manual support this reasoning. The additional training program and the manual with well-defined descriptions probably optimized the test conditions in terms of standardization of the measurements performed by the observers during the second measurement attempt,

improving the reproducibility of the DIGEST measurements. This context-specific manual was based mainly on the difficulties experienced by the novice observers during the first measurement attempt in the present experiment. Therefore, the content of the manual cannot be extrapolated to different settings. Yet the use of the DIGEST under different conditions is encouraged, as this will contribute to its external validity.

Furthermore, bolus consistency can have an impact on the measurements in FEES exams [6, 10, 11]. For example, during the first measurement attempt, the interobserver agreement on the PPR was sufficient when analyzing all bolus consistencies together. However, interobserver agreement on the PPR was insufficient for thin liquid. The estimation of the amount of residue of thin liquid bolus can be challenging, since this less cohesive bolus spreads into the pharyngeal recesses more easily. Therefore, the percentage of thin liquid bolus remaining in the pharynx is more difficult to estimate compared to thick liquid, which is more cohesive when measured during the fork-drip test according to the IDDSI [34]. Bite-sized cracker also had an effect on observer agreement, as agreement for bite-sized cracker was often insufficient using linearly weighted kappa coefficient. This could be explained by the lack of variation of the scores across the PAS or PPR scales and the limited number of bolus swallows with bite-sized cracker. HNC patients frequently had incomplete dentition and/or severe xerostomia causing difficulty in mastication and swallowing of bite-sized cracker.

The findings of the present study were obtained using linearly weighted Cohen's kappa coefficient to calculate observer agreement. Kappa is the most commonly reported measure of observer agreement in the medical literature [38]. During the second measurement attempt interobserver agreement on both PAS and PPR was not sufficient for bite-sized cracker ($\kappa \leq 0.55$), yet the corresponding percentage of interobserver agreement on both PAS and PPR was high (≥82%). This statistical phenomenon, also called 'first paradox', of a high percentage of agreement between observers but low kappa values has been described extensively in the literature [39]. Kappa is a chance-corrected measure, but the level of agreement expected by chance alone is dependent on the distribution of marginal totals. Skewed distributions of scores across categorical scales can result in lower kappa values but this does not mean that the observer agreement is poor [40, 41].

Data collection and the DIGEST measurements of this study were performed prior to the publication of the study on the adaptation and validity of the DIGEST for FEES by Starmer et al. [19]. The design of the present study was based on the DIGEST protocol developed for VFSS, as published in the 'original' DIGEST study by Hutcheson et al. [18]. The measurements during the first measurement attempt were solely based on the information provided by the 'original' DIGEST study [18], and the insufficient observer agreement in our study showed the need for a more detailed description of the boundaries of each level of the ordinal variables. The 'original' DIGEST study determined interobserver agreement on the safety, efficiency, and summary DIGEST grades [18], yet our study also determined intra and interobserver agreement on the PAS and the PPR.

It is also important to emphasize that a videofluoroscopic measurement scale such as the DIGEST cannot be transformed directly, one-on-one into a FEES scale. Therefore, we also explored the criterion validity of the DIGEST in FEES by analyzing the correlation between the safety, efficiency, and summary DIGEST grade versus the EAT-10, FOIS, TNM, and MDADI. The EAT-10, FOIS, and MDADI were chosen as criterion measurements as they are patient-reported outcome measures (PROMs) which are part of the usual care protocol in our Comprehensive Cancer Center, representing different dimensions of swallowing impairment [42]. We found a significant correlation between the DIGEST efficiency grade versus the EAT-10 for both observers, implying that patients who presented increased levels of pharyngeal residue, had a higher level of self-perceived symptom severity on the EAT-10.

Limitations of the Study

This study has some limitations. Only two observers were involved in our study. Results on observer agreement might have been different if a higher number of observers was included or if the degree of experience of the observers was different. We followed the original DIGEST protocol as described in the VFSS validation study [18] to the extent possible. However, different bolus consistencies and volumes were used in our study as data was collected in daily clinical practice using our standardized FEES protocol [9, 11, 31]. This may have led to different safety and efficiency grades and consequently to a different criterion validity. Next, the DIGEST only measures pharyngeal dysphagia. However, patients with isolated oral dysphagia with preservation of pharyngeal swallowing function, which is common in patients with carcinoma of the anterior mouth floor, will not be captured by the DIGEST. Furthermore, at the time of submission of the present study, a revised version of the DIGEST for VFSS ('DIGEST version 2') was published refining the measurement of the safety grade [43]. Yet both our study as well as prior research on the DIGEST [18, 19, 43] aim to improve the DIGEST, promoting wider use of the DIGEST by multiple professionals and also improve its external validity.

Conclusion

The DIGEST showed to be a reproducible measurement for FEES in terms of observer agreement. However, agreement between novice observers on the DIGEST was only reached after specific observer-tailored training. Observer agreement should be analyzed by taking bolus consistency into account during training, as this might affect the interpretation of the outcome. A manual with well-defined descriptions can optimize the reproducibility of DIGEST measurements.

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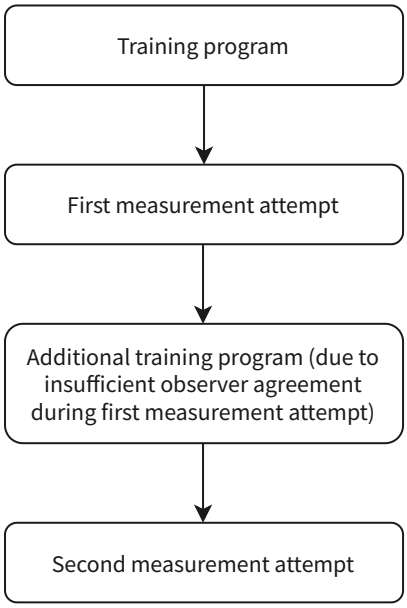
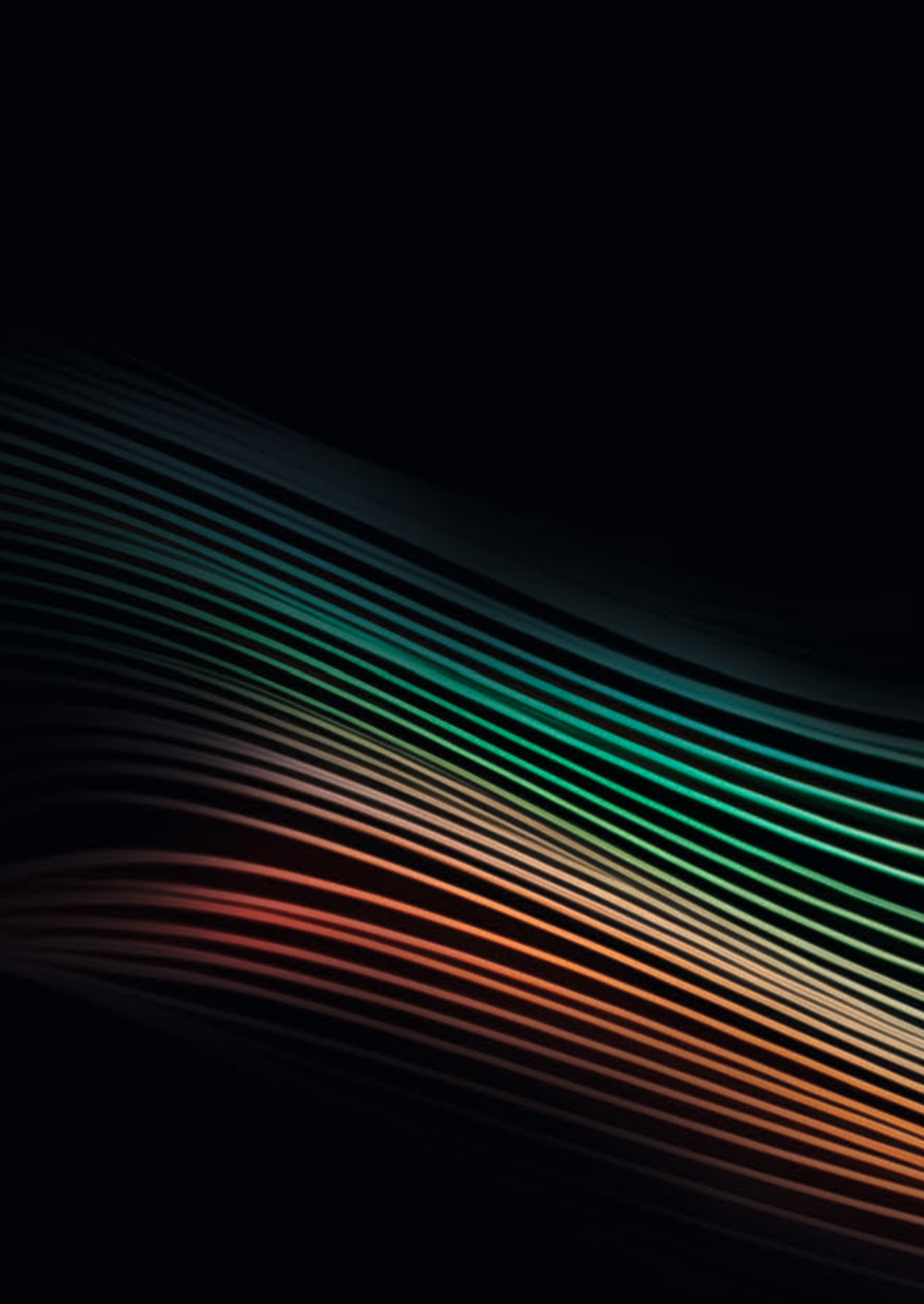
Supplementary Information

Online Resource 1 Flowchart of the training process of the novice observers





AUTHOR'S REPLY TO THE LETTER TO THE EDITOR "INTRA AND INTEROBSERVER AGREEMENT OF THE DYNAMIC IMAGING GRADE OF SWALLOWING TOXICITY SCALE (DIGEST) IN FIBEROPTIC ENDOSCOPIC EVALUATION OF SWALLOWING (FEES): THE IMPORTANCE OF OBSERVER-TAILORED TRAINING"

Laura W.J. Baijens, Sorina R. Simon

Eur Arch Otorhinolaryngol. 2023 Jun;280(6):3047-3049

Dear Editor,

We thank the authors Dr Hutcheson and Dr Starmer for their comments and the opportunity for a methodological discussion following the publication of our article "Intra and interobserver agreement of the Dynamic Imaging Grade of Swallowing Toxicity Scale (DIGEST) in fiberoptic endoscopic evaluation of swallowing (FEES): the importance of observer-tailored training" [1].

First, we would like to emphasize that our study is not a replication of the DIGEST-FEES study by Starmer et al., which had not yet been published when our study was conducted [2]. This was clearly stated in our study, as were all the criteria and variables used for the interpretation of FEES [1]. Therefore, we agree with Dr Hutcheson and Dr Starmer that there are many methodological differences between the studies that certainly influence the results [1, 2]. The reader can easily spot these differences as the methodology of our study is described in detail in the manuscript. Even though the studies have different designs, it is interesting to look at and learn from both [1, 2].

One of the comments of the authors of the letter to the editor concerns the level of experience of the raters. We take this opportunity to emphasize that we consider it appropriate that not only speech and language pathologists (SLPs) use the DIGEST [3], but also other health professionals with expertise in dysphagia. Think of otolaryngologists, radiologists, occupational therapists, etc. In Europe, FEES and videofluoroscopic swallowing study (VFSS) are widely used by health professionals other than SLPs [4]. In many European countries SLPs are not legally authorized nor trained to carry out FEES.

Dutch master of medicine students, in their final year, were chosen as raters for this experiment because they are also expected to learn and perform measures of FEES/VFSS interpretation during their residency of otorhinolaryngology, radiology, etc. Even if the outcome of a measurement scale is highly reproducible when performed by experienced SLPs, the question remains what about the reproducibility in case of novice raters, whom we examined in the current study.

The current study also differs from the previous DIGEST studies as it reports the (dis) agreement between raters in more detail, i.e., by consistency and not only on the DIGEST safety and efficiency grades but also on the measures of the penetration-aspiration scale and the 'percentage of pharyngeal residue' (PPR), the modifiers, etc. This allows a better understanding of the final scores, reasons of disagreement, and the learning process of rating.

The main purpose of our study was to explore the reproducibility of the DIGEST measures in terms of observer agreement. An additional objective was to explore criterion validity of the DIGEST for FEES in a population of Dutch head and neck cancer patients that differs from North American patients in the previous studies on DIGEST. To evaluate criterion validity, both studies [1, 2] calculated the correlation between the results of the DIGEST-FEES measures

and the results of various criterion measures. Both studies used the MD Anderson Dysphagia Inventory (MDADI) and Functional Oral Intake Scale (FOIS). The study of Starmer et al. also used the Secretion Severity Scale (SSS) and the Yale Pharyngeal Residue Severity Rating Scale (YPRSRS). Simon et al. (our study) used the Eating Assessment Tool-10 (EAT-10) and the tumor, nodes, and metastasis classification (TNM classification, 8th edition). All criterion measures of both studies mentioned here are methodologically defensible. It is therefore interesting to see that in both studies the efficiency ratings were generally more closely correlated to criterion measures than safety ratings.

We agree with the comment of the authors of the letter to the editor about the importance of understanding the difference between the DIGEST criteria for VFSS and FEES. However, the references mentioned in the letter could not be applied to the study of Simon et al. because they had not yet been published when our study was designed and conducted.

Furthermore, the authors of the letter state that the operational definitions and cut-off points for pharyngeal residue estimation differ in the DIGEST-FEES study of Starmer et al. based on supporting psychometric work by Pisegna et al. [5-7]. The study of Simon et al. applied the PPR measure as described in the original DIGEST-VFSS study [8]. The studies of Pisegna et al. carefully describe the advantages and disadvantages of using ordinal ratings for pharyngeal residue compared to continuous VAS ratings. Pisegna et al. recommend that residue should not be measured in equally-spaced intervals (mild/moderate/severe), but rather in a non-linear fashion (on a ratio scale such as a VAS). However, they also recommend further discussion of how residue is best measured and describe multiple limitations in their studies such as that raters appear to avoid rating at the severe end of the VAS scales. The study by Simon et al. shows that the PPR from the original DIGEST- VFSS study is reliably reproducible during FEES. In our view, the use of the PPR and its findings cannot be regarded as methodologically incorrect, it is a different methodological choice in a study design of an experiment that ran simultaneously with the study by Starmer et al. [1, 2].

The other important methodological comment of the authors of the letter surrounds the bolus protocol. The authors of the letter address differences between the bolus protocol of their study and the present study of Simon et al. We thank the authors for the clarification regarding the bolus consistencies used in the validation study of the DIGEST-VFSS, as these parameters were not adequately described in the article and there was no report of a DIGEST training manual [8].

Regarding the differences in the number of bolus trials used in our study to identify swallowing safety patterns, there is no evidence that 5 trials of thin liquid would be better than 3 trials in detecting impaired swallowing safety, as the authors of the letter admit. In addition, we refer to a previously published study showing that FEES protocols using a limited number of swallow trials can underestimate the risk of aspiration in both oncological and neurological patients suffering from oropharyngeal dysphagia, especially when using thin liquid boluses [9]. However, the oncology and neurology patients in that study significantly differed in the

number of swallow trials required to determine aspiration for thin liquids (median values 2 and 7 respectively, P = 0.006). The present study of Simon et al. used three trials of thin liquid with the exact same recipe as in the aforementioned study. So, we consider the number of thin liquid trials at least evidence-based in the study of Simon et al. [9].

Again, we thank Dr Hutcheson and Dr Starmer for their careful considerations and hope that our reply provides transparency for the methodological choices that were made in the study by Simon et al.

Sincerely,
Laura W.J. Baijens, MD, PhD
Sorina R. Simon, MD

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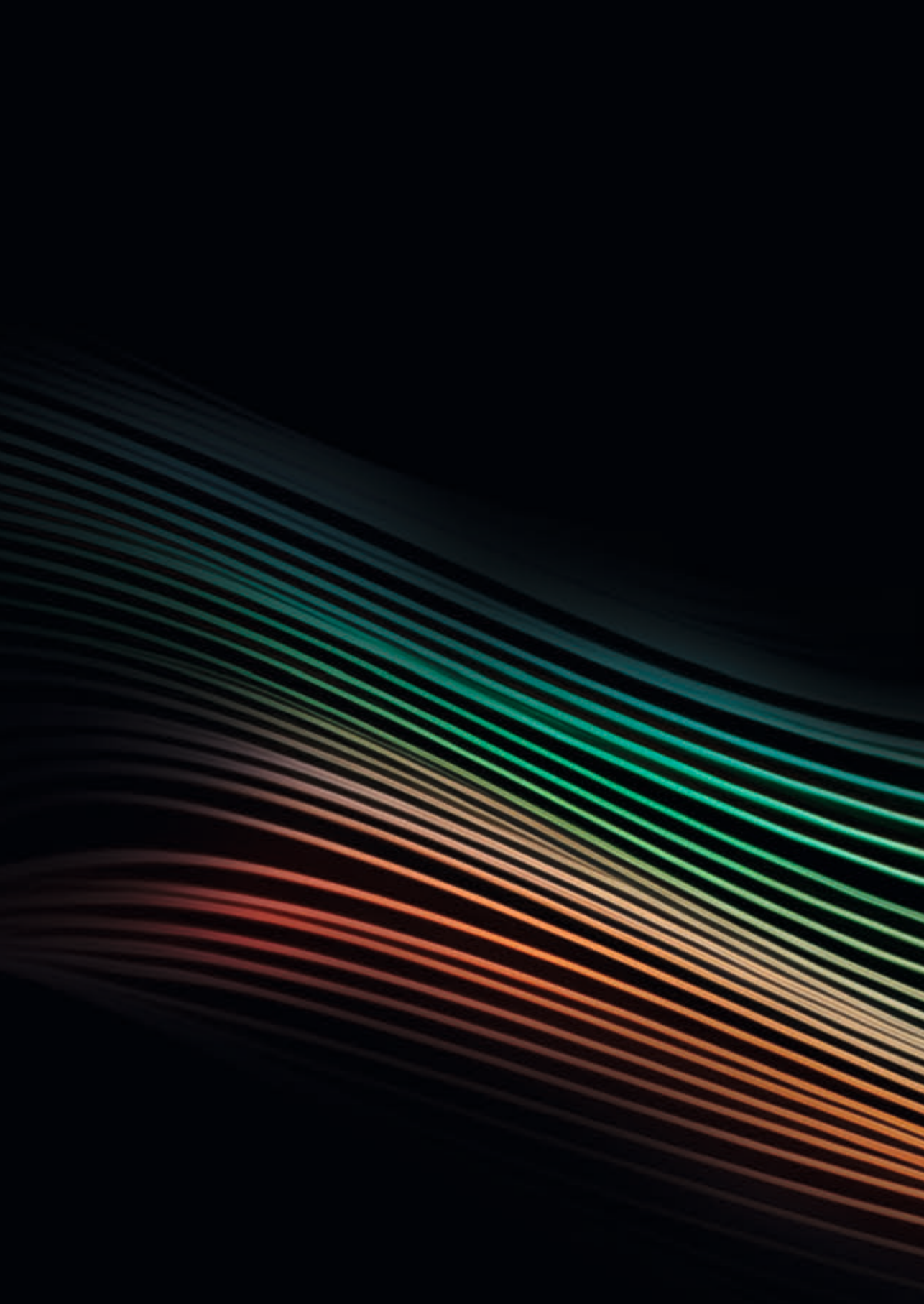

CHAPTER 6

MALNUTRITION SCREENING IN HEAD AND NECK CANCER PATIENTS WITH OROPHARYNGEAL DYSPHAGIA

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Abstract

Background & aims

Malnutrition in head and neck cancer (HNC) patients is associated with increased morbidity and mortality. The purpose of this study is two-fold: to identify the risk of malnutrition in patients with oropharyngeal dysphagia (OD) secondary to HNC, and to determine the relationship between the risk of malnutrition versus tumor characteristics, treatment modality, time interval (between the end of oncological treatment and swallowing assessment date), level of oral intake, body mass index (BMI), aspiration, pharyngeal pooling, and OD-related quality of life (QoL).

Methods

The Short Nutritional Assessment Questionnaire (SNAQ) was used to screen patients for the risk of malnutrition. Patients underwent a standardized swallowing examination protocol including an endoscopic evaluation of swallowing.

Results

Seventy-five dysphagic HNC patients were included. Forty-eight percent of the patients presented a high risk of malnutrition using SNAQ. The majority of the patients (81.3%) was on a total oral diet. Moreover, BMI did not appear to be a reliable measure to screen for malnutrition as a normal BMI was often associated with an increased risk of malnutrition on the SNAQ. In contrast, patients who were underweight or overweight did not show an association with a high risk of malnutrition. With the exception of BMI, no other patient and tumor characteristics were found to be associated with the risk of malnutrition.

Conclusions

This study emphasizes the importance of early nutritional screening in dysphagic HNC patients, as almost half of these patients presented a high risk of malnutrition. Malnutrition screening using SNAQ can identify HNC patients with OD who are at risk of malnutrition and subsequently need to be referred to a dietician for additional nutritional assessment, diagnosis of malnutrition, and nutritional support, even when their BMI is within normal range.

Introduction

Patients with head and neck cancer (HNC) have an increased risk of malnutrition at diagnosis and during the tumor treatment trajectory including follow-up [1-4]. The cause of malnutrition in HNC patients is multifactorial. Next to cancer induced metabolic aberrations, the tumor (location) may cause impaired swallowing function or impaired bolus passage, negatively affecting an adequate oral intake of calories [5, 6]. Moreover, the nutritional status can be affected by adverse effects of HNC treatment (surgery, radiotherapy, chemoradiotherapy, or combinations thereof – multimodality treatment) [6, 7]. In a systematic review on the nutritional status of HNC patients, oropharyngeal dysphagia (OD) was the most commonly reported symptom affecting oral intake [8]. The estimated prevalence of OD among HNC patients is high, as up to 64% of HNC patients suffer from OD following oncological treatment [9]. However, OD can also have other clinically significant consequences such as aspiration pneumonia [10]. Furthermore, HNC patients often have a pre-existent compromised nutritional status due to an unhealthy lifestyle with excessive use of alcohol and tobacco, and a diet lacking various nutrients [5, 6]. Weight loss in HNC patients is clinically relevant as it is associated with poor quality of life (QoL) [11], and increased morbidity and mortality [12, 13].

Clinically relevant symptoms of malnutrition may include: decreased appetite; unintentional weight loss; and the need for an adjusted diet including supplemental drinks or tube feeding [14, 15]. Previous studies showed that tumor characteristics (including advanced tumor classification and tumor location), multimodality oncological treatment, and OD severity (including aspiration and poor OD-related QoL) may affect the nutritional status [2, 11, 16-18]. Two of these studies investigated the relationship between swallowing function and malnutrition [16, 17]. However, none of these studies specifically investigated instruments used for the screening of risk of malnutrition in HNC patients with confirmed OD. Screening is an important step prior to the final diagnostic assessment of malnutrition in this patient population. Although most comprehensive cancer centers include a malnutrition screening into the standard protocol for HNC patients, the relationship between the risk of malnutrition and OD is still poorly assessed.

It is hypothesized that OD has a close relationship with malnutrition, implying that dysphagic patients present a higher risk of malnutrition. The understanding of this relationship may help us in the clinical context to be able to identify dysphagic HNC patients that may benefit from a more appropriate nutritional management plan. Therefore, the purpose of this study is two-fold: (1) to identify the risk of malnutrition in patients with OD secondary to HNC, and (2) to determine the relationship between the risk of malnutrition on the one hand versus tumor characteristics, HNC treatment modality, time interval between the end of oncological treatment and the swallowing assessment, Functional Oral Intake Scale (FOIS), body mass index (BMI), aspiration, pharyngeal pooling, and OD-related QoL on the other hand.

Materials & Methods

Patient information

This cross-sectional cohort study included HNC patients who visited the outpatient clinic for OD between January 2011 and January 2018 in the University Hospital Comprehensive Cancer Center. Individuals were enrolled in the study if they had completed the curative HNC treatment (surgery, radiotherapy, chemoradiotherapy, or combinations - multimodality treatment) at least 3 months before recruitment and their disease was in total remission (i.e., they were disease-free). All patients presented subjective swallowing complaints. Exclusion criteria were: severe odynophagia; radiation mucositis; more than one primary tumor in the head and neck region; osteoradionecrosis of the maxilla or mandible; a concurrent neurological disease (stroke, Parkinson disease, etc.) or other non-HNC primary cancer sites (e.g. esophagus or thyroid cancer); scoring below 23 on a Mini Mental State Examination (MMSE) [19]; being older than 85 years; a status following total laryngectomy; and illiteracy or blindness. All primary tumors were classified according to the tumor, nodes, and metastasis (TNM) classification 7th edition [20]. All patients underwent oncological treatment in the form of surgery, radiotherapy, chemoradiotherapy, or combinations thereof – multimodality treatment according to the Dutch National Guideline on Head and Neck Cancer Management [21]. Written informed consent was obtained from all patients before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the study was approved by the medical ethics committee (METC 2018-0855).

Assessment protocol

All patients underwent the standardized examination protocol used in daily clinical practice at the outpatient clinic for OD. This protocol comprises the dysphagia severity scale (DSS) and the dysphagia quality of life scale (DQL), the Short Nutritional Assessment Questionnaire (SNAQ), the Functional Oral Intake Scale (FOIS), a Body Mass Index (BMI), and a standardized fiberoptic endoscopic evaluation of swallowing (FEES). Patients' perception of swallowing impairment was assessed using two self-report visual analogue scale tools: the dysphagia severity scale (DSS) and the dysphagia quality of life scale (DQL) [22]. These scales quantify the severity of the swallowing disorder and the extent of impairment experienced by the patient. The scores range from 0 to 100, with 0 being extremely impaired and 100 standing for 'normal swallow'. To determine risk of malnutrition, the validated Dutch version of the Short Nutritional Assessment Questionnaire (SNAQ) was used [15, 23]. The SNAQ is a screening tool used to evaluate the risk of malnutrition. The questionnaire consists of 4 items to screen patients for the risk of moderate (2 points) and severe (≥ 3 points) malnutrition. Patients with a score <2 were considered low risk thus well-nourished [15, 23]. The advantages of this valid screening instrument include a short, quick, and easy to use method which needs no calculation and is readily accessible, reproducible, and inexpensive. The SNAQ focusses on malnutrition screening. It is not a diagnostic tool for malnutrition assessment. The SNAQ provides a comprehensible outcome (screening score with a validated cut-off value) which may lead to subsequent referral to the dietician and a more elaborate nutritional assessment,

including bioelectrical impedance analysis (BIA), estimation of muscle mass (using the Scored Patient-Generated Subjective Global Assessment and imaging, such as computed tomography-derived fat-free mass index), muscle strength measurements (functional tests), blood analysis (vitamin status, inflammation), etc. [24, 25]. Using these measurements, the dietician can diagnose the actual presence of malnutrition and suggest a patient-tailored nutritional treatment plan. The validated Dutch version of the SNAQ questionnaire is therefore widely used across healthcare institutions in the Netherlands [15]. The functional oral intake of food and liquid was assessed using the FOIS. The FOIS is an ordinal scale tool that ranges from one to seven [26]: nothing by mouth (level 1), tube dependency with minimal attempts of food or liquid (level 2), tube dependency with consistent oral intake of food or liquid (level 3), total oral diet of a single consistency (level 4), total oral diet with multiple consistencies requiring special preparation or compensations (level 5), total oral diet with multiple consistencies without special preparation, but with specific food limitation (level 6), and a total oral diet with no restrictions (level 7). All patients underwent an examination of the swallowing function, using a standardized FEES protocol, to identify the presence of pharyngeal residue and/or aspiration. During the FEES examination patients were offered three trials of thin liquid, three trials of thick liquid, and one bite-sized cracker of 2 g (Delhaize Mini Toast 80 g®). Each liquid trial contained 10 cc of water or applesauce (applesauce; One 2 fruit®) dyed with 5% methylene blue (10 mg/ml). The viscosity of the liquid bolus consistencies was measured at 25 ^{0}C and 50 s-1 of shear rate resulting in 1 mPa.s for thin liquid and 1200 mPa.s for thick liquid. During the flow test, thick liquid met the descriptive criteria for 'moderately thick' according to the International Dysphagia Diet Standardisation Initiative [27-30]. The tip of the flexible fiberoptic endoscope Pentax FNL-10RP3 (Pentax Canada, Mississauga, Ontario, Canada) was positioned just above the epiglottis in what is called the 'high position'. FEES images were obtained with the Xion SD camera, Xion EndoSTROBE camera control unit (PAL 25 fps), and Matrix DS data station with DIVAS software (Xion Medical, Berlin, Germany) and stored on the hospital network drive. The images were recorded at 30 frames per second. Neither a nasal vasoconstrictor nor a topical anesthetic was administered to the nasal mucosa. For each FEES swallow trial two visuoperceptual ordinal variables were scored: aspiration and pharyngeal pooling. Aspiration was defined as entry of the bolus into the larynx below the level of the vocal folds (also including the vocal commissures) before, during or after swallowing. Pooling or residue was defined as the amount of bolus remaining in the pyriform sinuses and/or valleculae after spontaneous clearing swallows. Aspiration and pharyngeal pooling were scored dichotomously (present or absent) by two observers who received a training program described in a previous study [30]. The observers were blinded for the medical history of the patient and to each other's ratings (independent rating). All swallows were scored in a randomized order.

Statistical analysis

Descriptive statistics were reported as numbers and percentages for categorical variables and as means with standard deviations (SDs) or medians with 25th and 75th percentile for numerical variables. Parametric tests were used in case of normal distribution of variables,

whereas non-parametric tests were used in case of non-normal distribution of variables. Where appropriate, missing values were reported. For statistical analysis, patients were divided in two groups based on the SNAQ cut-off value ≥2: low risk of malnutrition (0-1 point) versus high risk of malnutrition (≥ 2 points). A cut-off value ≥2 was used as this has been shown to provide an optimal balance between sensitivity and specificity [15, 23]. To avoid group sizes that are too small to obtain reliable estimates, categorical and numerical variables were dichotomized before analysis. As sensitivity analysis, to see whether this dichotomization yielded a loss of information, the numerical variables were also analyzed as continuous variables. Tumor classification was divided into T3 and T4 (advanced stage tumors) versus T1 and T2 (early stage tumors). Type of HNC treatment modality was divided into multimodality versus single modality treatment (single modality treatment implies radiotherapy or surgery). The time interval between the end of oncological treatment and the swallowing assessment date was divided in < 5 years and > 5 years. This cut-off point was based on the 5 year follow-up period of HNC patients in the Netherlands [21]. The levels of the FOIS scale were also pooled in two groups: score of 1-3 (tube feeding dependent) versus a score of 4-7 (oral intake without tube feeding). Additionally, BMI was divided into three categories: underweight (BMI<18.5), normal BMI (18.5-24.9), and overweight (BMI≥25.0). Likewise, aspiration and pharyngeal pooling were categorized in two groups: presence or absence of aspiration and pharyngeal pooling, respectively. The intraobserver and interobserver agreement levels for the FEES variables aspiration and pharyngeal pooling were calculated using linear weighted kappa coefficient [31]. The differences between patients with a low risk of malnutrition versus patients with a high risk of malnutrition were first analyzed using chi-square or Fisher's exact test, where appropriate, for categorical variables, and independent samples t-test or Mann-Whitney U test, where appropriate, for numerical variables. Thereafter, multivariable logistic regression analysis was performed regarding the association between the risk of malnutrition on the one hand versus tumor characteristics, HNC treatment modality, time interval between the end of oncological treatment and the swallowing assessment date, FOIS, aspiration, pharyngeal pooling, and OD-related QoL on the other hand. Each analysis was corrected for age and gender, as both age and gender have an effect on cancer metabolism [32, 33]. Additional correction for tumor classification (T3-4 versus T1-2) and BMI was performed in the logistic regression analysis. As sensitivity analyses, logistic regression analyses were performed with correction for age, gender, and one of the following three continuous variables: time interval between the end of oncological treatment and swallowing assessment date in days, FOIS, or BMI. Based on these results, post-hoc analyses were performed using a chi-square, Fisher's exact, independent samples t-, or Mann-Whitney U test. A two-sided p-value ≤ 0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 23.0 (IBM, Armonk, NY).

Results

Study population

Seventy-five dysphagic HNC patients were included in this study, of whom 58 (77.3%) were male. The mean age of the patients was 65.9 (SD 10.0) years. The median (25^{th} -75^{th} percentile) time interval between the end of oncological treatment and the swallowing assessment date was 43.2 (7.9-121.6) months. Sixty-one patients (81.3%) were on a total oral diet (FOIS 4-7). Thirty-six patients (48%) presented a high risk of malnutrition (SNAQ score ≥ 2). The mean BMI was 25.0 (SD 5.7). Aspiration was identified in 35 (47.3%) patients. One patient did not undergo the FEES examination and the reason is unknown. The median score (25^{th} -75^{th} percentile) of the DSS and DQL was 45.5 (23.0-66.3) and 29.0 (18.0-53.0), respectively. Baseline characteristics of patients with a low risk of malnutrition (N=39) versus patients with a high risk of malnutrition (N=36) are presented in Table 1. Baseline characteristics of the entire study population are presented in Table S1 in the supplementary material. Additional descriptive statistics were performed to compare the subgroups of patients evaluated < 5 years resp. > 5 years after the end of oncological treatment. Patients evaluated > 5 years after the end of oncological treatment were more frequently showing a low risk of malnutrition (SNAQ score <2) and reported being on a total oral diet (FOIS 4-7) more often (93.3% versus 73.3%, resp.), compared to patients evaluated < 5 years after the end of oncological treatment.

Table 1 Characteristics of patients with a low risk of malnutrition (N=39) versus patients with a high risk of malnutrition (N=36), including univariable analysis[a]

Variables	Low risk of malnutrition (N=39)	High risk of malnutrition (N = 36)	p-value
Male gender N (%) (N=75)	30 (76.9)	28 (77.8)	0.930
Age at evaluation in years (mean± SD) (N=75)	67.7 ± 8.9	64.0 ± 10.9	0.114
Tumor site (N=74)			0.095
Pharynx N (%)	10 (26.3)	17 (47.2)	0.030[d]
Larynx N (%)	13 (34.2)	12 (33.3)	0.259
Oral cavity and salivary gland N (%)	15 (39.5)	7 (19.5)	0.060
T classification (N=68)			
T3-T4 N (%)	15 (44.1)	17 (50.0)	0.627
Treatment modality (N = 75)			
Multimodality treatment N (%)	24 (61.5)	24 (66.7)	0.644
Time interval between end of oncological treatment and swallowing assessment date (N=75)			
< 5 years[b] N %	22 (56.4)	23 (63.9)	0.509
Months (median (25^{th}-75^{th} percentile))	44.8 (10.3-146.0)	20.3 (6.0-109.6)	0.181
FOIS (N=75)			
FOIS level 1-3 Tube dependent N (%)	5 (12.8)	9 (25.0)	0.176
Mean ± SD	5.1 ± 1.7	4.4 ± 1.6	0.090

Table 1 Continued

Variables	Low risk of malnutrition (N=39)	High risk of malnutrition (N = 36)	p-value
BMI[c] (N=73)			0.152
BMI < 18.5 N (%)	4 (10.5)	3 (8.6)	0.547
BMI 18.5-24.9 N (%)	13 (34.2)	20 (57.1)	0.049[d]
BMI ≥ 25 N (%)	21 (55.3)	12 (34.3)	0.072
Mean ± SD	26.5 ± 6.4	23.5 ± 4.2	0.021[d]
Presence of aspiration N (%) (N = 74)	16 (42.1)	19 (52.8)	0.358
Presence of postswallow pharyngeal pooling N (%) (N= 74)	29 (76.3)	28 (77.8)	0.881
DSS median (25^{th}-75^{th} percentile) (N=50)	46.0 (23.0-69.0)	45.0 (15.0-57.0)	0.483
DQL median (25^{th}-75^{th} percentile) (N=50)	31.0 (16.0-60.0)	25.0 (18.0-48.0)	0.397

N Number of patients; *SD* Standard Deviation; *FOIS* Functional Oral Intake Scale; *BMI* Body Mass Index; *DSS* Dysphagia Severity Scale; *DQL* Dysphagia Quality of Life Scale.
[a]Patients were divided in two groups based on the SNAQ cut-off value ≥2: low risk of malnutrition (0-1 point) (N = 39) versus high risk of malnutrition (≥ 2 points) (N = 36). Univariable analysis was performed using, where appropriate, chi-square test, Fisher's exact test, independent samples t-test, and Mann-Whitney U test.
[b]The time interval between the end of oncological treatment and the swallowing assessment date was divided in < 5 years and > 5 years, and this cut-off point was based on the 5 year follow-up period of HNC patients in the Netherlands.
[c]Each BMI category was compared to the remaining BMI categories.
[d]Statistically significant (p ≤ 0.05).

Observer agreement

The interobserver and intraobserver agreement levels were sufficient for the FEES variables aspiration and pharyngeal pooling (Kappa coefficients ≥ 0.71, indicating substantial to almost perfect agreement).

Univariable analysis

Using univariable analysis, no significant association was found between the risk of malnutrition subgroups (N=39 low risk of malnutrition; N=36 high risk of malnutrition) on the one hand versus the variables gender, age, tumor classification, type of HNC treatment modality, time interval between the end of oncological treatment and the swallowing assessment, FOIS score, aspiration, pharyngeal pooling, and OD-related QoL on the other hand (Table 1). Tumor site was found to be related to the risk of malnutrition, as patients with a tumor located in the pharynx (versus a tumor located in the oral cavity or salivary gland) showed a significant association with a high risk of malnutrition (p=0.030). As expected, the mean BMI score (SD) of patients with a high risk of malnutrition according to the SNAQ scale, was significantly lower (23.5 ± 4.2) compared to the group with a low risk of malnutrition (26.5 ± 6.4) (p=0.021). Surprisingly, patients with a normal BMI had significantly more often a high risk of malnutrition (p=0.049) than patients with an abnormal BMI.

Multivariable analysis

The results of multivariable logistic regression analysis with correction for age and gender, and additional correction for tumor classification and BMI are presented in Table 2. After correction for age and gender, no significant association was found between a high risk of malnutrition (SNAQ score ≥2) versus tumor classification, type of HNC treatment modality, time interval between the end of oncological treatment and the swallowing assessment, FOIS score, aspiration, pharyngeal pooling, and OD-related QoL. After additional correction for tumor classification (T3-4 versus T1-2) and BMI, similar results were seen.

A significant association was found between tumor site and risk of malnutrition: a tumor located in the pharynx (versus a tumor located in the oral cavity or salivary gland) showed a positive association with a high risk of malnutrition (p=0.048). After correction for BMI, this association remained statistically significant (p=0.034). However, after correction for tumor classification, the significance of the association disappeared (p=0.065). No significant association was found between laryngeal tumors (versus a tumor located in the oral cavity or salivary gland) and the risk of malnutrition. Furthermore, patients with a normal BMI presented a high risk of malnutrition significantly more often, compared to patients with an abnormal BMI (p=0.023). After additional correction for tumor classification, similar results were seen (p=0.036). This association was not found for patients who were underweight or overweight.

Table 2 Multivariable logistic regression analysis with correction for age, gender, and additional correction for tumor classification and BMI, regarding the association between tumor characteristics, HNC treatment modality, time interval between end of oncological treatment and swallowing assessment date, FOIS, BMI, aspiration, pharyngeal pooling, and OD-related quality of life versus the risk of malnutrition (defined as high risk of malnutrition versus low risk of malnutrition patients) (total number of patients = 75)[a]

Variables	Risk of malnutrition (with correction for age and gender)		Risk of malnutrition (with correction for age, gender, and tumor classification)		Risk of malnutrition (with correction for age, gender, and BMI)	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Tumor site		0.136		0.175		0.077
Pharynx vs. oral cavity or salivary gland	3.392 (1.012, 11.369)	0.048[c]	3.158 (0.931, 10.706)	0.065	4.176 (1.114, 15.562)	0.034[c]
Larynx vs. oral cavity or salivary gland	2.270 (0.663, 7.772)	0.192	2.229 (0.605, 8.217)	0.229	3.682 (0.927, 14.630)	0.064
Pharynx vs. larynx	1.494 (0.468, 4.769)	0.497	1.417 (0.415, 4.843)	0.578	1.134 (0.323, 3.988)	0.845
Tumor classification						
Advanced stage tumors (T3-4) vs. early stage tumors (T1-2)	1.350 (0.511, 3.567)	0.545	/	/	1.326 (0.468, 3.758)	0.595
Treatment						
Multimodality vs. single modality treatment	1.034 (0.384, 2.784)	0.948	0.901 (0.308, 2.636)	0.849	0.814 (0.283, 2.340)	0.703
Time interval between end of oncological treatment and swallowing assessment date[b]						
< 5 years vs. > 5 years	1.255 (0.483, 3.265)	0.641	1.093 (0.384, 3.110)	0.867	1.177 (0.432, 3.205)	0.750
FOIS[b]						
FOIS score 1-3 vs. FOIS score 4-7	2.301 (0.678, 7.804)	0.181	1.753 (0.487, 6.310)	0.391	2.381 (0.627, 9.041)	0.202
BMI[b]		0.233		0.362	/	/
BMI<18.5 vs. BMI ≥ 18.5	0.604 (0.118, 3.088)	0.545	0.546 (0.105, 2.827)	0.470	/	/
BMI between 18.5-24.9 vs. underweight and overweight	3.348 (1.183, 9.474)	0.023[c]	3.132 (1.076, 9.113)	0.036[c]	/	/
BMI ≥25 vs. BMI <25	0.382 (0.142, 1.025)	0.056	0.425 (0.154, 1.175)	0.099	/	/

Table 2 Continued

Variables	Risk of malnutrition (with correction for age and gender)		Risk of malnutrition (with correction for age, gender, and tumor classification)		Risk of malnutrition (with correction for age, gender, and BMI)	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Aspiration	1.763 (0.672, 4.630)	0.249	2.032 (0.700, 5.902)	0.192	1.619 (0.565, 4.644)	0.370
Pharyngeal pooling	1.278 (0.410, 3.984)	0.672	0.922 (0.264, 3.226)	0.899	1.303 (0.376, 4.514)	0.677
DSS	0.991 (0.969, 1.015)	0.459	0.989 (0.965, 1.014)	0.386	0.990 (0.966, 1.014)	0.413
DQL	0.991 (0.968, 1.015)	0.467	0.991 (0.966, 1.016)	0.461	0.991 (0.967, 1.016)	0.487

OR Odds Radio; *CI* confidence interval; *FOIS* Functional Oral Intake Scale; *BMI* Body Mass Index; *DSS* Dysphagia Severity Scale; *DQL* Dysphagia Quality of Life Scale.
[a]Logistic regression analysis was performed with correction for age and gender, and additional correction for tumor classification (T3-4 versus T1-2) and BMI. Risk of malnutrition was defined as high risk of malnutrition (SNAQ score ≥ 2) versus low risk of malnutrition (SNAQ score < 2).
[b]Additional sensitivity analysis was performed for the following continuous variables: time interval between the end of oncological treatment and swallowing assessment date in days, FOIS, and BMI. The continuous variables time interval between the end of oncological treatment and swallowing assessment date in days, and FOIS did not show a significant association with risk of malnutrition. The continuous variable BMI showed a significant association with malnutrition with correction for age and gender (p=0.034), however, no significant association was found after correction for age, gender, and tumor classification (p=0.053).
[c]Significance at $p \leq 0.05$.

Post hoc analysis

Additionaly, post-hoc analyses were performed to confirm the significant association shown in the univariable and/or multivariable analyses between the risk of malnutrition versus the pharyngeal tumor site and normal BMI. Patients with a tumor located in the pharynx demonstrated a significantly higher frequency of aspiration compared to patients with a tumor in the oral cavity or salivary gland (63.0% vs 27.3%) (p=0.013). However, there were no significant differences between these two groups regarding mean BMI (p=0.258), mean FOIS score (p=0.344), and the frequency of pharyngeal pooling (p=0.510). Also no significant differences regarding the multimodality treatment (versus single modality treatment) (p=0.732), advanced stage tumor (versus early stage tumor) (p=0.343), and median time interval between the end of oncological treatment and swallowing assessment date (p=0.154) were found. Additional analysis comparing the group of patients with a normal BMI (BMI between 18.5-24.9) versus the group of patients with an abnormal BMI (BMI<18.5 or BMI ≥25) showed no significant differences regarding the mean FOIS score (p=0.108), presence or absence of aspiration (p=0.252), presence or absence of pharyngeal pooling (p=0.184), frequency of multimodality treatment (versus single modality treatment) (p=0.382), advanced stage tumor (versus early stage tumor) (p=0.672), and median time interval between the end of oncological treatment and swallowing assessment date (p=0.528).

Discussion

Discussion

This study identified the prevalence of malnutrition risk in patients with OD secondary to HNC and determined the relationship between risk of malnutrition on the one hand versus tumor characteristics, HNC treatment modality, time interval between the end of oncological treatment and swallowing assessment, level of oral intake, BMI, aspiration, pharyngeal pooling, and OD-related QoL on the other hand.

In our study, almost half of the HNC patients with OD presented a high risk of malnutrition (SNAQ score ≥ 2). The risk of malnutrition in HNC patients is not a novelty. A study in HNC patients treated with chemoradiotherapy reported that almost 20% of the patients presented a moderate or high risk of malnutrition during oncological follow-up [4]. In the same study, half of the HNC population was identified to be dysphagic based on videofluoroscopic swallow study (VFSS). However, the study did not explore the relationship between risk of malnutrition and dysphagia in HNC patients. In the present cohort almost 1 in 5 patients was feeding tube dependent (FOIS 1-3). Among patients having full oral intake, those with a high risk of malnutrition required more adaptations on the food consistency and/or compensations to warrant oral intake compared to patients with a low risk of malnutrition. Despite that, restrictions on oral intake were not significantly associated with the presence of risk of malnutrition. Although lacking statistical significance, the results showed a trend towards more impaired functional oral intake of food and liquid in patients with a high risk of

malnutrition. It is expected that oral intake restrictions can lead to an altered or unbalanced diet, contributing to weight loss.

Regarding the effect of time after HNC treatment on the functional oral intake level, the subgroup of patients evaluated > 5 years after the end of oncological treatment showed not only more favorable characteristics on functional oral intake, i.e. higher percentage of patients was on a total oral diet, but also a lower risk of malnutrition than patients evaluated within 5 years before the end of the oncological follow-up. Future studies should investigate this aspect further as it seems that restriction on oral intake in HNC survivors can be present for more than 10 years following chemoradiotherapy [34].

Although there was a high percentage of patients with tube feeding or oral intake restrictions, the BMI indicated a normal mean BMI in this cohort following oncological treatment.

Our study showed that, although patients with high risk of malnutrition had a lower BMI compared to patients with low risk, their BMI was still in the normal range. This may be explained by the societal trend of increasing BMI (obesity) in which HNC patients may show substantial weight loss, including loss of lean body mass, but still have a normal BMI [8, 35]. Along this line of reasoning, other studies already reported a high pre-treatment BMI as a predictor of weight loss in HNC patients [2, 18, 36, 37]. However, we also found that patients with a normal BMI demonstrated a risk of malnutrition significantly more often, compared to patients with an abnormal BMI. Interestingly, patients who were underweight or overweight did not show an association with the risk of malnutrition. This finding supports the need to screen all HNC patients visiting an outpatient clinic for OD for the risk of malnutrition by using a validated screening tool, as BMI did not appear to be a reliable measure to screen for malnutrition in this category of HNC patients.

To further understand the relationship between the risk of malnutrition and OD in HNC patients, possible risk factors in the context of tumor characteristics, tumor site, and tumor classification were included in the logistic regression analysis. An association was found between tumor site (pharynx) and risk of malnutrition. However, the significance of the association disappeared after correction for tumor classification. Tumor classification itself did not seem to be an indicator for the presence of a risk of malnutrition in our cohort. This finding was unexpected as an advanced tumor classification may lead to increased tumor growth-related tissue destruction, advanced neck node classification, and tissue destruction due to the multimodality oncological treatment, thus promoting swallowing impairment and a decreased oral intake [18, 38]. Moreover, an increased tumor metabolism is expected in advanced stage HNC, with higher levels of tumor-derived cytokines inducing sarcopenia [39]. However, the effect of tumor-derived cytokines is expected to be negligible during follow-up, as oncological treatment has already been completed and patients having recurrent disease were excluded in the present study.

A lack of association was also found between risk of malnutrition and type of HNC treatment modality (surgery, radiotherapy, chemoradiotherapy, or combinations - multimodality treatment). In the literature it is well-reported that treatment-induced alterations, including fibrotic and neuropathic changes, can lead to pharyngeal sensory deficits and impaired pharyngeal contraction. These alterations may contribute to further impairment of both deglutition and nutritional status [10]. The lack of an association between the risk of malnutrition and type of HNC treatment modality and tumor size might have been caused by a modest sample size, which made statistical stratification impossible.

As oncological treatment can cause various acute and late adverse effects, the severity of malnutrition may vary over time [40]. However, when comparing time interval from the end of the HNC treatment until the swallowing assessment, no significant difference was found between the category of low risk of malnutrition versus the high risk category. It shows that weight loss can continue after completion of oncological treatment, and stresses the importance of a nutritional follow-up [2]. The median time interval between the end of oncological treatment and the swallowing assessment date was 43.2 months. It shows that a substantial number of patients sought help for their swallowing impairment long after the oncological follow-up period was ended. This indicates that OD and malnutrition remain sustainable points of attention in HNC survivors after 5 years of oncological follow-up.

In this study, no significant associations between the risk of malnutrition and the presence of aspiration or pharyngeal pooling during FEES were found. Unfortunately, the body of literature on the relationship between the risk of malnutrition and specific signs of OD including aspiration and pharyngeal pooling remains poor. Weight loss was previously reported to be associated with aspiration in HNC patients [16, 17]. However, these studies did not investigate the specific category of HNC patients with OD, making comparison with the present study difficult.

Next, the lack of an association between patients' perception of the impact of OD on their QoL and the risk of malnutrition, may be explained by the fact that, although a group of patients were classified as being at risk of malnutrition, they did not have a low BMI. It means that although they have lost weight, their BMI was still within the normal range, and for that reason among others it did not have a significant effect on their OD-related QoL. Another reason might be that the DSS and DQL scales were insufficiently able to reveal group differences in this specific patient population. Maybe other instruments (including the MD Anderson Dysphagia Inventory) could have led to different insights.

Finally, future research could investigate the direction and causality of the relationship between the risk of malnutrition and OD severity in HNC patients in a longitudinal research design using a larger sample size.

Limitations

This study has some limitations. Whereas some statistically significant results were found, the sample size was too modest to allow detailed group stratification for tumor subsites, oncological treatment modalities, time after treatment, and tumor characteristics. A significant number of patients with advanced stage HNC die within five years after oncological treatment, making it difficult to achieve a large sample size [41]. Furthermore, the most critical marker of OD is aspiration [42].

For our study, a previously published modified aspiration scale was used making no distinction between silent and non-silent aspiration [27, 30]. The decision to use a modified scale in the present study was based on a recently published psychometric review on measurement scales in FEES and VFSS including among others the Penetration Aspirations Scale, showing that their psychometric status was either poor or lacking data on validity, reliability, and responsiveness [43-45].

A different malnutrition screening tool might have led to different results but the current data were available as the SNAQ is used as standard tool for all oncological care lines in our University Hospital Comprehensive Cancer Center. Finally, we do not know for sure whether there is a causal relationship between OD and the risk of malnutrition in HNC patients. Other factors may play a role in this relationship too.

Conclusions

Our study shows the importance of early nutritional screening in dysphagic HNC patients, as almost half of the HNC patients with OD presented a high risk of malnutrition. Moreover, despite a normal BMI, there was a high risk of malnutrition in this HNC patient subgroup. Furthermore, the lack of an association between the risk of malnutrition and many of the other variables studied, such as OD-related variables and tumor-related variables, emphasizes the need for a specific screening for malnutrition in the category of HNC patients with OD. Therefore, it is highly recommended to screen the nutritional status after oncological treatment and during long term follow-up in all HNC survivors, including the ones presenting with a normal BMI. The screening can identify HNC patients with OD that need to be referred to a dietician for additional nutritional assessment, diagnosis of malnutrition, and nutritional support even when their BMI is within normal range.

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Supplementary data

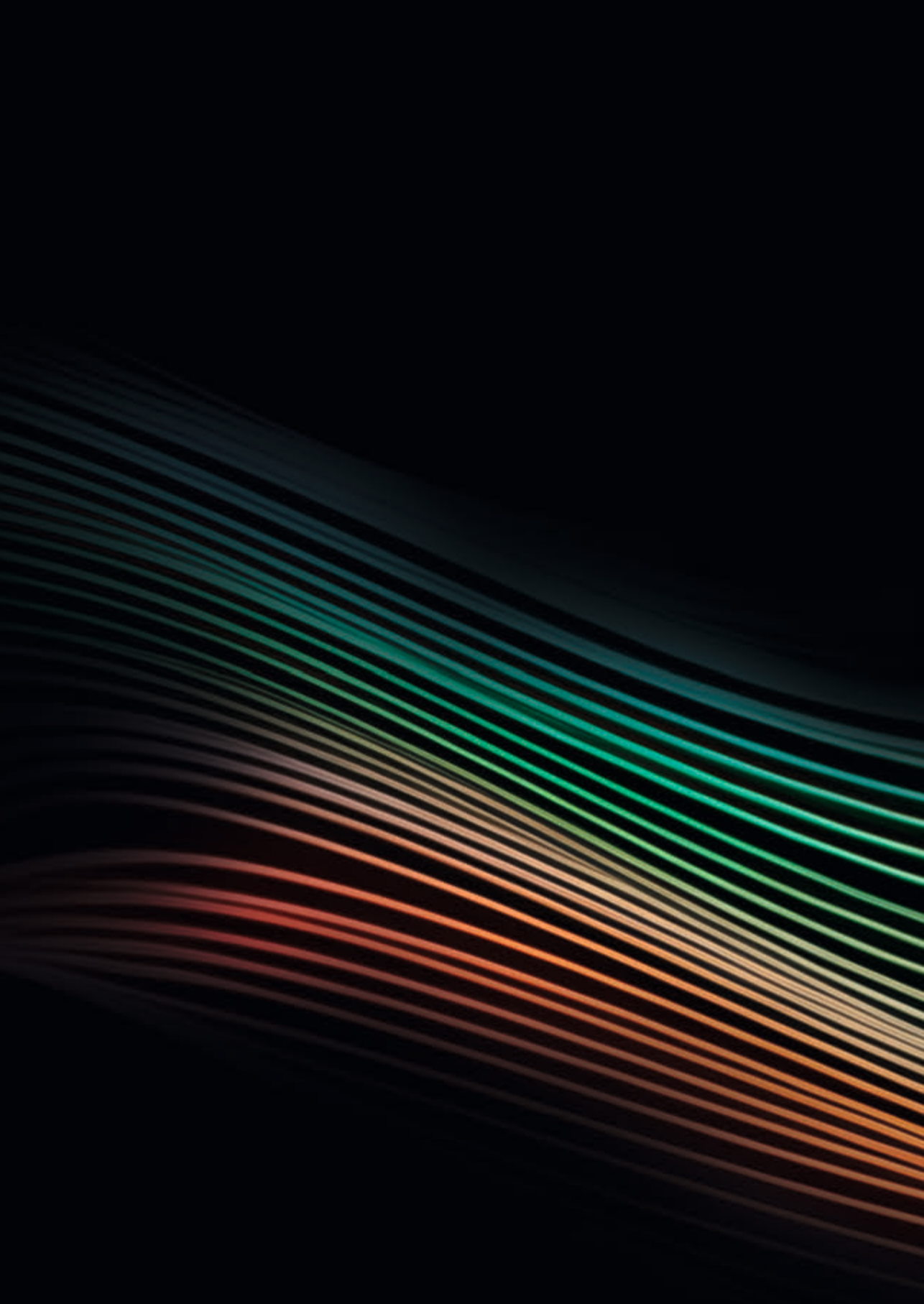
Table S1 Frequency distributions of HNC patient characteristics (total number of patients = 75)

Variables	Total number of patients = 75
Male gender N (%) (N=75)	58 (77.3)
Age at evaluation in years (mean± SD) (N=75)	65.9 ± 10.0
Tumor site N % (N=74)	
Pharynx	27 (36.5)
Oral cavity and salivary gland	22 (29.7)
Larynx	25 (33.8)
T classification N % (N=68)	
T1-2	36 (52.9)
T3-T4	32 (47.1)
N classification N (%) (N = 70)	
N0	36 (51.4)
N1	8 (11.4)
N2	24 (34.3)
N3	2 (2.9)
Histology N (%) (N = 62)	
Squamous cell carcinoma	54 (87.1)
Adenocarcinoma	5 (8.1)
Carcinoma-ex-pleiomorph adenoma	3 (4.8)
Treatment modality N % (N = 75)	
Surgery	7 (9.3)
Radiotherapy	20 (26.8)
Chemoradiotherapy	19 (25.3)
Surgery and adjuvant radiotherapy	28 (37.3)
Surgery and adjuvant radio(chemo)therapy	1 (1.3)
Multimodality treatment N (%)	48 (64)
Time interval between end of oncological treatment and swallowing assessment date (N = 75)	
Days (median (25^{th}-75^{th} percentile))	1316.0 (240.0-3701.0)
< 5 years N %	45 (60.0)
> 5 years N %	30 (40.0)
Presence of permanent tracheotomy N % (N = 74)	11 (14.9)
SNAQ N% (N=75)	
Score 0-1	39 (52)
Score 2-7	36 (48)

Table S1 Continued

Variables	Total number of patients = 75
FOIS (N = 75)	
Mean ± SD	4.8 ± 1.7
Level 1-3 Tube dependent N %	14 (18.7)
Level 4-7 Oral diet N %	61 (81.3)
BMI (N = 73)	
Mean ± SD	25.0 ± 5.7
BMI < 18.5 N (%)	7 (9.6)
BMI 18.5-24.9 N (%)	33 (45.2)
BMI ≥ 25 N (%)	33 (45.2)
Presence of aspiration N (%) (N = 74)	35 (47.3)
Postswallow pharyngeal pooling during FEES N % (N= 74)	
Vallecular pooling	24 (32.4)
Pyriform sinus pooling	5 (6.8)
Both vallecular and pyriform sinus pooling	28 (37.8)
No pooling	17 (23.0)
Presence of postswallow pharyngeal pooling N (%) (N= 74)	57 (77.0)
DSS median (25^{th}-75^{th} percentile) (N=50)	45.5 (23.0-66.3)
DQL median (25^{th}-75^{th} percentile) (N=50)	29.0 (18.0-53.0)

HNC Head and Neck Cancer; *N* Number of patients; *SD* Standard Deviation; *SNAQ* Short Nutritional Assessment Questionnaire; *FOIS* Functional Oral Intake Scale; *BMI* Body Mass Index; *DSS* Dysphagia Severity Scale; *DQL* Dysphagia Quality of Life Scale.



CHAPTER 7

PATIENTS WITH HEAD AND NECK CANCER: DYSPHAGIA AND AFFECTIVE SYMPTOMS

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Abstract

Objective

Affective symptoms are common in patients with head-and-neck cancer. This study determined the association between the presence of aspiration and symptoms of anxiety and depression, as well as patient characteristics in patients with head-and-neck cancer and dysphagia.

Methods

Eighty-four patients with head-and-neck cancer and dysphagia completed the Hospital Anxiety and Depression Scale and underwent a standardized fiberoptic endoscopic evaluation of swallowing. Linear regression analysis was performed to explore the associations.

Results

Fifty-two (61.9%) patients presented clinically relevant symptoms of anxiety or depression. Forty-eight (57.1%) patients presented with aspiration during fiberoptic endoscopic evaluation of swallowing. A significant negative association was found between the presence of aspiration and affective (anxiety and depression) symptoms ($p = 0.04$). Male patients presented significantly lower symptom scores of anxiety compared to females ($p = 0.04$).

Conclusions

Clinically relevant affective symptoms were present in more than half of all patients with head-and-neck cancer and dysphagia. Surprisingly, a significant negative association was found between the presence of aspiration and these affective symptoms. Gender was also significantly associated with affective symptoms. These results suggest that there is a need for further investigation into the impact of psychological distress on patients with head-and-neck cancer and dysphagia.

Introduction

Oropharyngeal dysphagia (OD) is common in patients with head-and-neck cancer (HNC). Swallowing function may be affected by oncological treatment such as surgery with or without (neo)adjuvant (chemo)radiotherapy or definitive (chemo)radiotherapy [1]. The main OD complaints are difficulty in chewing, regurgitation, coughing, odynophagia, and choking while eating [2]. OD severity can vary among patients. Aspiration seems to be the most critical marker of OD since aspiration might increase the risk of severe complications such as aspiration pneumonia (associated with a mortality range from 20% to 65%) and malnutrition due to restrictive dietary adaptations made by the patient [3, 4].

Besides these physical consequences, OD is also accompanied by anxiety, reduced self-esteem, and social isolation [5-8]. The recognition and treatment of the psychosocial burden in patients with HNC is important as distress may interfere with their coping to the disease and its treatment [9]. In diverse oncological healthcare settings (pre-, during and post treatment), the Hospital Anxiety and Depression Scale (HADS) is frequently used to screen for clinically relevant affective symptoms [10-13]. Anxiety and depression are associated with decreased health-related quality of life (HRQoL), non-adherence to rehabilitation programs, and increased use of healthcare services [8, 9, 14]. The impact of OD on symptoms of anxiety, depression, and HRQoL has already been studied in patients with HNC; the severity of OD has been correlated with a compromised HRQoL and clinically relevant affective symptoms [15, 16]. However, the presence of OD has a wide ranging impact on patients with HNC. A significant relationship is expected between aspiration and clinically relevant levels of anxiety and depressive symptoms in patients with HNC. There is a need for further investigation into the severity of OD and its impact on psychological distress to provide appropriate integrated care in this vulnerable population. A more complete understanding of the prevalence of affective symptoms, such as symptoms of anxiety and depression, in patients with HNC and OD can support allied health professionals in developing sustainable custom-made multidisciplinary OD support.

The aim of this study was to determine the association between the presence of aspiration and symptoms of anxiety and depression, as well as demographic characteristics (age, gender), level of the Functional Oral Intake Scale (FOIS), type of HNC treatment, and tumor location in patients with HNC and OD.

Materials and Methods

Study Population

For this cross-sectional cohort study, patients with HNC and OD were recruited from the outpatient clinic of the Department of Otorhinolaryngology at a tertiary university referral hospital between November 2011 and February 2016. Patients were referred by their speech and language pathologist (SLP) who had identified symptoms of OD. Individuals

were enrolled in the study if they had completed the HNC treatment (surgery, radiotherapy, chemoradiotherapy, or combinations thereof - multimodality treatment) at least 6 months before recruitment and their disease was in total remission (i.e., they were disease-free). Several exclusion criteria were applied: severe odynophagia (unable to swallow); radiation mucositis; more than one primary tumor in the head and neck region; osteoradionecrosis of the maxilla or mandible; presenting with a concurrent neurological disease (stroke, Parkinson disease, etc.); scoring below 23 on a Mini Mental State Examination (MMSE) [17]; being older than 85 years; having undergone a total laryngectomy; and being illiterate or blind. All primary tumors were classified according to the tumor, nodes, and metastasis (TNM) classification 7th edition [18]. The study protocol was approved as non-WMO (*Wet Medisch-Wetenschappelijk Onderzoek*) research by the medical ethics committee in compliance with the Medical Research Involving Human Subjects Act (WMO) [19]. Informed was obtained from all patients and reported in the electronic patient file according to the non-WMO Act [19].

In total, 84 patients with HNC and complaints of OD were enrolled in the study. The mean (SD) age of the study population was 65.8 (10) years. The median (IQR) FOIS score was 5 (4; 6). Ten (11.9%) patients were using psychotropic medication (atypical antipsychotics or Selective Serotonin Reuptake Inhibitors) at the time of the FEES examination. An overview of the patient characteristics is given in Table 1.

Table 1 Patient characteristics (total number of patients = 84)

Patient characteristics	***n* (%)**
Gender	
Male	58 (69)
Female	26 (31)
T classification	
T1	16 (21.9)
T2	19 (26.0)
T3	16 (21.9)
T4	20 (27.4)
Tis	1 (1.4)
Tx (unknown primary)	1 (1.4)
Missing	11
N classification	
N0	41 (57.9)
N1	7 (9.8)
N2	22 (30.9)
N3	1 (1.4)
Missing	13

Table 1 Continued

Patient characteristics	***n* (%)**
M classification	
M0	84 (100)
Therapy	
Definitive radiotherapy (single modality)	29 (34.5)
Definitive chemoradiotherapy	17 (30.2)
Surgery (single modality)	8 (9.5)
Surgery and adjuvant (chemo)radiotherapy	30 (35.7)
Tumor location	
Pharynx	33 (39.3)
Larynx	30 (35.7)
Oral cavity	13 (15.5)
Other location[a]	8 (9.5)
Tumor histopathology	
Squamous cell carcinoma	64 (87.7)
Adenocarcinoma	2 (2.7)
Verrucous carcinoma	1 (1.4)
Other histopathology	6 (8.2)
Missing	11
FOIS[b]	
Level 1	9 (10.7)
Level 2	6 (7.1)
Level 3	1 (1.2)
Level 4	6 (7.1)
Level 5	34 (40.5)
Level 6	19 (22.6)
Level 7	9 (10.7)
Aspiration	
Yes	48 (57.1)
No	36 (42.9)
Psychotropic medication	
Yes	10 (11.9)
No	74 (88.1)

[a]Nasal (sinus) cavity, salivary glands.
[b]*FOIS* Functional Oral Intake Scale.

Examination Protocol

All patients underwent the standardized examination protocol used in daily clinical practice at the outpatient clinic for OD, thereby providing prospectively collected data. This protocol comprises a structured interview, the HADS questionnaire, the MMSE, a standardized otorhinolaryngological examination, a standardized fiberoptic endoscopic evaluation of swallowing (FEES) examination, and the FOIS. The FOIS is a scale that indicates the clinically relevant level of dietary intake. Its scores range from one (nothing by mouth/ tube feeding only) to seven (total oral diet with no restrictions) [20]. At levels 1 – 3 there is tube feeding dependency and levels 4 -7 indicate a total oral diet. The HADS questionnaire is a validated screening tool for clinically relevant symptoms of anxiety or depression also named affective symptoms [21]. Of its 14 items, 7 are related to anxiety symptoms (HADS-A) and 7 to depressive symptoms (HADS-D). Each item is scored from 0 to 3, depending on the severity of the symptoms, where 0 indicates their absence and 3 almost continuous presence of symptoms. The sum of the scores ranges from 0 to 21 for either the HADS-A or HADS-D subscale, and a maximum of 42 points for the HADS total score (HADS-T). A score of 8 or more on each subscale indicates the presence of clinically relevant symptoms of anxiety or depression [21, 22]. A translated and validated Dutch version of the HADS questionnaire was used in this study [23]. All HADS and FEES examinations were performed at least 6 months after completion of the HNC treatment (median (IQR) 42 months (7.5; 122)).

The FEES examinations were carried out by an experienced laryngologist together with a SLP. During the examination all patients performed three cued swallows of 10cc thin liquid (water) followed by three cued swallows of 10cc thick liquid (applesauce; One 2 fruit®). All liquids were dyed with 5% methylene blue (10 mg/ml). The viscosity of the liquid bolus consistencies was measured at 25^0C and 50 s-1 of shear rate resulting in 1 mPa.s for thin liquid and 1200 mPa.s for thick liquid. During the flow test, the thick liquid met the criteria for 'moderately thick' according to the International Dysphagia Diet Standardisation Initiative (IDDSI) [24]. A flexible fiberoptic endoscope, Pentax FNL-10RP3 (Pentax Canada Inc., Mississauga, Ontario, Canada), was used during the FEES examination. The tip of the endoscope was in 'high position', just above the epiglottis, where the scope could not interfere with closure of the laryngeal vestibule [25]. The FEES videos were obtained with the Xion SD camera, Xion EndoSTROBE camera control unit (PAL 25 fps), and Matrix DS data station with DIVAS software (Xion Medical, Berlin, Germany) and recorded on a DVD. No topical anesthetic or nasal vasoconstrictor was used during the procedure. For each FEES swallow the visuoperceptual ordinal variable 'aspiration' was scored dichotomously (present versus absent) by two observers who had followed the training program described in previous studies [26, 27]. Aspiration was defined as entry of the bolus into the larynx below the level of the vocal folds including bolus at the level of the vocal commissures during the swallow as described in a previous observer agreement study [28, 29]. The observers were blinded to the patients' identity, medical history, HADS scores, and to each other's rating scores (independent rating). All swallows were evaluated twice by observer 1 (blinded, in randomized order and with a time lag of 2 weeks) to assess intraobserver agreement. Half of all FEES trials were scored by a second

independent observer to determine interobserver agreement. Each observer was asked to limit the evaluation period to a maximum of 2 hours in order to maintain optimal attention and reduce fatigue-related bias.

Statistical Analysis

Descriptive statistics were presented as numbers and percentages for categorical variables and as the mean (standard deviation - SD) or median (interquartile range - IQR) for numerical variables. The statistical analysis was performed on the presence of aspiration independent of the bolus consistency. For the visuoperceptual ordinal FEES variable aspiration, both inter- and intraobserver agreement were calculated using the linear weighted kappa coefficient [30]. Interobserver agreement levels of the FEES outcome variable aspiration were substantial (κ=0.76). Intraobserver agreement levels for observer 1 and observer 2 were κ=0.81 and κ=0.71.

The possible association between the presence of aspiration and symptoms of anxiety and depression, as well as demographic factors (age, gender), level of the FOIS, type of HNC treatment, and tumor location was assessed using linear regression analyses, where aspiration (yes/no), gender (male/female), age (in years), type of oncological treatment (surgery with or without (neo)adjuvant (chemo)radiotherapy or definitive (chemo) radiotherapy, etc.),tumor location (pharynx, larynx, oral cavity, or other location), and FOIS (level 1-3/ level 4-7) were included in the model. Adjusted estimated associations (regression coefficients) were reported together with their 95% confidence intervals (CI) and p-values. Two-sided p-values $\leq$ 0.05 were considered statistically significant. Missing data were not imputed. Variables included in the regression analyses did not contain any missing data. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 24.0 (IBM, Armonk, NY: IBM Corp.)

Results

HADS Questionnaire

All patients completed the HADS questionnaire. Fifty-two (61.9%) patients scored 8 or more points on the HADS subscales, indicating the presence of clinically relevant symptoms of anxiety or depression. Clinically relevant symptoms of anxiety were present in 39 (46.4%) patients and clinically relevant symptoms of depression were present in 46 (54.7%) patients. The median (IQR) HADS-A and HADS-D scores were 7 (5; 11) and 8 (4; 10). No floor or ceiling effects were found, as few patients (<2.0%) had the highest or the lowest score on the questionnaire. The median (IQR) HADS-A and HADS-D scores of patients using psychotropic drugs were 13 (11; 15) and 11 (9; 16). The HADS-A and HADS-D median (IQR) scores were 7 (4; 11) and 7 (4; 9) for patients who did not use psychotropic drugs.

Association between patient characteristics and HADS scores

Forty-eight (57.1%) patients presented with aspiration of at least one bolus consistency during the FEES examination. The adjusted associations between aspiration and patient

characteristics, such as gender, age, level of the FOIS, type of HNC treatment, and tumor location versus the HADS scores are shown in Table 2 (HADS-A), Table 3 (HADS-D), and Table 4 (HADS-T). Few statistically significant associations were found. The associations between aspiration and HADS-A, HADS-D, and HADS-T scores were statistically significant ($p = 0.05$, $p = 0.04$, $p = 0.04$). Compared to dysphagic patients who did not aspirate, dysphagic patients presenting with aspiration scored on average 2.0, 2.2, and 4.2 points lower on the HADS-A, HADS-D, and HADS-T scale, representing lower symptom scores for anxiety and depression. Significant associations between gender and HADS-A and HADS-T scores were also found ($p = 0.01$, 0.04). Male patients scored on average 2.8 points lower on the HADS-A scale compared to the females, indicating that the men had significantly lower symptom scores on anxiety than the women. Other patient characteristics such as age, level of the FOIS, type of HNC treatment, and tumor location were not significantly associated with HADS-A, HADS-D, or HADS-T scores.

Table 2 Association between patient characteristics and HADS-A scores

Outcome HADS-A	**Observed mean HADS-A (SD)**	**Estimated association[a] (95% CI)**	***p* value**
Aspiration			**0.05**
Yes (*n* = 48)	7.3 (4.5)	-2.0 (-4.1 to 0.0)	
No (*n* = 36)	9.1 (4.3)	Ref	
Age, years		0.1 (-0.02 to 0.2)	0.10
Gender			**0.01**
Male (*n* = 58)	7.2 (4.2)	-2.8 (-5.0 to -0.6)	
Female (*n* = 26)	10 (4.4)	Ref	
Therapy			0.90
Definitive radiotherapy (*n* = 29)	8.2 (4.1)	Ref	
Definitive chemoradiotherapy (*n* = 17)	7.6 (3.5)	0.0 (-2.9 to 2.9)	
Surgery (single modality) (*n* = 8)	9.6 (4.8)	0.8 (-3.8 to 5.4)	
Surgery and (chemo)radiotherapy (*n* = 30)	7.8 (5.3)	-0.5 (-3.3 to 2.2)	
Tumor location			0.94
Pharynx (*n* = 33)	7.7 (4.2)	0.6 (-1.9 to 3.1)	
Larynx (*n* = 30)	7.9 (4.5)	Ref	
Oral cavity (*n* = 13)	9.1 (5.0)	1.0 (-2.9 to 4.9)	
Other locations[b] (*n* = 8)	8.8 (5.2)	0.2 (-3.8 to 4.1)	
FOIS			0.64
1-3 (*n* = 16)	8.1 (5.0)	Ref	
4-7 (*n* = 68)	8.1 (4.4)	-0.6 (-3.2 to 2.0)	

Ref reference.
[a]Estimated association between the corresponding variable and the HADS-A score obtained using multiple linear regression analyses after adjustment for the other variables mentioned in this table.
[b]Nasal (sinus) cavity, salivary glands.

Table 3 Association between patient characteristics and HADS-D scores

Outcome HADS-D	Observed mean HADS-D (SD)	Estimated association[a] (95% CI)	*p* value
Aspiration			**0.04**
Yes (*n* = 48)	6.7 (4.6)	2.2 (-4.3 to -0.1)	
No (*n* = 36)	8.8 (3.8)	Ref	
Age, years		0.1 (-0.1 to 0.2)	0.37
Gender			0.18
Male (*n* = 58)	7.1 (4.2)	-1.5 (-3.7 to 0.7)	
Female (*n* = 26)	8.6 (4.8)	Ref	
Therapy			0.70
Definitive radiotherapy (*n* = 29)	6.9 (4.5)	Ref	
Definitive chemoradiotherapy (*n* = 17)	7.9 (4.3)	1.0 (-2.0 to 3.9)	
Surgery (single modality) (*n* = 8)	9.3 (3.8)	1.2 (-3.5 to 5.8)	
Surgery and (chemo)radiotherapy (*n* = 30)	7.6 (4.6)	0.3 (-2.5 to 3.1)	
Tumor location			0.90
Pharynx (*n* = 33)	7.6 (4.7)	0.9 (-1.7 to 3.5)	
Larynx (*n* = 30)	7.0 (4.4)	Ref	
Oral cavity (*n* = 13)	9.0 (4.2)	1.4 (-2.5 to 5.4)	
Other locations[b] (*n* = 8)	7.5 (3.6)	-0.7 (-4.8 to 3.3)	
FOIS			0.89
1-3 (*n* = 16)	7.1 (4.7)	Ref	
4-7 (*n* = 68)	7.7 (4.4)	0.2 (-2.5 to 2.8)	

Ref reference.
[a]Estimated association between the corresponding variable and the HADS-D score obtained using multiple linear regression analyses after adjustment for the other variables mentioned in this table.
[b]Nasal (sinus) cavity, salivary glands.

Table 4 Association between patient characteristics and HADS-T scores

Outcome HADS-T	Observed mean HADS-T (SD)	Estimated association[a] (95% CI)	*p* value
Aspiration			**0.04**
Yes (*n* = 48)	14 (8.7)	-4.2 (-8.1 to -0.3)	
No (*n* = 36)	17.8 (7.6)	Ref	
Age		0.1 (-0.1 to 0.3)	0.18
Gender			**0.04**
Male (*n* = 58)	14.3 (8.1)	-4.3 (-8.4 to -0.2)	
Female (*n* = 26)	18.7 (8.6)	Ref	
Therapy			0.83
Definitive radiotherapy (*n* = 29)	15.1 (8.3)	Ref	
Definitive chemoradiotherapy (*n* = 7)	15.5 (7.2)	1.0 (-4.6 to 6.5)	
Surgery (single modality) (*n* = 8)	18.9 (8.3)	2.0 (-6.8 to 10.8)	
Surgery and (chemo)radiotherapy (*n* = 30)	15.4 (9.4)	-0.2 (-5.4 to 5.1)	
Tumor location			0.92
Pharynx (*n* = 33)	15.2 (8.5)	1.5 (-3.4 to 6.4)	
Larynx (*n* = 30)	14.9 (8.4)	Ref	
Oral cavity (*n* = 13)	18.1 (8.9)	2.4 (-5.0 to 9.8)	
Other locations[b] (*n* = 8)	16.3 (8.4)	-0.6 (-8.2 to 7.0)	
FOIS			0.87
1-3 (*n* = 16)	15.2 (9.4)	Ref	
4-7 (*n* = 68)	15.8 (8.2)	-0.4 (-5.4 to 4.6)	

Ref reference.
[a]Estimated association between the corresponding variable and the HADS-T score obtained using multiple linear regression analyses after adjustment for the other variables mentioned in this table.
[b]Nasal (sinus) cavity, salivary glands.

Discussion

This cross-sectional cohort study described the association between the presence of aspiration and symptoms of anxiety and depression, as well as demographic factors (age, gender), level of the FOIS, type of HNC treatment, and tumor location. More than half of all participants showed clinically relevant affective symptoms (HADS A/D > 8). The results of this study showed that the presence of aspiration was accompanied by significantly lower scores on affective symptoms. Furthermore, male patients presented significantly lower symptom scores for anxiety compared to female patients with HNC. On the other hand, age, level of the FOIS, type of HNC treatment, and tumor location were not significantly associated with the HADS scores.

A diagnosis of cancer is accompanied by a high level of distress, which can manifest itself in symptoms of anxiety and depression [31]. These may increase due to disease progression,

physical symptoms caused by the disease such as fatigue, visibility, and impairment of basic functions such as eating and speaking [32]. The recognition and treatment of clinically relevant anxiety and depression symptoms in patients with HNC and OD is important as these symptoms may inhibit their capacity for coping with the disease and its treatment. The HADS questionnaire is one of the most frequently used tools to measure symptoms of anxiety and depression in oncologic patients. Zigmond and Snaith defined a HADS score of ≥8 as the cut-off point for clinically relevant HADS-A and HADS-D scores [21]. In the current study, this cut-off value of 8 with only HADS scores ≥8 was not applied in the linear regression analysis in an effort to obtain the highest possible statistical power. The whole range of scores of the HADS scales was used in the statistical analysis to explore the association between the entire severity range of affective symptoms and aspiration in this HNC population. A previous study determined a minimal clinically important difference (MCID) of 1.7 for the HADS subscales in patients with cardiovascular disease, representing the smallest change in a HADS outcome that an individual patient would identify as important [33]. In the present study, the average score differences on the HADS scales between non-aspirating patients with OD versus aspirating patients were all higher than 1.7 points. So, the counter-intuitive negative association between aspiration and affective symptoms seems to be clinically meaningful in this patient group.

Aspiration during the FEES examination occurred in more than half of the study population. This finding corresponds with the frequencies of aspiration reported in previous studies (36 – 94%) [34, 35]. In the present study, the finding of aspiration during FEES was accompanied by significantly lower scores on self-reported symptoms of anxiety and depression compared to the HADS scores of non-aspirating patients with HNC and OD. A possible explanation for this counter-intuitive finding might lie in a decreased laryngeal sensitivity due to the oncological treatment, which reduces the patient's perception of swallowing impairment [36, 37]. Moreover, a previous study on the perspective of patients with OD and of caregivers reported that depression is more likely to occur when the impairment has a higher impact on patient's well-being and not only on the swallowing function itself. For instance, when patients are not able to eat their favorite food, or when they feel embarrassed and avoid eating with family or friends [38]. Another possible explanation may be related to the time interval between the end of the HNC treatment and the period of data collection. All HADS and FEES examinations were performed at least 6 months after completion of the HNC treatment. It is possible that patients with HNC got used to the OD symptoms and adjusted to living with the limitations as time passed [39].

The severity of the affective symptom scores in patients with HNC may be determined by many factors besides the presence of OD. For instance, social support may have a positive influence on HADS scores [40]. Factors like a psychiatric history, toxicomania, or reduced sexuality may also affect HADS scores. [40, 41] The HADS questionnaire measures the level of the affective symptom scores in general and is not specifically related to OD. However, some motor areas of the cerebral cortex seem to be important in the stress and depression

connectome, and it has been suggested that anxiety might increase motor response inhibition [42, 43]. So it remains unclear whether the affective symptoms can be fully attributed to swallowing impairment or, conversely, whether affective symptoms might worsen OD.

The use of psychotropic drugs would presumably lead to an underestimation of the affective symptom scores. In the present study, however, the HADS scores of patients on psychotropic drugs were higher than those of patients not using this medication. Future studies should take the use of alcohol into account, as excessive alcohol consumption is often seen in patients with HNC and it is associated with psychological distress [41].

In conclusion, a counter-intuitive negative association was found between the presence of aspiration and affective symptoms. Gender was also significantly associated with affective symptoms. The high prevalence of clinically relevant affective symptoms in all patients with HNC and OD (aspirators and non-aspirators) justifies the recommendation of a systematic screening for affective symptoms and of a subsequent collaboration between the psychosocial team and the multidisciplinary dysphagia team.

Limitations

This study has some limitations. Whereas some statistically significant results were found, the sample size was too small to allow detailed group stratification, which would be needed to detect all relevant associations. The most critical marker of OD is aspiration [3, 4] For this study, a previously published modified aspiration scale was used making no distinction between silent and non-silent aspiration [26, 27] Maybe this specification in aspiration would have been helpful in further optimizing the interpretation of the results. However, this decision to use a modified scale in the present study was based on a recent psychometric review on visuoperceptual measures in FEES and videofluoroscopy including among others the Penetration Aspirations Scale showing that their psychometric status was either poor or lacking data on validity, reliability, and responsiveness [44]. Finally, future research could investigate the direction of the relationship between affective symptoms and different grades of OD in patients with HNC in a longitudinal research design using a larger sample size. Because of the explorative nature of the study Bonferroni correction was not applied.

Conclusions

Clinically relevant affective symptoms were present on the HADS in more than half of all patients with HNC and OD (aspirators and dysphagic non-aspirators). Surprisingly, a significant negative association was found between the presence of aspiration and these affective symptoms. Gender was also significantly associated with affective symptoms. These results suggest that there is a need for further investigation into the impact of psychological distress on patients with HNC and OD.

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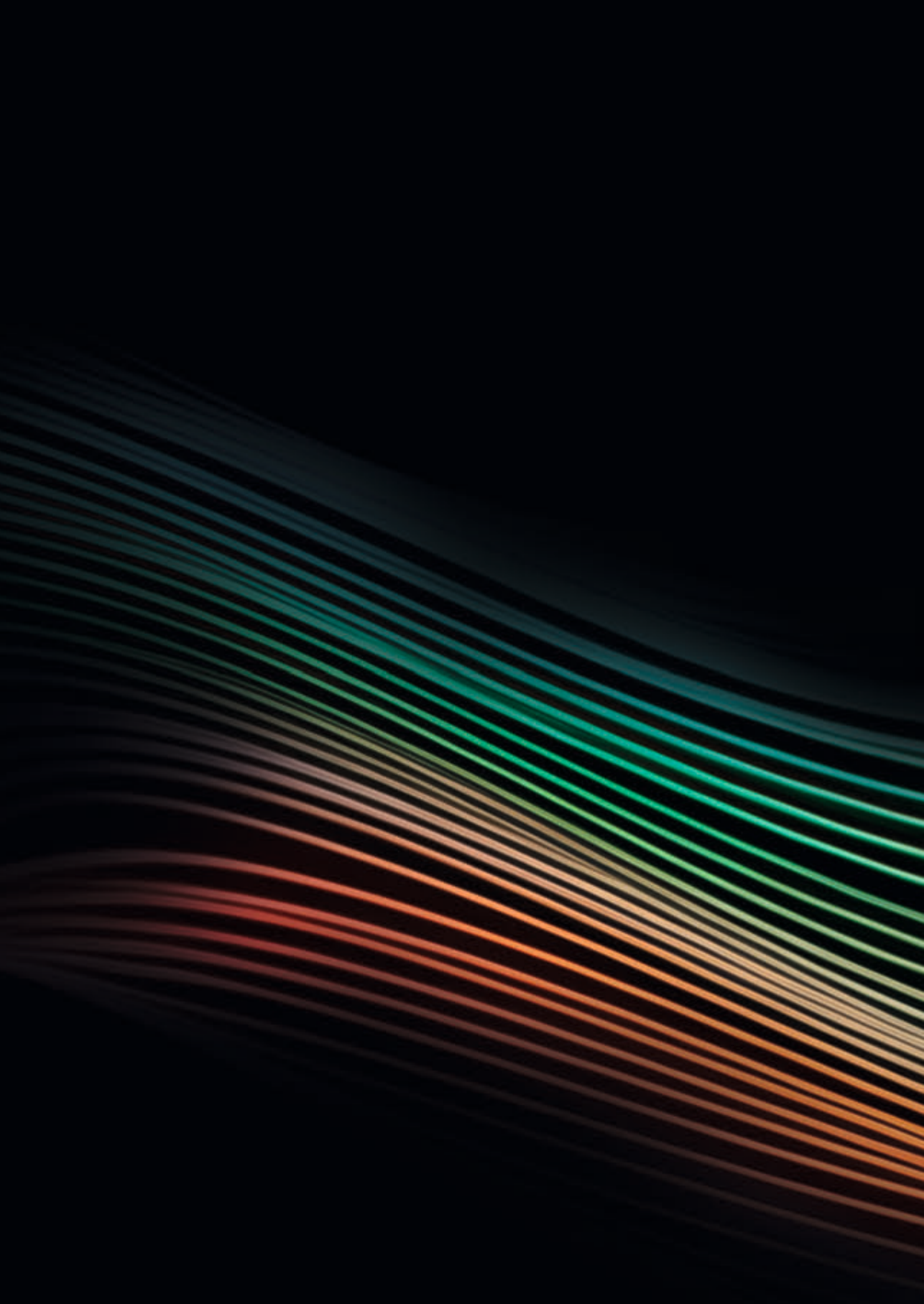

CHAPTER 8

GENERAL DISCUSSION

This thesis provides new insights into the diagnostic workup of oropharyngeal dysphagia (OD) in head and neck cancer (HNC) patients by exploring and integrating different dimensions of OD namely patient-reported outcome measures (PROMs) on swallowing impairment and on OD-related consequences and clinician-reported outcome measures (CROMs) on swallowing using instrumental imaging techniques. The integration of information on the actual nature and severity of OD and the patient's perspective on swallowing and on OD-related consequences will lead to a more holistic view of the extent and impact of swallowing impairment. Finally, this integration of information forms the foundation for developing person-centered OD (p)rehabilitation.

New insights into the diagnostic workup of oropharyngeal dysphagia in head and neck cancer patients

Despite the growing body of evidence on swallowing evaluation in HNC patients with OD, multiple clinical questions regarding the diagnostic workup of OD still remain. The studies in this thesis are based on such clinical questions that emerged from our daily practice.

After a short introduction in **part I**, **part II** of this thesis starts with a very relevant clinical question regarding the safety of the fiberoptic endoscopic evaluation of swallowing (FEES) protocol that we apply in daily practice. Is the off-label use of methylene blue as food dye safe during FEES? Methylene blue is used in small amounts to improve visualization of pharyngeal bolus transit. However, there is no evidence on its safety for this particular use. The systematic review in **chapter 3** shows that a small amount of methylene blue can be used safely as food dye during FEES, thereby clarifying a recurrent topic of discussion between health professionals and researchers working in the field of OD. The results of the review reveal that adverse events resulting from the oral intake of methylene blue are rare and related to high doses of methylene blue.

Alternatives to methylene blue during FEES have been described such as milk and yellow pudding [1-3] or blue and green food dyes [4-6]. Yet, these alternatives are not necessarily superior to methylene blue. First, dairy products are not suitable for patients with lactose intolerance or milk allergy. Second, food dyes are commercially available without any information on safety for medical purposes. Next, dairy products spoil if not refrigerated, and food dyes are usually manufactured in non-sterile, multiuse bottles posing a risk of bacterial contamination. In a highly regulated environment such as a hospital, preventing food intolerances or allergies, providing refrigerated storage facilities, keeping track of expiration dates, etc., are logistic challenges. In this context, where patient safety and evidence-based healthcare are key concerns, methylene blue has added value as it is an approved prescription-only drug manufactured in sterile, single-use ampoules. Methylene blue is safe to handle and easy to store as the product is stable at room temperature in closed containers/ampoules [7]. Lactose-free milk can be an alternative for patients with lactose intolerance, but it requires storage in a refrigerator and frequent tracking of expiration dates, unlike methylene blue. Therefore, methylene blue is the preferred food dye for evaluation of swallowing using FEES.

Another relevant clinical question arising from our daily practice concerns the interpretation of FEES and in particular the integration of the outcomes as it may help us to better understand the underlying pathophysiology causing swallowing impairment. Several visuoperceptual FEES measures can be carried out to evaluate the safety and efficiency of swallowing such as the Penetration Aspiration Scale or the Yale Pharyngeal Residue Severity Rating Scale [5, 8-10]. These measures are used to describe the severity of swallowing impairment. However, measuring the severity of aspiration or residue itself provides little or no information about the causes of their occurrence. In other words, often no attention is paid to the underlying pathophysiological causes of aspiration or residue during the interpretation of FEES. **Chapter 4** sheds light on the underlying pathophysiology by studying the association between visuoperceptual FEES measures of impaired swallowing safety and efficiency. The results show that identifying specific characteristics of pharyngeal residue such as location and amount of residue codetermines the probability of aspiration during FEES, and may enable the clinician to identify patients at risk of aspiration, even when aspiration does not occur during the evaluation. A better understanding of the interaction and even synergistic underlying pathophysiological mechanisms of impaired swallowing safety and efficiency during FEES [11] may guide choices for OD rehabilitation.

The results of the study in **chapter 4** also serve as an alert for the indiscriminate use of thick or thickened liquids as a therapeutic strategy to reduce the risk of aspiration in HNC patients [12]. By thick liquid we mean naturally thicker drinks such as yoghurt drinks and by thickened liquids we mean the addition of a thickening agent approved for medical use. Although thickened liquids are believed to be effective for neurogenic dysphagia in patients with Parkinson's or dementia [13], there is limited evidence on the effectiveness of this therapeutic strategy to prevent aspiration in the HNC population [14, 15]. Previous studies on the influence of liquid consistency report that thick liquid seems to reduce the risk of penetration/aspiration, yet may increase the risk of post-swallow pharyngeal residue [12, 15]. Furthermore, a recent study shows no evidence to support the use of thickened liquids to prevent aspiration pneumonia in HNC patients with OD [16]. The conclusions of our study also fail to substantiate the use of thick liquids in the context of OD rehabilitation. The findings suggest that pharyngeal residue and aspiration are clearly associated during the intake of thick liquid bolus consistency. Severe pyriform sinus residue of thick liquid is likely to increase the probability of aspiration in HNC patients with OD. Therefore, the use of thick or thickened liquids as a therapeutic strategy should be carefully considered and evaluated case-by-case.

Following **chapter 4** on the association between visuoperceptual FEES measures of impaired swallowing safety and efficiency, **chapter 5** focuses on the reproducibility of visuoperceptual FEES measures. Reproducibility in terms of observer agreement is essential for FEES, as it concerns the degree to which repeated measurements provide similar results [17]. The Dynamic Imaging Grade of Swallowing Toxicity (DIGEST) is a recently developed scale to quantify the severity of overall pharyngeal dysphagia in HNC patients, and it uses the integration of swallowing safety (penetration/aspiration) and efficiency (pharyngeal residue)

to arrive at a final composite severity score for pharyngeal dysphagia during FEES [18, 19]. There is very little evidence in the literature with regard to the reproducibility and external validity of the DIGEST in FEES as only one study has been published on this topic [19]. As presented in **chapter 5**, the DIGEST shows to be a reproducible measurement for FEES in terms of observer agreement. The importance of observer-tailored training is emphasized, as agreement between novice observers on the DIGEST was only reached after observer-tailored training. Identifying factors that may affect observer agreement such as bolus consistency is important to guide training programs and manuals in order to improve observer agreement. A successful learning curve of the observers due to repeated observer-tailored training using a manual with well-defined descriptions of visuoperceptual DIGEST measures optimized the reproducibility of these measurements in terms of observer agreement.

With the publication of our study, two studies on the psychometric properties of the DIGEST-FEES exist [19]. The level of experience of the observers differs between both studies, as novice observers were trained in our study as opposed to experienced speech and language pathologists (SLPs) in the study by Starmer et al. In the United States of America FEES is almost exclusively carried out by SLPs. On the European continent, FEES is carried out by a much more diverse group of health professionals with expertise in OD, depending among others on the country in question. Even if the outcome of a measurement scale is highly reproducible when performed by experienced American SLPs, the question remains what about the reproducibility in case of young starting health professionals without a track record in FEES. Therefore we consider it useful to study reproducibility of DIGEST in case of novice observers [18, 19]. Furthermore, our study explores criterion validity of the DIGEST-FEES in a population of Dutch HNC patients that differs from North American HNC patients. This cross-cultural expansion of the research population also benefits the external validity. To evaluate criterion validity, both studies calculated the correlation between the results of the DIGEST-FEES measures and the results of various criterion measures. In both studies the DIGEST efficiency grade was generally more closely correlated to criterion measures than the DIGEST safety grade. Our study shows a significant correlation between the DIGEST efficiency grade versus the Eating Assessment Tool (EAT-10) [20], suggesting that patients with more severe pharyngeal residue experience a higher level of self-perceived symptom severity on the EAT-10. It is unknown whether this correlation represents a high co-occurrence rate or a true causal relationship.

According to the authors, the DIGEST was developed to establish a standardized grading system for pharyngeal dysphagia as a toxicity endpoint for curative chemoradiation in HNC [18]. The DIGEST provides a shared language for researchers and health professionals and facilitates communication and comparison of research findings, and remains a composite symptom severity score based on the visuoperceptual FEES variables aspiration and residue. The DIGEST-FEES expresses the severity of pharyngeal dysphagia but it fails to determine the actual underlying pathophysiological mechanisms of and interaction between aspiration and residue. Future studies should focus on developing valid and feasible measurement

methods for FEES that provide insight into the underlying pathophysiology of swallowing impairment in HNC patients.

Patient-reported outcome measures of great significance in the diagnostic workup of oropharyngeal dysphagia

Besides investigating several aspects of the FEES protocol and of the interpretation of FEES using CROMs, this thesis also draws attention to the importance of exploring and integrating PROMs on different domains of health that can be affected by swallowing impairment. As stated before, based on the integration of CROMs and PROMs into the diagnostic workup of OD, a more holistic view of the extent and impact of swallowing impairment can be obtained. This integration of information forms the foundation for developing person-centered OD (p) rehabilitation. It is likely that such a foundation can improve patients' adherence to treatment and rehabilitation outcome. OD rehabilitation is person-centered, meaning that the content of the rehabilitation program is based on and meets the patient's needs, preferences, and experiences [21], stressing the importance of integrating PROMs on swallowing impairment and on OD-related consequences into the diagnostic workup.

In the last two decades, an increasing number of studies was published regarding PROMs on OD-related symptom burden and on health-related quality of life (HRQoL) in HNC patients with OD [22] including the MD Anderson Dysphagia Inventory (MDADI) [23], Swallowing Quality of Life questionnaire (SWAL-QOL) [24], EAT-10, etc. [20]. The relationship between biophysiological features of OD versus patient-reported perspectives on swallowing impairment and on OD-related consequences still raises relevant clinical questions. This includes the relationship between OD versus important consequences related to OD such as the risk of malnutrition and affective symptoms. It is assumed that these phenomena interrelate, but the underlying mechanisms of the relationship between OD versus malnutrition and affective symptoms are not yet elucidated [25-28] .

The studies presented in **part III** of this thesis used PROMs to screen for risk of malnutrition and for clinically relevant symptoms of anxiety and depression in HNC patients with OD.

As previously mentioned, nutritional status and OD interrelate and therefore particular attention should be paid to determine the risk of malnutrition in HNC patients with OD. The Short Nutritional Assessment Questionnaire (SNAQ) is a validated screening method to provide a quick identification of a patient's nutritional risk profile [29, 30]. The SNAQ is used as a standard tool for all oncological care lines in our University Hospital Comprehensive Cancer Center. Patients with a positive nutritional risk screening are subsequently referred to the dietician for in-depth nutritional assessment and treatment. Our findings in **chapter 6** emphasize the need for early nutritional risk screening of HNC patients with OD, as almost half of them presented a high risk of malnutrition. Even though some clinical practices rely on the body mass index (BMI) to identify the risk of malnutrition, BMI did not appear to be a reliable measure to screen for malnutrition in HNC patients with OD. In our patients, a normal

BMI was often accompanied by an increased risk of malnutrition. This can be explained by the fact that the BMI is only a snapshot measurement, while the SNAQ also takes into account weight loss during the past 6 months. This may mean that someone with a high BMI has lost weight leading to a normal BMI as a result of altered nutritional status. Malnutrition related to cancer-metabolic disturbances can lead to muscle catabolic activity and, as such, probably lead to loss of swallowing muscle mass and function [31-33]. However, we did not find an association between the presence of aspiration or pharyngeal residue during FEES versus the risk of malnutrition. The absence of an association between the presence of aspiration or pharyngeal residue versus the risk of malnutrition in our study can be explained by the fact that these HNC patients were disease-free survivors without cancer-metabolic disturbances. Despite the absence of an association between the presence of aspiration or pharyngeal residue versus the risk of malnutrition, a vicious circle between OD, malnutrition, and loss of skeletal muscle mass is likely in HNC survivors with severe swallowing impairment. In light of the lack of an association, our findings indicate that OD and malnutrition remain sustainable points of attention in HNC survivors even after completing the 5-year oncological follow-up and being disease-free. Besides the HNC-related causes of OD, the effects of aging on swallowing function of HNC survivors should not be underestimated, stressing the importance of repeated nutritional risk and OD screening in all HNC survivors.

The importance of timely nutritional risk screening of all HNC survivors with OD also becomes clear when looking at nutritional interventions such as the initiation of tube feeding (TF). Usually, TF is initiated in malnourished HNC patients, but TF has its pros and cons. TF will improve among others dietary protein intake, increase skeletal muscle mass, and consequently it can help to improve swallowing function if OD was caused by loss of muscle mass. On the other hand, absent or minimal oral intake in case of TF may lead to sensorimotor deprivation of the upper aerodigestive tract. The absence of sensory stimuli such as smell, taste, temperature, and proprioceptive stimuli, and the absence of motor stimuli such as swallowing different bolus consistencies and textures can lead to deconditioning of the 'swallowing system'. Inactivity of swallowing muscles may lead to disuse atrophy, but sensory deprivation can also contribute to decreased supraspinal motor planning and execution of swallowing [34]. Less activation of the supraspinal sensorimotor neural pathways will make the central nervous system forget how to perform swallowing. This is called the 'use it or lose it' theory [32, 35]. To conclude, early nutritional risk screening and oral nutritional interventions are important points of interest in HNC survivors with OD in order to prevent TF or initiate TF early in selected patients so that they can maintain their oral intake in addition to TF.

It is well known that OD can impact several domains of health. Not only physical health can be affected by OD, psychosocial well-being can also be affected. Psychological distress is common in HNC patients and may be related to tobacco and alcohol consumption [36], to the cancer diagnosis, low occupational status [37], or issues regarding swallowing impairment such as social isolation [26, 38]. Psychological distress in HNC patients with OD may further adversely affect a patient's swallowing function, as a patient with anxiety and/or depression

may not be able to cope with the demands of OD rehabilitation. Moreover, it has been suggested that psychological and somatic symptoms may be interconnected (so-called 'gut-brain axis') and that psychological distress may worsen somatic symptoms of swallowing impairment in patients already having OD [39, 40]. Elaborating on this potential bidirectional body-brain pathway, the question even arises whether imbalances in neurotransmitters in patients with anxiety and depression may have a negative effect on the supraspinal sensorimotor neural pathways of swallowing. **Chapter 7** shows that more than half of all HNC patients with OD had clinically relevant affective symptoms. Surprisingly, our study shows that aspiration is accompanied by significantly lower symptom scores of anxiety and depression, compared to the scores of non-aspirating HNC patients with OD. In the literature, aspiration is generally regarded as a symptom of more severe dysphagia [41]. One might expect aspirating patients to experience higher levels of anxious and/or depressed feelings as it is stressful to choke, cough in public or have difficulty eating and drinking. However, there may be multiple explanations for this unexpected finding. This discrepancy may be explained by a decreased laryngeal sensitivity due to the oncological treatment, which may reduce the patient's perception of aspiration and as such the burden of OD [42, 43]. Patients may learn to gradually develop problem-solving abilities including diet modification, the use of thickened liquids, behavioral swallowing techniques, etc., in order to manage or minimize the risk of aspiration, which consequently may decrease the patient's affective symptom burden. Moreover, as the primary focus of HNC patients often lies on survival, patients may downplay the severity of their swallowing problem or psychological distress and regard these problems as less-important side issues compared to the oncological condition and survival. HNC survivors with OD may even decide not to disclose their affective symptoms to health professionals because of the stigma surrounding mental health issues [44].

These considerations indicate the importance of early screening, detection, and counseling of clinically relevant affective symptoms in all HNC survivors with OD. Early identification of clinically relevant affective symptoms and appropriate integrated care may prevent both worsening of somatic swallowing impairment due to supraspinal sensorimotor disturbances and worsening of psychosocial distress due to swallowing problems.

Concluding remarks

The findings in this thesis support a multidimensional approach in the diagnostic workup of OD in HNC patients in which the integration of CROMs and PROMs on swallowing, symptom burden, and on OD-related consequences plays a crucial role. This requires dedicated health professionals such as physicians and allied health professionals with expertise in both HNC and swallowing impairment working together in a transdisciplinary team. It is likely that a transdisciplinary approach in exploring the aforementioned different dimensions of OD in HNC patients will result in best practice care. The risk of developing or aggravating OD should play an important role during shared decision making on person-centered oncological treatment, as the equivalent oncological treatment modality that better matches patients' characteristics should be selected, hereby lowering the risk of developing OD or improving

the adherence to OD (p)rehabilitation. Transdisciplinary care for HNC patients with OD will take both the person-centered oncological treatment and OD (p)rehabilitation to the next level. In the future, artificial intelligence (AI) prediction models such as digital twin models could help to select more precise cancer treatment options for HNC patients by using computer algorithm-based methods [45-47]. The current thesis contributes to a more holistic understanding, unveiling the knowledge about the integration of CROMs and PROMs on OD in the diagnostic workup of HNC survivors. There is still much progress to be made when it comes to further designing person-centered cancer care including OD (p)rehabilitation for HNC patients and ultimately the development of AI prediction models using this integration of CROMs and PROMs on OD for best practice. However, it holds great promise and we believe that with this thesis we have taken a step forward in optimizing the care of HNC patients with OD.

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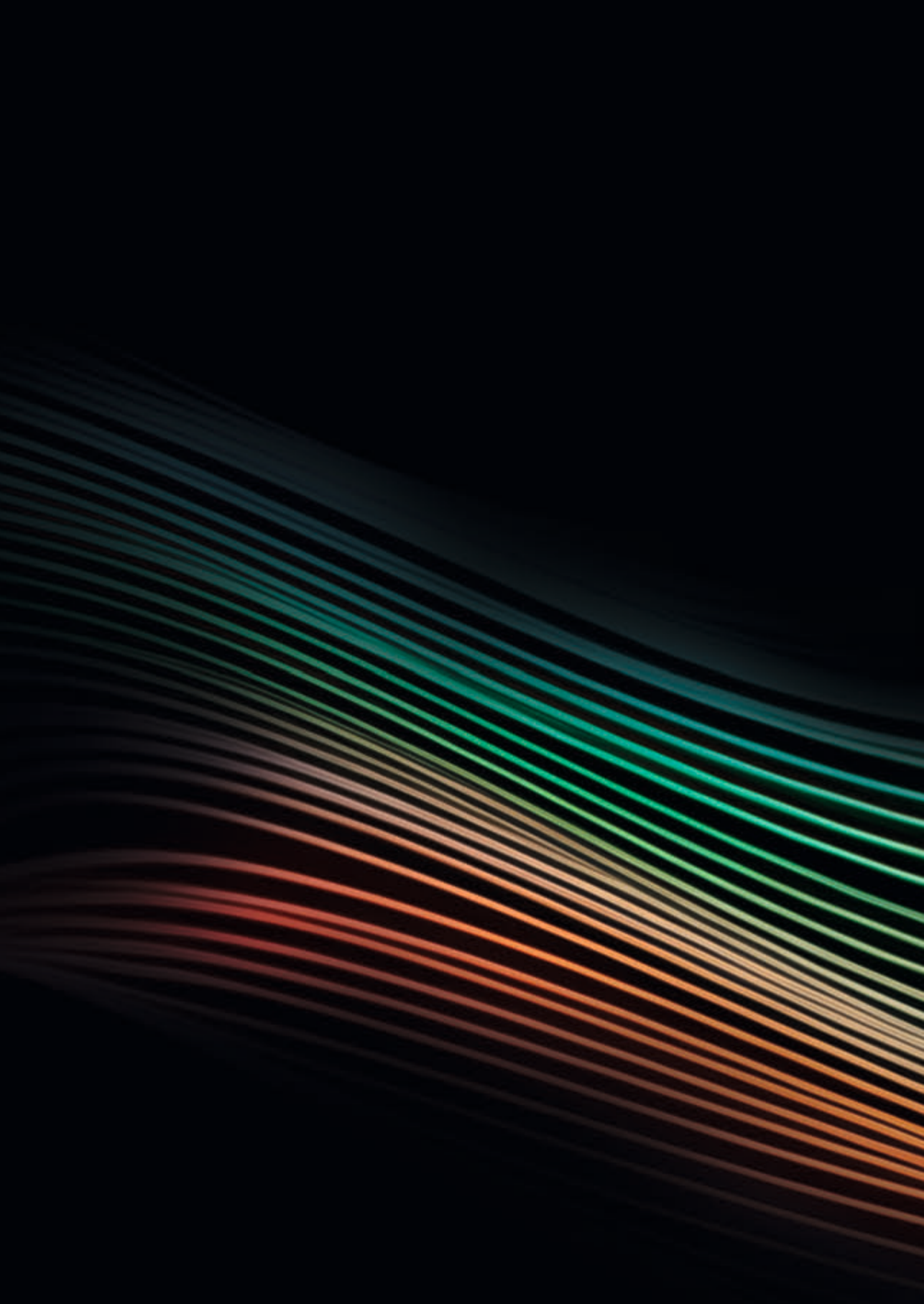
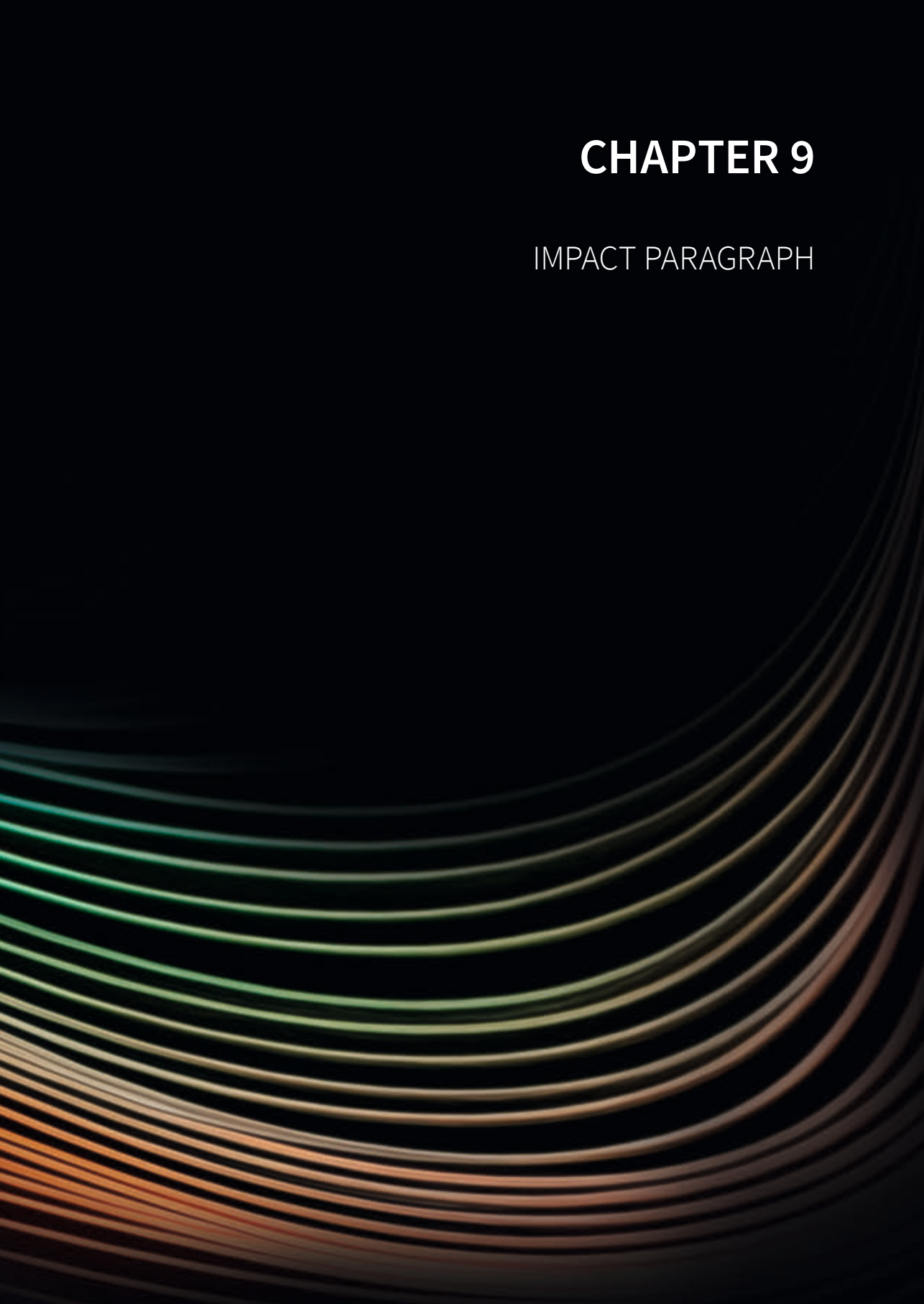


CHAPTER 9

IMPACT PARAGRAPH



Head and neck cancer (HNC) patients represent almost 900.000 new cases per year worldwide [1]. The proportion of elderly people with HNC and the average life expectancy are increasing. As a result, the number of people with swallowing disorders as a consequence of HNC is increasing. Despite being cancer-free, HNC survivors often suffer from swallowing impairment, i.e., oropharyngeal dysphagia (OD), which deeply affects one's life. Although clinical practice increases our understanding of HNC-related OD, only through research we can gather evidence that allows us to further develop this field. The outcomes of this thesis shed light on the interrelationship between the actual nature and severity of OD during instrumental imaging techniques for swallowing versus the patient's perspective on swallowing and on OD-related consequences. The knowledge obtained from this thesis has the potential to be implemented in clinical practice and may influence the way health professionals diagnose and treat OD, thereby improving patient care. Moreover, this knowledge can serve as a basis for future studies on OD (p)rehabilitation.

Aims, most relevant findings, and conclusions of this dissertation

Despite the growing attention in the literature on screening, diagnosis, and treatment of swallowing disorders in HNC, many aspects related to swallowing assessment remain underexplored in this patient population. Although OD assessment is performed worldwide, there is no consensus regarding the diagnostic workup of OD in HNC patients.

The aim of this thesis is to improve the diagnostic workup of OD including the integration of clinician-reported outcome measures (CROMs) and patient-reported outcome measures (PROMs) in HNC patients with OD. We show that methylene blue is the preferred food dye for evaluation of swallowing using fiberoptic endoscopic evaluation of swallowing (FEES). In addition, a commonly used HNC-specific overall severity scale for pharyngeal dysphagia (DIGEST) appears to be a reproducible measurement for FEES in terms of observer agreement. We also underline the importance of integrating visuoperceptual FEES measures of impaired swallowing safety and efficiency as this may help us better understand the underlying pathophysiology causing the swallowing disorder.

As mentioned, OD can have a substantial impact on a patient's life as it can affect several domains of health. While CROMs applied during FEES provide valuable information about the actual nature and severity of OD, the patient's perspective on swallowing and on OD-related consequences must also be integrated into the diagnostic workup. Our findings indicate that OD and risk of malnutrition remain an ongoing concern in HNC survivors, and we emphasize the need for early nutritional risk screening of HNC patients with OD. In addition to malnutrition, the importance of early screening of clinically relevant affective symptoms in all HNC survivors with OD is emphasized. While health professionals mainly focus on quality of care and survival, the patient's perspective almost self-evidently focuses on quality of life. Unfortunately, for the majority of HNC patients, there is no cure for their swallowing disorders. Therefore, optimizing a person's health-related quality of life (HRQoL) should be one of the cornerstones of conventional swallowing therapy in HNC patients with OD. This means that

PROMs should not be missing in a diagnostic workup aimed at person-centered OD care that matters to the patient. This can even mean that, based on the integration of CROMs and PROMs, more attention and help is needed for the psychosocial aspects of OD than for somatic consequences of swallowing disorders. Therefore, this thesis makes an important contribution to the knowledge about the integration of information that is essential in an interdisciplinary multidimensional care pathway for OD. This knowledge will support shared decision-making, based on a more holistic view of the extent and impact of OD, further optimizing person-centered (p)rehabilitation of OD. The results of our studies can also be implemented in patient care and clinical practice guidelines.

Scientific relevance

The high incidence of OD in HNC patients, resulting in a significant societal impact of swallowing disorders, calls for a vision for the future, both in terms of scientific research and in patient care.

This thesis has great scientific relevance. The findings of our studies increase the body of evidence on HNC-related OD and lay the foundations for future studies. We show that integration of visuoperceptual outcome measures during instrumental imaging techniques for swallowing improves our understanding of the underlying pathophysiology of OD. In addition, we underline the importance of studying the reproducibility of pharyngeal dysphagia scales. We also stress the relevance of repeated nutritional risk and OD screening in all HNC survivors, as well as the importance of early screening of clinically relevant affective symptoms in HNC survivors with OD. Our findings can, among others, contribute to the development of new protocols on OD diagnosis.

The personal impact of OD on patients and their families should not be underestimated. Eating is one of the most basic human needs and eating together connects people in social interaction. Because they cannot eat or drink, or may choke while eating or drinking, HNC patients avoid social interactions involving food. This takes its toll on their well-being, as social interactions provide emotional and social support. Improving the diagnostic workup of OD in HNC patients may lead to early identification and more effective treatment, allowing HNC patients to participate in social interactions involving food without the embarrassment of choking or coughing while eating.

Target audience and societal impact

The conclusions of this dissertation are relevant for a wide audience. HNC patients with OD can benefit from improved accuracy and alignment of diagnostic tests for OD. Our findings will enable national and international patient associations for HNC patients to provide up-to-date information on HNC-related OD. Additionally, this thesis aims to expand the knowledge of health professionals involved in the care of HNC patients with OD, creating opportunities for improved integrated patient care. National and international professional associations within the field of both HNC and OD can also benefit from the insights unraveled in our

dissertation. For example, our findings may support the update of current clinical practice guidelines for HNC patients with OD [2]. The results of our thesis may also be relevant for policymakers, politicians, and insurance companies involved in healthcare. In view of the remaining knowledge gaps, scientific research groups are encouraged to continue research within the field of HNC-related OD, as the results of this thesis lead to new studies to improve quality of care for HNC patients with OD.

Knowledge transfer

The findings of this thesis have been published in peer-reviewed journals, and several studies have been made freely and permanently accessible to everyone through open access publishing. Open access publishing also encourages optimal reproducibility of our studies. The studies in this thesis have been presented at multiple national and international conferences in the field of dysphagia and otolaryngology, including the General Meeting of the Dutch Association of Otorhinolaryngology and Head and Neck Surgery (2017 and 2018, Nieuwegein, The Netherlands), The Annual Meeting of the Dysphagia Research Society (2018, Baltimore, Maryland, United States; 2021, Virtual Meeting), The Annual Congress of European Society for Swallowing Disorders, (2018, Dublin, Ireland), and The Congress of The Confederation of the European Otorhinolaryngology and Head and Neck Surgery (2019, Brussels, Belgium). Participation in these conferences provided many opportunities to interact with colleagues from around the world and discuss research ideas and projects.

The clinical relevance of our research was also recognized by receiving the following rewards: the Pélerin Prize for Senior Year Medical Master Students (2017, Maastricht, The Netherlands), the Springer Publishing Travel Scholarship (Under-Represented in Discipline Award) (2018, The Annual Meeting of the Dysphagia Research Society, Baltimore, United States), and the Dr. Catharine van Tussenbroek Foundation Travel Grant (2018).

The valuable input of the patients in the research processes and in disseminating the results of this thesis is acknowledged. The Dutch patient society for HNC (PVHH - Patiëntenvereniging Hoofd-Hals) will be asked for help to disseminate the results to their members.

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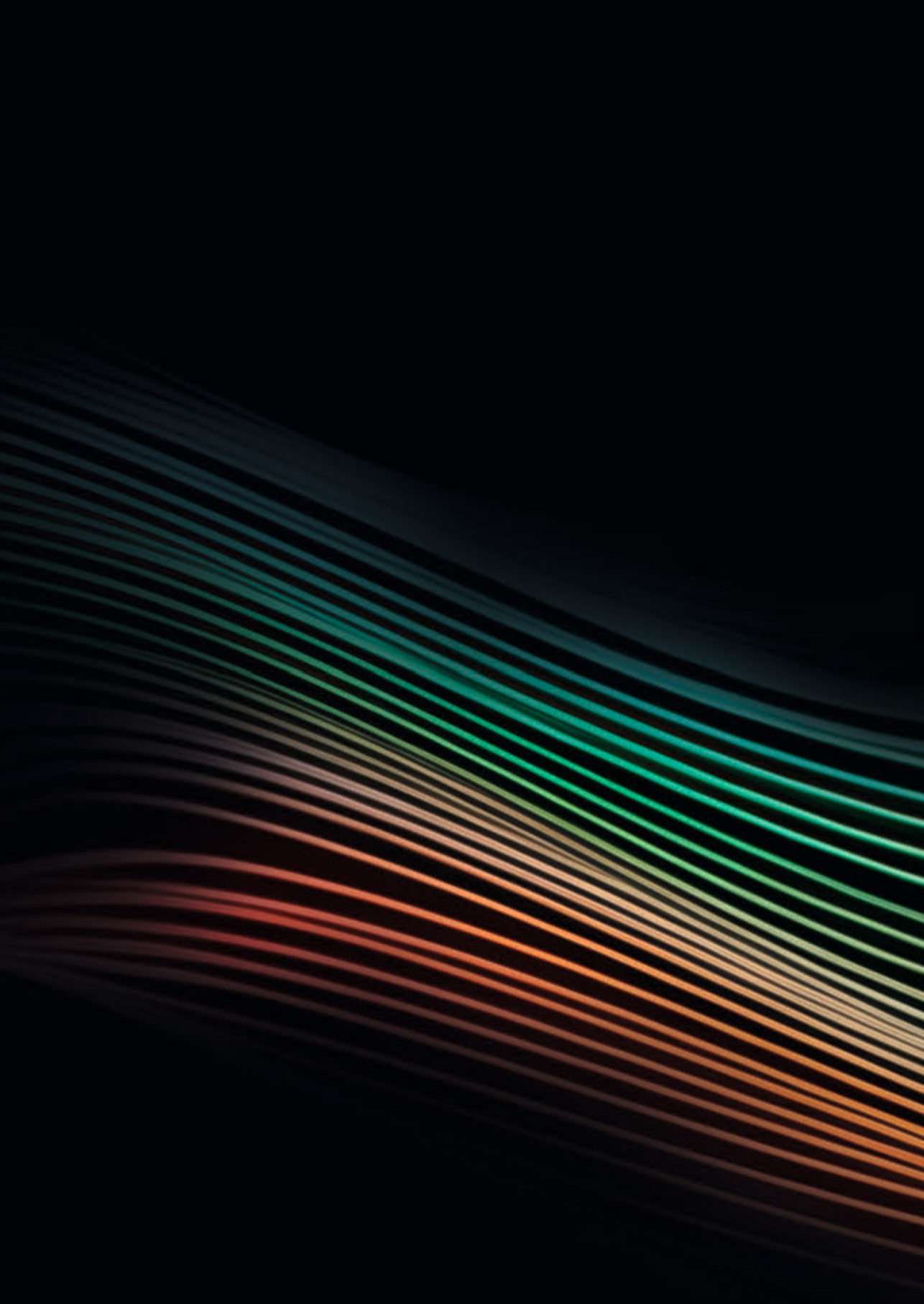
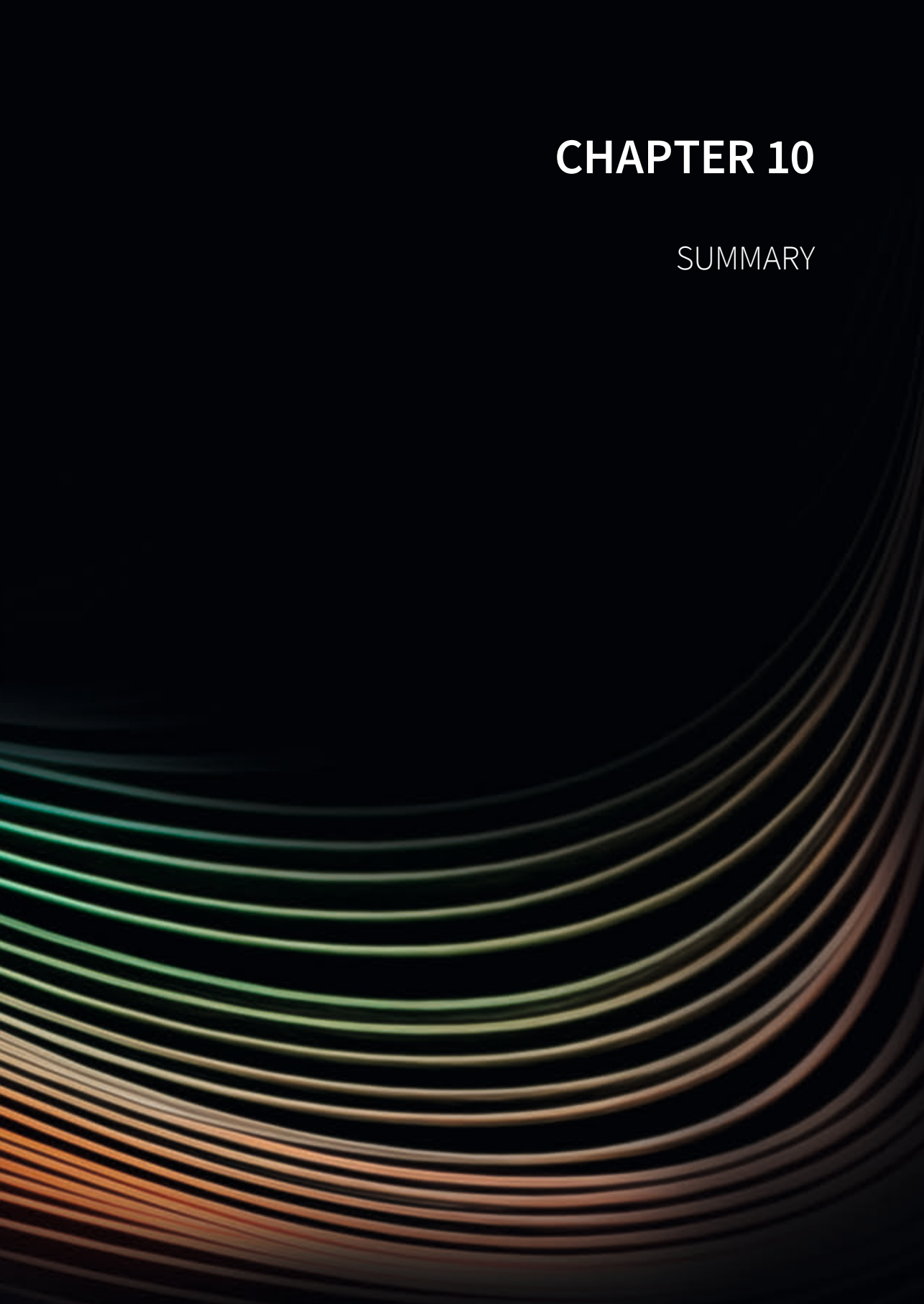


CHAPTER 10

SUMMARY



This thesis provides new insights into the diagnostic workup of oropharyngeal dysphagia (OD) in head and neck cancer (HNC) patients by exploring and integrating different dimensions of OD namely patient-reported outcome measures (PROMs) on swallowing impairment and on OD-related consequences and clinician-reported outcome measures (CROMs) on swallowing using instrumental imaging techniques. The integration of information on the actual nature and severity of OD and the patient's perspective on swallowing and on OD-related consequences will lead to a more holistic view of the extent and impact of swallowing impairment.

New insights into the diagnostic workup of oropharyngeal dysphagia in head and neck cancer patients

During fiberoptic endoscopic evaluation of swallowing (FEES), methylene blue is frequently administered to enhance visualization of bolus transit in the pharynx and/or larynx, yet there is no consensus whether it is safe and feasible to use small amounts of methylene blue during FEES. A systematic literature review to investigate the evidence on the safety of using certain amounts of methylene blue as food dye during FEES is presented in **chapter 3.** Seventeen studies were included resulting in a pooled population of 1902 patients who received oral methylene blue for various indications including malaria, psychiatric disorders, and during colonoscopy to aid visualization of mucosal abnormalities. In three children, serious adverse events related to oral administration of methylene blue were reported, i.e., repeated vomiting, anemia, and hemolysis. Serious adverse events due to oral administration of methylene blue were rare (0.16%), and were related to a high dose of methylene blue. Only one serious coincident adverse event, i.e., gastro-intestinal hemorrhage was reported in adults, but was deemed unrelated to methylene blue. Methylene blue-related non-serious adverse events showed a dose-related trend and were usually mild and self-limiting. This systematic literature review indicates that it is safe to use small amounts of methylene blue as a food dye during swallowing examinations in children and adults.

The presence of postswallow pharyngeal residue after swallowing may be a risk factor for aspiration of residue, however limited research is available on this potential association in HNC patients. The cross-sectional study described in **chapter 4** investigates the association between postswallow pharyngeal residue and aspiration in dysphagic HNC patients. Ninety dysphagic HNC patients underwent FEES. During FEES, three ordinal visuoperceptual measures were scored per swallow: postswallow vallecular residue, postswallow pyriform sinus residue, and aspiration. The results showed no significant association between vallecular residue and aspiration of thin liquid bolus consistency. However, severe postswallow vallecular residue of thick liquid bolus consistency was significantly associated to aspiration. Severe pyriform sinus residue was significantly associated to aspiration of thick liquid bolus consistency The results of this study indicate that location of pharyngeal residue (valleculae versus pyriform sinuses), type of bolus consistency, and amount of postswallow pharyngeal residue have an influence on the probability of aspiration in dysphagic HNC patients. This study emphasizes the need to carefully consider the presence of pharyngeal residue, even in the absence of aspiration during FEES.

The Dynamic Imaging Grade of Swallowing Toxicity (DIGEST) is a multi-component visuoperceptual scale to grade the overall severity of pharyngeal dysphagia during videofluoroscopic swallowing study (VFSS) or FEES in HNC patients.

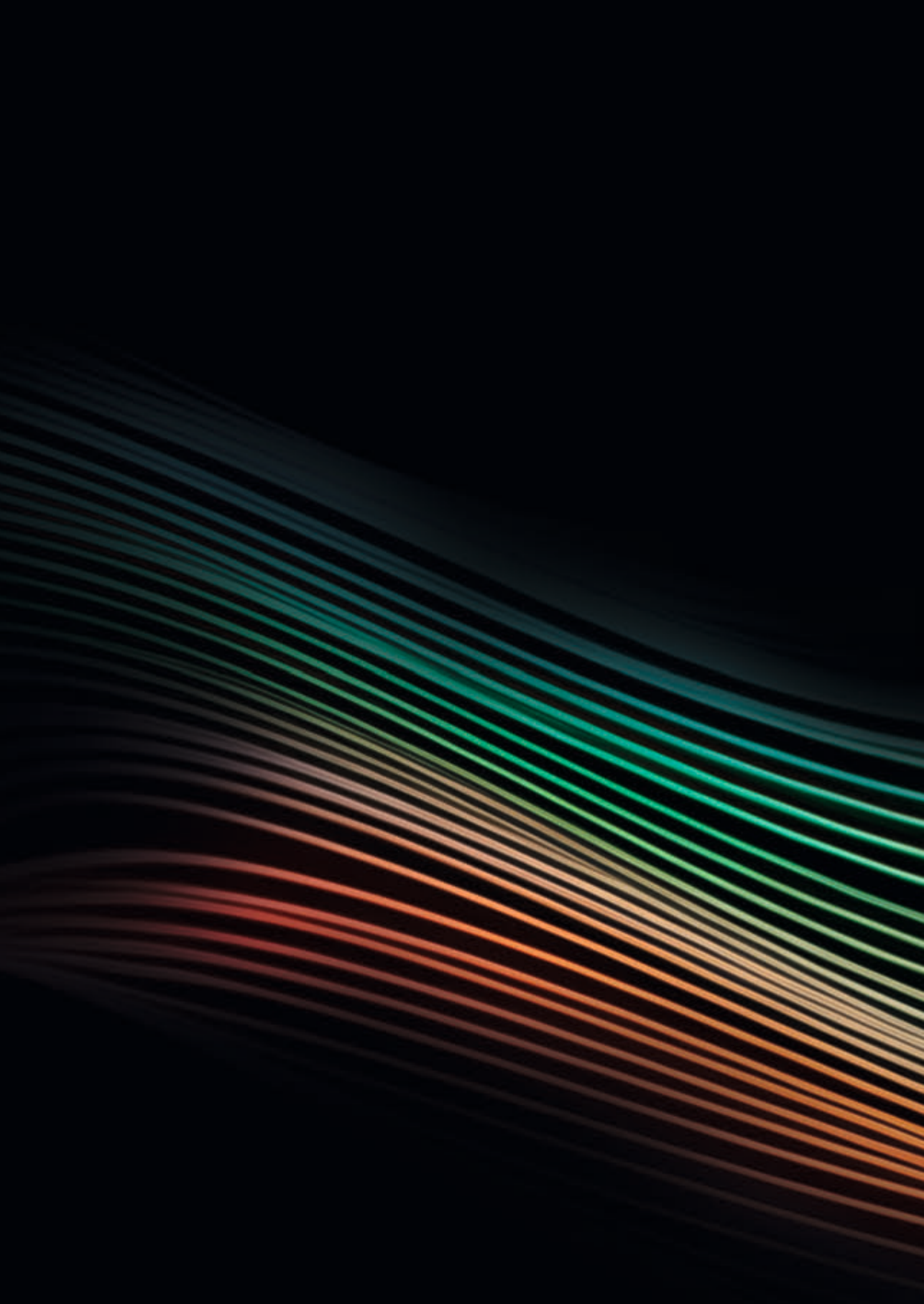
Reproducibility of measurements concerns an important aspect of the quality of measurement scales for OD, yet there is little evidence in the literature with regard to the reproducibility and external validity of the DIGEST in FEES. **Chapter 5** focuses on observer agreement on visuoperceptual measures of the DIGEST in FEES. This study also explores the challenges of reaching agreement among observers. Twenty-seven dysphagic HNC patients were enrolled, and two novice observers completed a training program for DIGEST in FEES. Observer agreement on visuoperceptual measures of the DIGEST was determined for ordinal measures including the Penetration-Aspiration Scale, percentage of pharyngeal residue, and the multi-component final DIGEST grade. During the first measurement attempt, overall observer agreement levels on several bolus consistencies were insufficient. Sufficient agreement on the DIGEST was only reached after additional observer-tailored training following a detailed analysis of the discrepancies between observers. Thereafter, a manual with detailed descriptions of the visuoperceptual measures was elaborated. To evaluate criterion validity of the DIGEST-FEES, the study also calculated the correlation between the results of the DIGEST-FEES measures and the results of various criterion measures. A significant correlation was found between swallowing efficiency (DIGEST efficiency grade) and the dysphagia-specific symptom questionnaire Eating Assessment Tool (EAT-10), suggesting that patients with more severe pharyngeal residue experience a higher level of self-perceived symptom severity on the EAT-10. To conclude, the DIGEST showed to be a reproducible measurement for FEES in terms of observer agreement. The study findings also indicate that observer-tailored training combined with a manual with well-defined descriptions can optimize the reproducibility of DIGEST measurements during FEES.

Patient-reported outcome measures in the diagnostic workup of oropharyngeal dysphagia

As it is hypothesized that dysphagic HNC patients present a higher risk of malnutrition, a cross-sectional cohort study examining the risk of malnutrition in patients with OD secondary to HNC is presented in **chapter 6.** The study also investigates the relationship between the risk of malnutrition versus patient and tumor characteristics. Seventy-five dysphagic HNC patients were included. All patients underwent malnutrition screening using the Short Nutritional Assessment Questionnaire (SNAQ) and a standardized FEES. This study emphasizes the relevance of early malnutrition screening in dysphagic HNC patients, as almost half of patients (48%) presented a high risk of malnutrition. In this study, body mass index (BMI) did not appear to be a reliable measure to screen for malnutrition as a normal BMI was often accompanied by an increased risk of malnutrition. In contrast, patients who were underweight did not show an association with a high risk of malnutrition. With the exception of BMI, no other patient and tumor characteristics were found to be associated with risk of malnutrition. Thus, malnutrition screening using SNAQ can identify dysphagic HNC patients who are at risk of malnutrition. Risk of malnutrition remains a sustainable point of attention

in HNC patients, even after oncological treatment and during long term follow-up in all HNC survivors, especially when OD is present.

The recognition and treatment of the psychosocial burden in HNC patients is important as psychological distress may interfere with their ability to cope with the disease and its treatment. An impaired swallowing function as a result of HNC such as aspiration of food and liquids into the airway, is assumed to negatively influence a patient's affective state, i.e., psychological distress. To this end, the association between the presence of aspiration and clinically relevant symptoms of anxiety and depression, i.e., affective symptoms in dysphagic HNC patients was investigated in the cross-sectional cohort study presented in **chapter 7**. This study also explored the association between aspiration versus patient and tumor characteristics. Eighty-four HNC patients with OD completed the Hospital Anxiety and Depression Scale (HADS) and underwent a standardized FEES. More than half of all dysphagic HNC patients (61.9%) presented clinically relevant symptoms of anxiety or depression on the HADS. Forty-eight patients (57.1%) presented aspiration during FEES. Surprisingly, a significant negative association was found between the presence of aspiration and affective symptoms, implying that the presence of aspiration was accompanied by significantly lower scores on affective symptoms. Gender was also significantly associated with affective symptoms, as male patients presented significantly lower symptom scores for anxiety compared to female patients. These study findings show that clinically relevant symptoms of anxiety and depression are common in HNC patients with OD, and these symptoms are associated with both aspiration and gender. The high prevalence of clinically relevant symptoms of anxiety and depression in dysphagic HNC patients justifies the recommendation of a systematic screening for affective symptoms.



CHAPTER 11

SUMMARY IN DUTCH (SAMENVATTING)

Dit proefschrift geeft nieuwe inzichten weer over de diagnostische workup van slikstoornissen ook wel orofaryngeale dysfagie (OD) genoemd bij hoofd-halskankerpatiënten. Hierbij worden verschillende dimensies van OD onderzocht en geïntegreerd namelijk patiënt-gerapporteerde uitkomstmaten (PROMs) over dysfagie en dysfagie-gerelateerde gevolgen, en clinician-gerapporteerde uitkomstmaten (CROMs) met betrekking tot de slikfunctie middels beeldvormende technieken. De integratie van informatie over de aard en ernst van de slikpathofysiologie en het perspectief van de patiënt ten aanzien van de slikstoornissen en daarmee samenhangende gevolgen zal leiden tot een meer holistische weergave van de ernst en impact van dysfagie.

Nieuwe inzichten in de diagnostische workup van orofaryngeale dysfagie bij hoofd-halskankerpatiënten

Gedurende endoscopisch slikonderzoek ook wel fiberoptic endoscopic evaluation of swallowing (FEES) genoemd wordt er regelmatig gebruik gemaakt van methyleenblauw om de verschillende bolus consistenties beter te visualiseren ter hoogte van de farynx en/of larynx. Er is echter geen consensus of het gebruik van kleine hoeveelheden methyleenblauw tijdens FEES veilig is ten aanzien van eventuele bijwerkingen. Een systematische literatuurstudie om de veiligheid van methyleenblauw als voedselkleurstof tijdens FEES te onderzoeken wordt beschreven in **hoofdstuk 3**. Zeventien studies werden geïncludeerd met een totale populatie van 1902 patiënten die oraal methyleenblauw kregen toegediend voor verschillende indicaties waaronder malaria, psychiatrische aandoeningen en ter visualisatie van mucosale afwijkingen tijdens coloscopie. Er werden bij drie kinderen ernstige bijwerkingen van het oraal gebruik van methyleenblauw gerapporteerd namelijk herhaaldelijk braken, anemie en hemolyse. Ernstige bijwerkingen van methyleenblauw na oraal gebruik waren zeldzaam (0.16%) en gerelateerd aan de inname van een hoge dosis methyleenblauw. Bij één volwassene werd een ernstige coïncidente afwijking (gastro-intestinale bloeding) gerapporteerd, maar deze afwijking werd niet geklasseerd als een bijwerking van methyleenblauw. Methyleenblauw-gerelateerde niet-ernstige bijwerkingen toonden een dosis-gerelateerde trend en waren meestal mild en zelflimiterend. Deze systematische literatuurstudie toont aan dat het gebruik van kleine hoeveelheden methyleenblauw als voedselkleurstof tijdens endoscopisch slikonderzoek als veilig mag worden beschouwd voor kinderen en volwassenen.

De aanwezigheid van residu in de farynx na het doorslikken van de bolus verhoogt mogelijk het risico op aspiratie oftewel verslikking. Er is echter weinig onderzoek verricht naar deze mogelijke associatie bij hoofd-halskankerpatiënten. In **hoofdstuk 4** wordt een cross-sectionele studie beschreven om de associatie tussen residu in de farynx na het doorslikken van de bolus en aspiratie te onderzoeken bij hoofd-halskankerpatiënten met slikstoornissen. Negentig hoofd-halskankerpatiënten met slikstoornissen ondergingen FEES. Tijdens FEES werden er drie visuoperceptieve ordinale uitkomstmaten gescoord per doorgeslikte bolus consistentie: residu in de vallecula na doorslikken van de bolus, residu in de sinus piriformis na doorslikken van de bolus en aspiratie. Er werd geen associatie gevonden tussen residu in de vallecula na doorslikken van dun vloeibare bolus consistentie en aspiratie. Ernstig

residu in de vallecula na doorslikken van dik vloeibare bolus consistentie bleek echter wel geassocieerd te zijn met aspiratie. Daarnaast was ernstig residu in de sinus piriformis na doorslikken van dik vloeibare bolus consistentie geassocieerd met aspiratie. De resultaten van deze studie tonen aan dat de locatie van residu in de farynx (vallecula versus sinus piriformis), type bolus consistentie en hoeveelheid residu in de farynx na het doorslikken van de bolus invloed lijken te hebben op het al dan niet optreden van aspiratie bij hoofd-halskankerpatiënten met slikstoornissen. Deze studie benadrukt het belang van residu in de farynx na het doorslikken van de bolus, ook als er tijdens FEES niet onmiddellijk aspiratie is opgetreden vanuit dit residu.

De Dynamic Imaging Grade of Swallowing Toxicity (DIGEST) is een multi-component visuoperceptieve meetschaal om de ernst van faryngeale slikstoornissen bij hoofd-halskankerpatiënten te beoordelen tijdens radiologisch slikonderzoek of tijdens FEES. Hoewel reproduceerbaarheid van metingen een belangrijk onderdeel vormt van de kwaliteit van een meetinstrument voor slikstoornissen zijn er tot op heden weinig studies verricht naar de reproduceerbaarheid en externe validiteit van de DIGEST tijdens FEES. De studie weergegeven in **hoofdstuk 5** onderzoekt de overeenstemming tussen beoordelaars met betrekking tot de visuoperceptieve metingen van de DIGEST tijdens FEES. Daarnaast beschrijft deze studie de uitdagingen die komen kijken bij het bereiken van overeenstemming tussen beoordelaars oftewel beoordelaarsovereenstemming. Zevenentwintig hoofd-halskankerpatiënten met slikstoornissen werden geïncludeerd en twee onervaren beoordelaars ondergingen een trainingsprogramma voor het uitvoeren van de DIGEST metingen tijdens FEES. Beoordelaarsovereenstemming voor de visuoperceptieve metingen van de DIGEST werd berekend voor de ordinale variabelen penetratie of aspiratie (Penetration-Aspiration Scale), het percentage van residu in de farynx en de multi-component eindscore van de DIGEST (DIGEST grade). Tijdens de eerste meetpoging was de beoordelaarsovereenstemming voor percentage van residu in de farynx van enkele bolus consistenties onvoldoende. Voldoende beoordelaarsovereenstemming werd pas bereikt na een gestructureerde aanvullende training die specifiek afgestemd was op de beoordelaars naar aanleiding van een gedetailleerde analyse van hun discrepanties. Hierna werd een handleiding uitgebreid met gedetailleerde beschrijvingen van de verschillende visuoperceptieve uitkomstmaten. Naast het onderzoeken van de reproduceerbaarheid van de DIGEST metingen tijdens FEES, onderzocht deze studie ook de correlatie tussen resultaten van de DIGEST uitkomstmaten en resultaten van verschillende criterium metingen met als doel om de criteriumvaliditeit van de DIGEST-FEES te evalueren. Er werd een significante correlatie gevonden tussen de efficiëntie van het slikken (DIGEST efficiency grade) en de dysfagie-specifieke symptoomvragenlijst Eating Assessment Tool (EAT-10), suggererend dat patiënten met ernstig residu in de farynx een hogere mate van zelf-waargenomen symptoom ernst ervaren met behulp van de EAT-10. Concluderend bleek de DIGEST als meetschaal reproduceerbare metingen op te leveren met betrekking tot beoordelaarsovereenstemming tijdens FEES. Bovendien toont deze studie aan dat de reproduceerbaarheid van DIGEST metingen tijdens FEES geoptimaliseerd kan

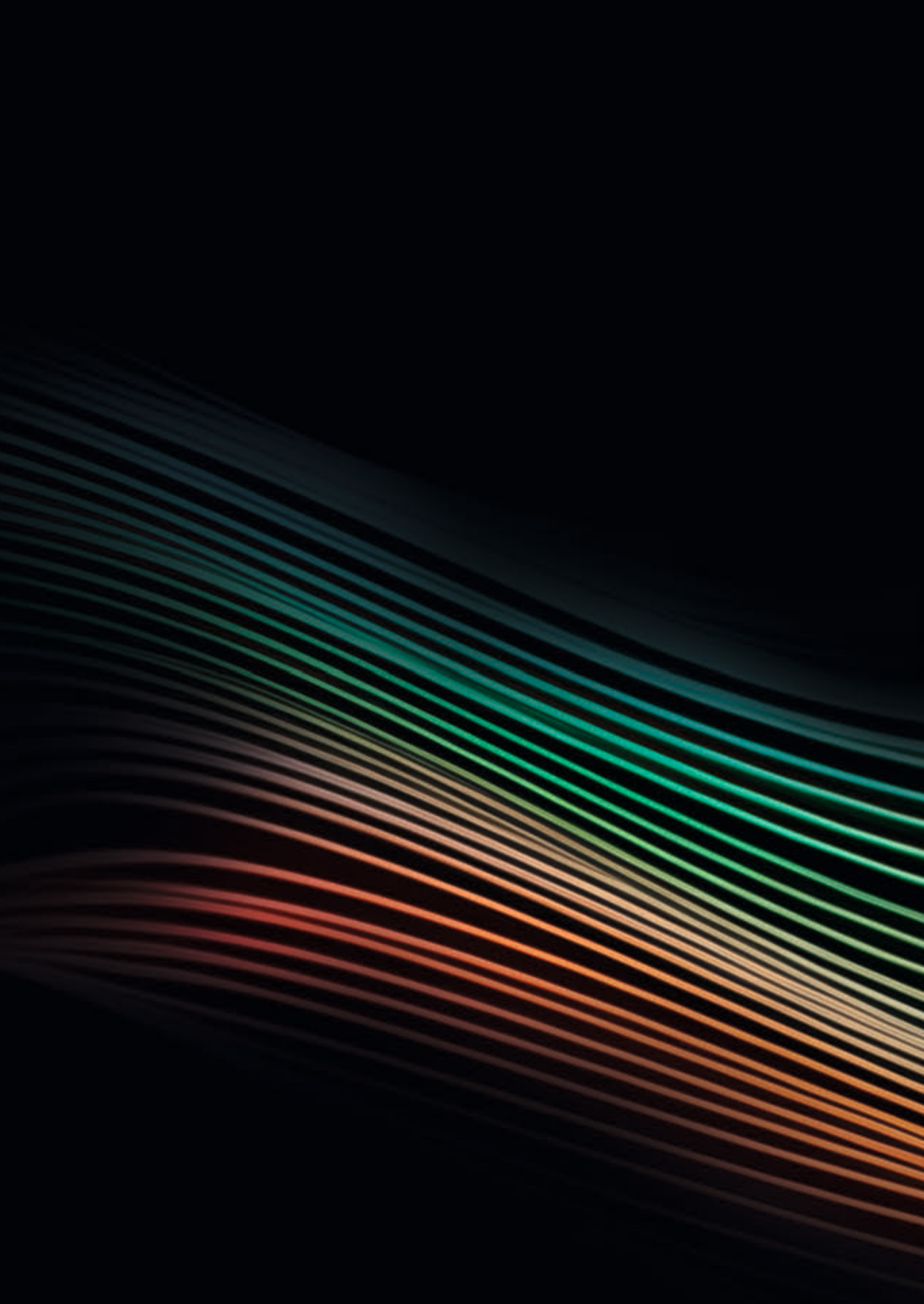
worden door een training afgestemd op de beoordeelaars in combinatie met het gebruik van een handleiding met goed gedefinieerde beschrijvingen.

Patiënt-gerapporteerde uitkomstmaten tijdens de diagnostische workup van orofaryngeale dysfagie

Er wordt verondersteld dat hoofd-halskankerpatiënten met slikstoornissen een verhoogd risico lopen op malnutritie oftewel ondervoeding. De cross-sectionele studie in **hoofdstuk 6** onderzoekt het risico op malnutritie bij hoofd-halskankerpatiënten met slikstoornissen. Deze studie onderzoekt ook de associatie tussen het risico op malnutritie versus verschillende factoren waaronder patiënt- en tumorkenmerken. Vijfenzeventig hoofd-halskankerpatiënten met slikstoornissen werden geïncludeerd in de studie. Alle patiënten ondergingen screening op malnutritie door middel van de Short Nutritional Assessment Questionnaire (SNAQ) evenals een gestandaardiseerde FEES. Dit onderzoek benadrukt het belang van vroegtijdige screening op malnutritie bij hoofd-halskankerpatiënten met slikstoornissen aangezien bijna de helft van alle patiënten (48%) een hoog risico op malnutritie had. In deze populatie was de body mass index (BMI) geen betrouwbare maat om te screenen op malnutritie, omdat een normale BMI-waarde vaak gepaard ging met een hoog risico op malnutritie. Daarentegen vertoonden patiënten met ondergewicht geen associatie met een hoog risico op ondervoeding. Met uitzondering van de BMI-waarde waren er geen andere patiënt- of tumorkenmerken geassocieerd met het risico op malnutritie. Screening op malnutritie met behulp van de SNAQ kan hoofd-halskankerpatiënten identificeren die risico lopen op malnutritie. Zelfs na oncologische behandeling en tijdens de lange termijn follow-up van overlevenden van hoofd-halskanker moet aandacht blijven worden besteed aan het risico op ondervoeding zeker in geval van OD.

Het herkennen en behandelen van psychosociale problemen bij hoofd-halskankerpatiënten is van groot belang omdat het de coping, dat wil zeggen het omgaan met de ziekte en de behandeling, kan beïnvloeden. Een verminderde slikfunctie met onder andere verslikken als gevolg van hoofd-halskanker kan een negatieve invloed hebben op de affectieve toestand van een patiënt en aanleiding geven tot psychologische distress. De associatie tussen de aanwezigheid van aspiratie oftewel verslikking versus klinisch relevante symptomen van angst en depressie (affectieve symptomen) bij hoofd-halskankerpatiënten wordt onderzocht in de cross-sectionele studie beschreven in **hoofdstuk 7**. Daarnaast onderzoekt deze studie de associatie tussen aspiratie versus patiënt- en tumorkenmerken. Vierentachtig hoofd-halskankerpatiënten met slikstoornissen vulden de Hospital Anxiety and Depression Scale (HADS) in en ondergingen een gestandaardiseerde FEES. Meer dan de helft van alle hoofd-halskankerpatiënten met slikstoornissen (61.9%) had klinisch relevante symptomen van angst en depressie volgens de HADS. Achtenveertig patiënten (57.1%) hadden last van aspiratie oftewel verslikking tijdens FEES. Verrassend genoeg werd er een significante negatieve associatie gevonden tussen de aanwezigheid van aspiratie en affectieve symptomen, implicerend dat de aanwezigheid van aspiratie gepaard gaat met een lagere affectieve symptoom score. Geslacht was ook geassocieerd met affectieve symptomen: mannelijke patiënten lieten

namelijk lagere symptoom scores voor angst zien vergeleken met vrouwelijke patiënten. Deze studieresultaten tonen aan dat klinisch relevante symptomen van angst en depressie vaak voorkomen bij hoofd-halskankerpatiënten met slikstoornissen en dat deze symptomen geassocieerd zijn met aspiratie en geslacht. De hoge prevalentie van klinisch relevante symptomen van angst en depressie bij hoofd-halskankerpatiënten met slikstoornissen rechtvaardigt de aanbeveling tot systematische screening op affectieve symptomen.



Acknowledgments

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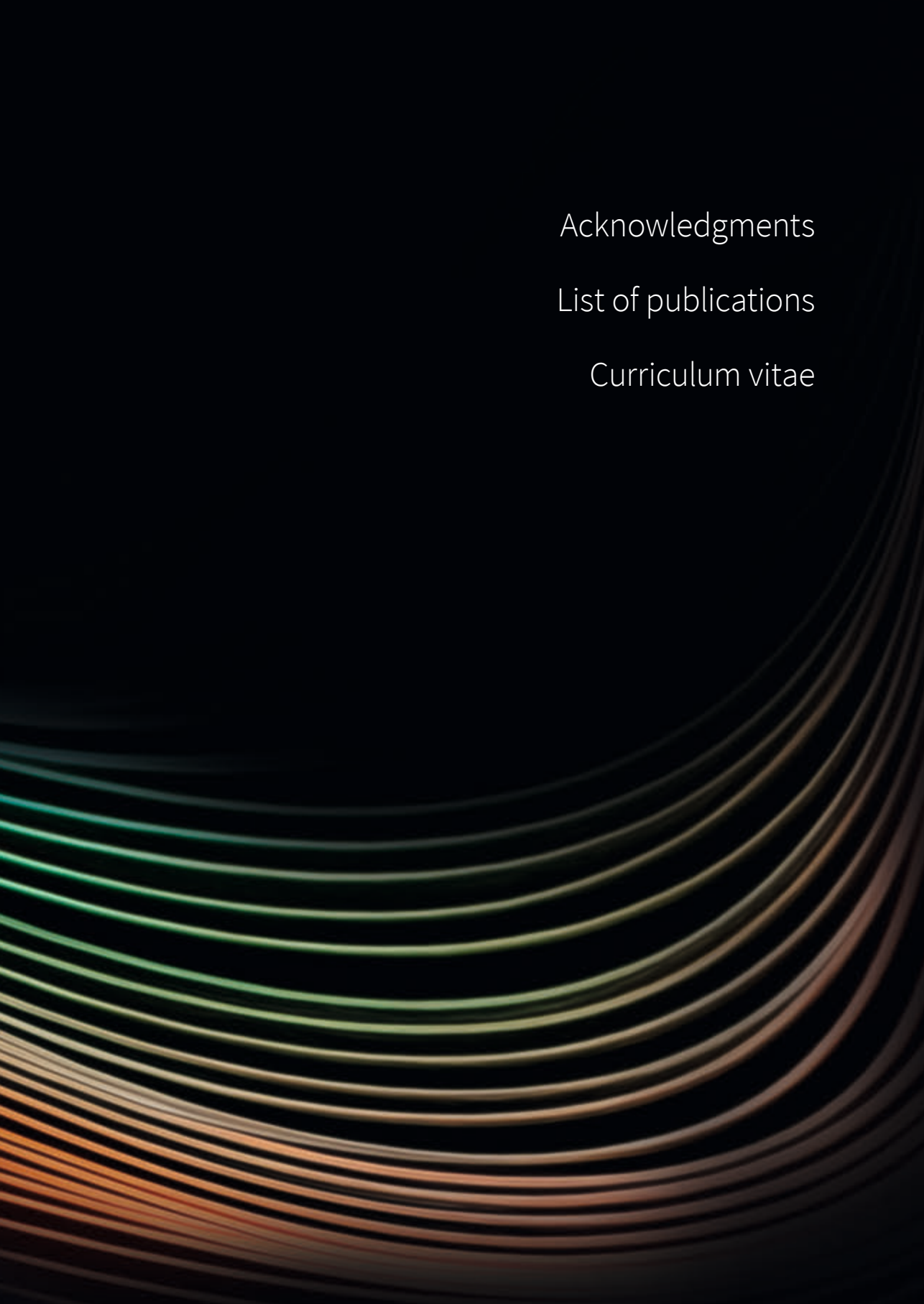

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CURRICULUM VITAE

Sorina Ruth Simon was born in Blaricum, The Netherlands, on 4 October 1993. After graduating with honors from the Trevianum Scholengroep high school in 2011, she attended Medicine at Maastricht University. As part of her medical training, she completed her senior clinical and scientific internship at the Department of Otorhinolaryngology, Head and Neck Surgery of Maastricht University Medical Center. During her scientific internship, she conducted research under the supervision of dr. Laura Baijens in the field of head and neck cancer patients with dysphagia, marking the beginning of a PhD trajectory. After obtaining her Medical degree in 2017, she worked as a resident-not-in-training at the Emergency Department of Laurentius Hospital and Department of Pulmonary Medicine of Zuyderland Medical Center. In January 2020, she started her residency at the Department of Radiology and Nuclear Medicine of Maastricht University Medical Center. She is currently a senior resident and interventional radiologist in training at Maastricht University Medical Center under the supervision of prof. dr. Michiel de Haan. In 2023, she already started her post-doc research projects in the field of both interventional neuroradiology and interventional oncology in the research team led by dr. Christiaan van der Leij. She expects to complete her interventional radiology training in 2025.