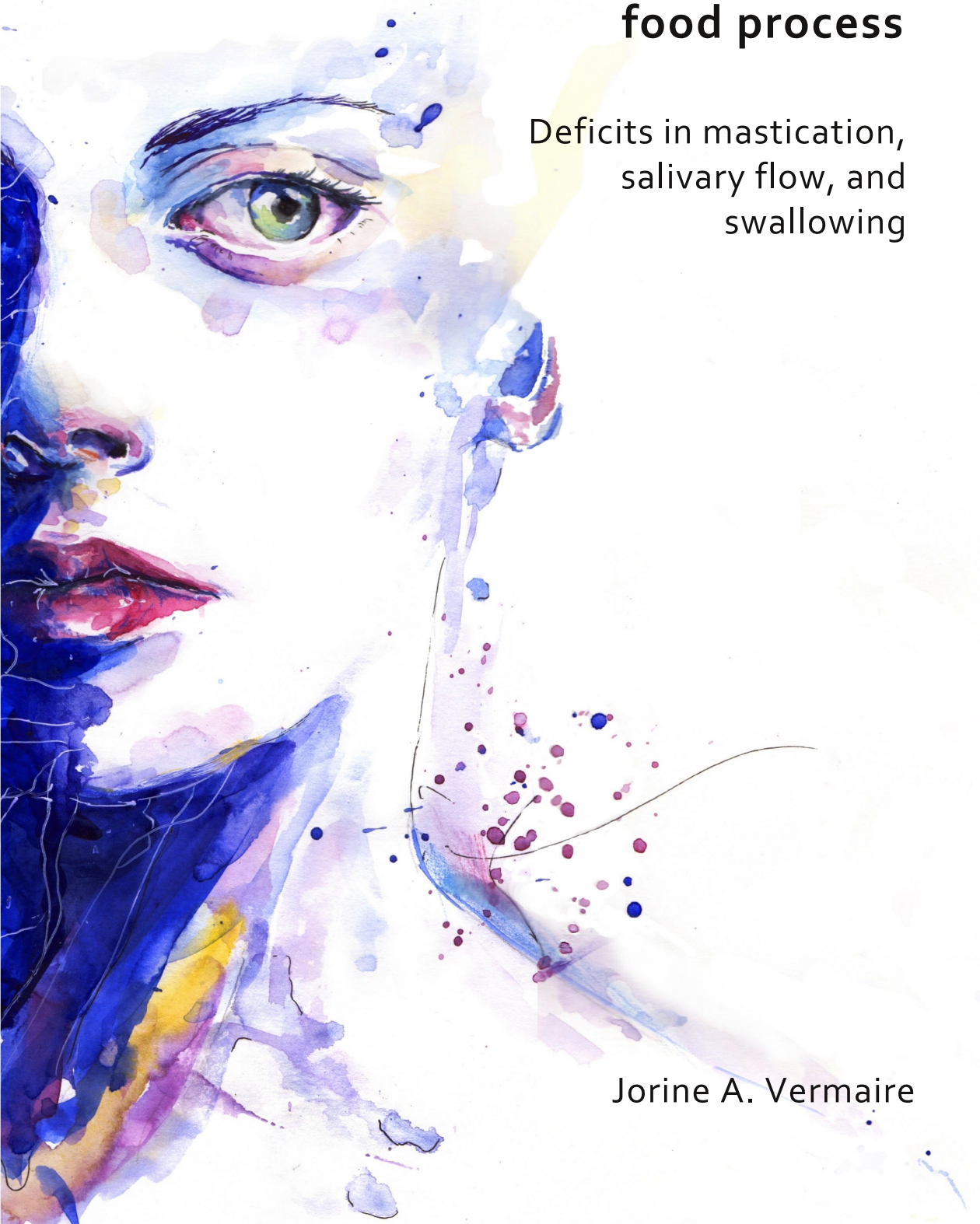
The effect of head and neck cancer on the oral food process

Deficits in mastication, salivary flow, and swallowing



Jorine A. Vermaire

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(met een samenvatting in het Nederlands)

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Chapter 1

Introduction

Food processing

The main purpose of mastication is to break down food into smaller particles that bind to each other through saliva, forming a food bolus ready for swallowing and digestion.[1,2] Mastication is a learned automatic complex process involving the interaction of hard and soft tissues in order to grind a food bolus prior to swallowing.[3] In the mouth, food undergoes several steps: First, the food is transported from the front teeth to the molars (stage I transport). Here the food is analyzed through taste, retronasal olfaction and oral receptors of the somatosensory system. In the second step, the food is converted into a food bolus by means of the teeth and with the aid of saliva and lingual and facial muscles. In the third step, the chewed food is transported backwards to the oropharyngeal surface of the tongue (stage II transport). Finally, the upper esophageal sphincter is opened. The chewing movement takes place as food conversion and backward transport occur almost simultaneously, and food moves across the tongue surface.[4] Through receptors in the oral cavity and nose, changes in food are sensed during chewing, which also leads to the perception of taste, smell, and texture of the food.[5] Chewing also initiates various digestive and metabolic activities, both in the mouth and through reflexes in the cephalic phase (the secretion of gastric juices before food enters the stomach, due to the taste, sight, smell and/or thought of food), which ensure that digestion starts.[4]

Mastication involves several nerves, muscles, and connective tissue structures.[6] The m. masseter, m. temporalis, m. pterygoidus medialis and m. pterygoidus lateralis are considered the main muscles of the masticatory system.[7] These muscles work in a coordinated way with other muscle groups of the face during chewing, such as the infrahyoidal, suprahyoidal, palatal and temporomandibular muscles.[8] During chewing, food hardness influences the masticatory force, activity and amplitude of mandibular (lower jaw) movements.[2] Chewing is characterized by a relatively rhythmic movement of the chewing muscles.[9] The cooperation between these jaw-opening and closing muscles is elicited by a central pattern generator in the brainstem.[1,2] This pattern generator receives signals from the mouth and motor cortex, which are converted into a rhythmic chewing movement.[9] Chewing can be unilateral, bilateral or alternating bilaterally. The preferred side in most cases depends on the number of occlusal units (the surface of a tooth that meets the surface of its opposing tooth in occlusion), and where they are positioned. When occlusion is the same on both sides, there is often a preference for alternating two-sided chewing; changing chewing sides regularly.[7]

Several factors influence the ability to chew efficiently, such as the maximum bite force, maximum mouth opening, sensory function of the tongue, tongue force, the number of occlusal units, and saliva flow. The maximum bite force depends on the muscle volume, the

muscle activity and the coordination between the different chewing muscles.[1] It determines the amount of available force to cut and crush food.[10] When the maximum mouth opening is reduced, this can have an adverse effect on food intake and the maintenance of good oral health, due to a lower masticatory efficiency.[11] The tongue plays an essential initial role in breaking down food into a food bolus and moving food between the molars. The number of teeth determine the size of the occlusal area where the food is grinded and broken down during each chewing cycle.[1,10] Tooth loss, the presence of cavities, inadequate restorations, malocclusion or periodontal disease can therefore adversely affect chewing function.[2,5] Finally, the production of sufficient saliva is indispensable for good chewing as it moistens the food and binds the particles into a coherent bolus that can be easily swallowed.[1,5] Saliva consists for 99% of water and 1% of ions, enzymes and other proteins. Chemicals in the food are dissolved in saliva and are therefore more easily transported to the taste buds, enabling us to taste food. Furthermore, saliva plays a role in the digestion of starch and lipids and in the clearance of food debris after swallowing.[5]

After the food is chewed and processed, swallowing takes place. This is a physiological process formed by oral, pharyngeal and esophageal phases.[12] Swallowing occurs due to neuromuscular actions involving sensitive cranial, motor and parasympathetic nerves.[13] Its purpose is to transport food from the mouth to the stomach, promoting hydration and nutrition. To transport food, a number of rapid, coordinated and accurate events have to occur, such as soft palate elevation, vocal fold closure, pharyngeal muscle contraction, laryngeal elevation and anteriorization and epiglottis lowering.[14] These mechanisms occur involuntarily after stimulation of sensory receptors, especially located in the oropharyngeal cavity.[13] The initiation of oral swallowing is voluntary, and depends on a threshold for food particle size and particle lubrication.[1] The pharyngeal phase is considered a reflex response, and the esophageal phase is mainly under dual control of the somatic and autonomic nervous systems.[15] The primary function of the oral phase is movement of the tongue, pressing the bolus against the hard palate, and initiating the movement of the bolus to the posterior part of the tongue and towards the oropharynx. In this stage, the contraction of the lips and cheek muscles are crucial to prevent the escape of solids and liquids from the oral cavity.[15]

The pharyngeal phase involves not only pharyngeal and laryngeal muscles, but also muscles in the oral cavity such as the tongue and suprahyoid muscles.[15] The shape of the pharynx is altered dynamically for breathing, eating and vocalization. The pharynx dilates in order to maintain airway patency for breathing, and is constricted to push the food bolus down the esophagus during swallowing.[16] The passage of food is separated from the lower airway and nasal cavity. It is essential that the coordination between respiration and digestion is well coordinated so that food can be efficiently transported to the stomach and intestines,

thus preventing aspiration of foreign materials into the trachea before or during swallowing.[16] Since there is a brief pause in breathing when swallowing food, food should be chewed well and mixed with saliva to minimize swallowing time and the associated brief cessation of breathing.[17] This pause in breathing is caused by the inhibition of respiration in neural control centers in the brainstem, and not simply due to closure of the upper airway.[16] The esophageal phase consists of a peristaltic wave of muscle contraction, which propagates to the stomach.

Head and neck cancer

Head and neck cancer (HNC) is the seventh most common cancer worldwide, and develops in the mucosal surfaces of the upper aero digestive tract.[18] HNC can be divided into different sub sites: the oral cavity (including the lips, tongue, floor of the mouth, hard palate, and gum), the pharynx (including the oropharynx, hypopharynx and nasopharynx), the larynx (supraglottic, glottic, and subglottic regions), the nasal cavity and paranasal sinuses, and the salivary glands. Risk factors for developing HNC are alcohol and tobacco (ab)use, or viral infections such as the human papilloma virus (HPV).[18] Curative treatment options for HNC include surgery, radiotherapy (RT), chemoradiotherapy (CRT), or a combination of these treatment modalities. The type of treatment depends on the tumor site, tumor stage and patient characteristics. Early-stage cancers are usually treated with either surgery or RT, while locally advanced cancers are treated with surgery followed by adjuvant radiation or chemoradiotherapy.[19] In addition, oral cavity tumors are most often treated with surgery, while oropharynx and larynx tumors are primarily treated with RT.

Surgery

The main goal of surgery is complete tumor resection while maximizing post-operative function. This is often difficult to achieve, and depends on several variables such as tumor size and location, neck involvement, type of surgical reconstruction and dental status of the patient.[3] Surgery may require wide resections of one or multiple sub sites, including tongue, floor of mouth, or lower gingiva.[20] It may be combined with reconstruction of the tumor site by a tissue transfer and/or neck dissection. A laryngectomy, in which the total larynx is removed, may be needed for advanced stage IV tumors.

Radiotherapy

RT uses ionizing radiation that damages and/or destroys all cells receiving a radiation dose, including normal tissue cells surrounding the tumor. By increasing the dose, the probability to destroy malignant cells increases as well. However, in order to spare healthy tissue, the dose to these fields has to be limited. It is therefore important to create a balance in which

the dose to the tumor can be maximized, while keeping the dose to the healthy tissues and organs at risk (OAR) acceptable.[21] RT for HNC is usually divided into 35 fractions of 2 Gy spread out over seven weeks. Between each fraction, healthy tissue can recuperate from the radiation dose while malignant cells, who are less able to repair themselves, do not recover. However, damage to normal tissue cells still occurs, also caused by the reduced regenerative potential of irradiated tissue.

Chemotherapy

Chemotherapy is administered concomitantly with radiotherapy. Frequently used classical chemotherapeutics include cisplatin and carboplatin which are provided 3 times during the course of radiotherapy. Cisplatin acts by binding to DNA, thereby inhibiting the DNA synthesis. It enhances the effect of RT by inhibiting the repair of cells.[22] Targeted therapy using the monoclonal antibody cetuximab is administered when patients are not fit enough to receive cisplatin. Cetuximab has fewer oral side effects, although systemic side effects such as acneiform rash, asthenia, and allergic reactions are common. Immunotherapy can be provided for patients with advanced head and neck cancer in a palliative setting, with immunotherapeutic agents such as nivolumab which can increase mean survival rates of patients.[23]

Toxicity after surgery

During the oral phase of food processing, the teeth and tongue need to work together to transport the food to the molars. In addition, the muscles together with nerves and connective tissues need to break down the food to form a bolus, and transport the food backwards to the oropharyngeal surface of the tongue. Chewing and swallowing are interrelated, because chewing plays a fundamental role in the process of swallowing food.[24]

Surgical resection of the tongue will compromise lingual mobility and strength.[3] Tongue dysfunction leads to impaired mastication, bolus formation and bolus transport, as tongue function is key to optimal mastication.[3,25] Resection of masticatory and facial musculature will lead to facial deformity and loss of oral competence. A reduced closing pressure of the lips may lead to drooling.[25] When nerves are transected, this may lead to sensory dysfunction of, e.g. the tongue, lips, chin, or facial musculature.[26] Neck dissection can lead to impaired neck and shoulder mobility.[27] Surgery may also result in alteration of the temporomandibular joint anatomy, disarticulation of the temporomandibular joint, loss and alteration of the masticatory muscles or loss of mandibular and maxillary structural integrity together with loss of teeth, leading to radical alteration of the oral anatomy.[3] This can result in decreased tooth-to-tooth contact, sensory and soft-tissue deficits, and thus compromising the patients' ability to form and manipulate a food bolus that is ready to be

swallowed. If mastication is compromised, tougher foods are more difficult to process because they require a higher muscle force and more chewing cycles.[28] Therefore, some patients switch their diet to softer foods, because the muscle force needed to break down food is too high. This can negatively affect orofacial muscle tonus or even nutritional status.[2,8] Malnutrition is defined as a state of nutrition in which a deficiency of energy, protein and other nutrients cause measurable adverse effects on tissue and body form.[29] Malnutrition can result in a higher morbidity, mortality, and care costs, because these patients are at a higher risk to develop diseases and infections, caused by the negative impact on the immune response.[24,30]

Surgical resection of the soft palate, floor of mouth, or base of tongue can cause severe problems by compromising lingual mobility, muscle strength, mastication, swallowing, muscle action, and muscle coordination.[31-33]

Surgery of the larynx (laryngectomy) is the optimal therapy for advanced stage IV local disease, resulting in severe effects on swallowing and speech. Over 40% of postoperative patients may experience subjective dysphagia in long term follow-up.[34] Dysphagia is a significant toxicity resulting in difficulty in swallowing, caused by abnormalities in structure or function of cartilaginous, bony, muscular or neural anatomy involved in normal swallowing.[33] Dysfunction of the pharynx can lead to impaired swallow initiation, ineffective bolus propulsion, and retention of a portion of the bolus in the pharynx after swallowing.[25] In addition, patients need to re-learn how to speak after a laryngectomy, for example by using esophageal speech, pneumatic speech, tracheoesophageal speech, or an electrolarynx. Similarly to masticatory problems, swallowing problems may also affect nutritional status, because a change in diet is often recommended when swallowing problems occur, by changing the consistency of liquids and/or food in order to prevent dysphagia.[24]

Toxicity after radiotherapy and chemo radiation

Radiotherapy of the oral cavity may result in acute effects such as pain, mucositis, dermatitis, a decrease in saliva production, or edema.[3,35,36] RT can also lead to necrosis of irradiated bone, resulting in osteoradionecrosis of the jaw.[3] To prevent this, some teeth may need to be extracted pre-treatment.[3] Loss of teeth reduces masticatory performance, as chewing can be prolonged, and particle size of the bolus becomes larger due to lower efficiency of mastication.[25] Saliva is needed to moisten the food, bind the particles into a bolus and transport the bolus. In addition, it dilutes flavor and alters food consistency during mastication.[37] Salivary glands are particularly sensitive to ionizing radiation, with doses to the parotid gland between 28 and 39 Gy leading to a 50% complication probability.[38] Doses

over 50 Gy cause irreversible hypofunction and permanent xerostomia.[39] When salivary glands are in the RT field, this will negatively affect saliva quantity and quality, exacerbating masticatory problems.[25] The submandibular glands are responsible for most of the saliva production (60-65%) in the non-stimulated state,[39] and are mainly responsible for flow rate during sleep. Most patients with HNC complain of a dry mouth at night caused by irradiation of the submandibular glands, with 65% of patients having severe complaints 1 year after RT.[40]

Long term RT damage may consist of fibrosis, periodontal disease, ulcers, or vascular toxicity. These effects can be attributed to hypoxic, hypo-vascular, or hypocellular tissue. RT often leads to fibrotic tissue and hyposalivation, which can also lead to trismus, xerostomia, and radiation-induced caries.[41-43] Chemotherapy can add to these effects, because it causes immunosuppression and is not tumor specific but acts on all cells in the body. As a result, patients exhibit acute toxicity with oral manifestations, such as oral mucositis, nausea, vomiting, renal insufficiency, loss of hearing and appetite, cytopenia, xerostomia, neurotoxicity, and stomatotoxicity.[37] In addition, it can enhance radiation-induced fibrosis of the muscles and cause edema.[35]

Irradiation of swallowing related normal tissues may lead to dysphagia, fibrosis, edema, ulcers, vascular toxicity, and osteoradionecrosis.[44,45] Complications such as malnutrition, aspiration and subsequent pneumonia can occur.[33] Irradiation of swallowing tissues may result in a thick, viscid saliva that impairs deglutition, resulting in significantly longer oral transit times and a delayed swallow initiation, a greater pharyngeal residue and decreased pharyngeal transport, a lower swallowing efficiency, a shorter cricopharyngeal opening duration, and ineffective laryngeal protection.[25] This also puts the patient at risk for coughing and aspiration.[3] Chemotherapy can add to the effects of RT and cause edema, mucositis and fibrosis of the swallowing structures.[33]

Food processing measurements

To measure food processing, objective and subjective measures can be used. Objective measures are based on how well a person can perform a task, irrespective of what they experience while performing the task. Subjective measures depend on individual values and priorities, and thus reflect a patients' expectation and personal importance of oral functioning on daily life satisfaction.

Objective masticatory performance can be measured with, for example, comminution methods, sieving and optical scanning methods, gummy jelly as test food, and mixing ability methods.[46] One method using the mixing ability method (the Mixing Ability Test (MAT)) has

proven to be highly reliable in patients with HNC.[47] Objective swallowing performance can be measured with, for example, Fibreoptic Endoscopic Evaluation of Swallowing (FEES), or in a non-invasive and fast manner with minimal equipment using a 100 mL Water Swallow Test (WST).[32,48,49] Measures of objective salivary flow rate from parotid and submandibular glands have been used for years to determine the dose response relationship between RT dose and degree of hyposalivation or sticky saliva.[38,39,43,50,51]

To obtain high quality measures, it is important to assess measurement properties such as reliability.[52] The reliability of a test measures the degree to which a certain test produces stable and consistent results. This can be achieved by, e.g., a test-retest with corresponding intraclass correlation coefficient (ICC) (for continuous data). In addition, inter- or intra-rater differences can be assessed. During each test, a measurement error is thought to occur, either by the measurement instrument itself, the measurement situation, the person taking the test, or the person being tested. The general idea is that, the lower the measurement error, the higher the reliability and thus the quality of the measurement.[52]

Subjective oral functioning can be measured with several validated questionnaires.[53] The European Organization for Research and Treatment of Cancer Quality of Life core Questionnaire, Head and Neck module (EORTC QLQ-H&N35) was especially developed to measure HNC specific problems and addresses different items of oral functioning.[54-56] The Dutch version of the Swallow Quality of Life questionnaire (SWAL-QOL) was developed to address swallowing and food processing related problems.[57,58] The Groningen Radiation-Induced Xerostomia (GRIX) was developed to observe xerostomia and sticky saliva during day and night.[59]

Thesis outline

As described above, mastication, swallowing and salivary flow are important functions which can deteriorate due to head and neck cancer itself, or because of its treatment. Therefore, the aim of this thesis is to further optimize the understanding of mastication, swallowing, and salivary flow in patients with head and neck cancer and investigate associated factors possibly affecting these functions, up to two years after treatment.

Chapter 2 consists of a review that was written about masticatory ability, to provide an overview of the existing literature about oral health related quality of life (QoL) as measured with the University of Washington Quality of Life (UW-QoL) questionnaire. This questionnaire is often used in oral cancer, in which patients have to state whether they can chew normally, can only chew soft food, or cannot chew soft (nor hard) food.

In order to predict the burden of masticatory and swallowing dysfunction, the first important step was to determine the reliability of the tests used to measure objective masticatory and swallowing function, and to determine the measurement error of these tests. **Chapter 3** was written to assess the reliability of the Mixing Ability Test (MAT), which measures masticatory performance. The reliability of the 100 mL Water Swallow Test (WST) to assess swallowing was described in **chapter 4**.

The next step was to determine the correlation between objective function outcomes and patient-reported outcomes, to investigate whether objective tests measure the same construct as patient-reported outcomes. **Chapter 5** therefore assesses this correlation between objective tests and questionnaires.

Based on **chapter 5**, associative models were created to investigate masticatory performance and swallowing function in relation to demographic and clinical factors, and to describe the course in time of these tests. In **chapter 6**, the associative model for masticatory performance was described, and in **chapter 7** the associative model for swallowing function was described. **Chapter 8** describes the course in time of the SWAL-QOL questionnaire, in which the whole food process from eating to swallowing, as well as mental problems caused by food processing difficulties, are taken into account. In addition, an associative model was created which describes patients that are most likely to experience problems after HNC treatment.

References

1. van der Bilt A, Engelen L, Pereira LJ, van der Glas HW, Abbink JH. Oral physiology and mastication. *Physiology & behavior.* 2006;89(1):22-27.

2. Pedroni-Pereira A, Marquezin MCS, Araujo DS, Pereira LJ, Bommarito S, Castelo PM. Lack of agreement between objective and subjective measures in the evaluation of masticatory function: A preliminary study. *Physiology & behavior.* 2018;184:220-225.

3. Pace-Balzan A, Shaw RJ, Butterworth C. Oral rehabilitation following treatment for oral cancer. *Periodontology 2000.* 2011;57(1):102-117.

4. Peyron MA, Woda A, Bourdiol P, Hennequin M. Age-related changes in mastication. *Journal of oral rehabilitation.* 2017;44(4):299-312.

5. Pereira LJ, van der Bilt A. The influence of oral processing, food perception and social aspects on food consumption: a review. *Journal of oral rehabilitation.* 2016;43(8):630-648.

6. Teguh DN, Levendag PC, Voet P, et al. Trismus in patients with oropharyngeal cancer: relationship with dose in structures of mastication apparatus. *Head & neck.* 2008;30(5):622-630.

7. Naeije M, van Loon LAJ. *Craniomandibulaire functie en dysfunctie.* Houten: Bohn Stafleu van Loghum; 1998.

8. de Groot RJ, Rosenberg AJWP, van der Bilt A, Aalto D, Merkx MAW, Speksnijder CM. The association between a mixing ability test and patient reported chewing ability in patients treated for oral malignancies. *Journal of oral rehabilitation.* 2019;46(2):140-150.

9. Gerstner GE, Madhavan S, Braun TM. Relationships between masticatory rhythmicity, body mass and cephalometrically-determined aesthetic and functional variables during development in humans. *Archives of oral biology.* 2014;59(7):711-721.

10. Julien KC, Buschang PH, Throckmorton GS, Dechow PC. Normal masticatory performance in young adults and children. *Archives of oral biology.* 1995;41(1):69-75.

11. Scott B, Butterworth C, Lowe D, Rogers SN. Factors associated with restricted mouth opening and its relationship to health-related quality of life in patients attending a Maxillofacial Oncology clinic. *Oral oncology.* 2008;44(5):430-438.

12. Costa MMB. Neural Control of Swallowing. *Arquivos de gastroenterologia.* 2018;55Suppl 1(Suppl 1):61-75.

13. Zancan M, Luchesi KF, Mituuti CT, Furkim AM. Onset locations of the pharyngeal phase of swallowing: meta-analysis. *CoDAS.* 2017;29(2).

14. Almeida RCA, Haguette RCB, de Andrade ISN. Swallowing with and without verbal commands: videofluroscopic findings. *Rev Soc Bras Fonoaudiol.* 2011;16(3):291-297.

15. Ertekin C, Aydogdu I. Neurophysiology of swallowing. *Clinical Neurophysiology.* 2003;114(12):2226-2244.

16. Matsuo K, Palmer JB. Coordination of Mastication, Swallowing and Breathing. *Jpn Dent Sci Rev.* 2009;45(1):31-40.

17. Fulks BA, Callaghan KX, Tewksbury CD, Gerstner GE. Relationships between chewing rate, occlusion, cephalometric anatomy, muscle activity, and masticatory performance. *Archives of oral biology.* 2017;83:161-168.

18. Rettig EM, D'Souza G. Epidemiology of head and neck cancer. *Surgical oncology clinics of North America.* 2015;24(3):379-396.

19. Mendenhall WM, Dagan R, Bryant CM, Fernandes RP. Radiation Oncology for Head and Neck Cancer: Current Standards and Future Changes. *Oral and maxillofacial surgery clinics of North America.* 2019;31(1):31-38.

20. Ohkoshi A, Ogawa T, Nakanome A, et al. Predictors of chewing and swallowing disorders after surgery for locally advanced oral cancer with free flap reconstruction: A prospective, observational study. *Surgical oncology.* 2018;27(3):490-494.

21. Gregoire V, Langendijk JA, Nuyts S. Advances in Radiotherapy for Head and Neck Cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2015;33(29):3277-3284.

22. Bhide SA, Nutting CM. Advances in chemotherapy for head and neck cancer. *Oral oncology.* 2010;46(6):436-438.

23. Ferris RL, Blumenschein G, Jr., Fayette J, et al. Nivolumab vs investigator's choice in recurrent or metastatic squamous cell carcinoma of the head and neck: 2-year long-term survival update of CheckMate 141 with analyses by tumor PD-L1 expression. *Oral oncology.* 2018;81:45-51.

24. Mann T, Heuberger R, Wong H. The association between chewing and swallowing difficulties and nutritional status in older adults. *Aust Dent J.* 2013;58(2):200-206.

25. Matsuo K, Palmer JB. Anatomy and physiology of feeding and swallowing: normal and abnormal. *Phys Med Rehabil Clin N Am.* 2008;19(4):691-707, vii.

26. Spiegel JH, Deschler DG. *Oral Cavity Reconstruction: Anatomy of the Oral Cavity and Related Structures* 1st edition ed: Taylor & Francis; 2006.

27. Speksnijder CM, van der Bilt A, Slappendel M, de Wijer A, Merkx MA, Koole R. Neck and shoulder function in patients treated for oral malignancies: a 1-year prospective cohort study. *Head & neck.* 2013;35(9):1303-1313.

28. van der Bilt A, Abbink JH. The influence of food consistency on chewing rate and muscular work. *Archives of oral biology.* 2017;83:105-110.

29. O'Keeffe M, Kelly M, O'Herlihy E, et al. Potentially modifiable determinants of malnutrition in older adults: A systematic review. *Clinical Nutrition.* 2019;38(6):2477-2498.

30. Favaro-Moreira NC, Krausch-Hofmann S, Matthys C, et al. Risk Factors for Malnutrition in Older Adults: A Systematic Review of the Literature Based on Longitudinal Data. *Adv Nutr.* 2016;7(3):507-522.

31. Kreeft AM, van der Molen L, Hilgers FJ, Balm AJ. Speech and swallowing after surgical treatment of advanced oral and oropharyngeal carcinoma: a systematic review of the literature. *Eur Arch Oto-Rhino-L.* 2009;266(11):1687-1698.

32. Russi EG, Corvo R, Merlotti A, et al. Swallowing dysfunction in head and neck cancer patients treated by radiotherapy: Review and recommendations of the supportive task group of the Italian Association of Radiation Oncology. *Cancer treatment reviews.* 2012;38(8):1033-1049.

33. Riffat F, Gunaratne DA, Palme CE. Swallowing assessment and management pre and post head and neck cancer treatment. *Current opinion in otolaryngology & head and neck surgery.* 2015;23(6):440-447.

34. Zenga J, Goldsmith T, Bunting G, Deschler DG. State of the art: Rehabilitation of speech and swallowing after total laryngectomy. *Oral oncology.* 2018;86:38-47.

35. Nemeth D, Zaleczna L, Huremovic A, et al. Importance of chewing, saliva, and swallowing function in patients with advanced oral cancer undergoing preoperative chemoradiotherapy: a prospective study of quality of life. *International journal of oral and maxillofacial surgery.* 2017;46(10):1229-1236.

36. Owosho AA, Pedreira Ramalho LM, Rosenberg HI, et al. Objective assessment of trismus in oral and oropharyngeal cancer patients treated with intensity-modulated radiation therapy (IMRT). *Journal of cranio-maxillo-facial surgery : official publication of the European Association for Cranio-Maxillo-Facial Surgery.* 2016;44(9):1408-1413.

37. Caputo JB, Campos SS, Pereira SM, et al. Masticatory performance and taste perception in patients submitted to cancer treatment. *Journal of oral rehabilitation.* 2012;39(12):905-913.

38. Dijkema T, Terhaard CH, Roesink JM, et al. Large cohort dose-volume response analysis of parotid gland function after radiotherapy: intensity-modulated versus conventional radiotherapy. *International journal of radiation oncology, biology, physics.* 2008;72(4):1101-1109.

39. Eisbruch A, Ten Haken RK, Kim HM, Marsh LH, Ship JA. Dose, volume, and function relationships in parotid salivary glands following conformal and intensity-modulated irradiation of head and neck cancer. *Int J Radiation Oncology Biol Phys.* 1999;45(3):577–587.

40. Dijkema T, Raaijmakers CP, Braam PM, Roesink JM, Monninkhof EM, Terhaard CH. Xerostomia: a day and night difference. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology.* 2012;104(2):219-223.

41. Wetzels JW, Merkx MA, de Haan AF, Koole R, Speksnijder CM. Maximum mouth opening and trismus in 143 patients treated for oral cancer: a 1-year prospective study. *Head & neck.* 2014;36(12):1754-1762.

42. Vissink A, Burlage FR, Spijkervet FKL, Jansma J, Coppes R. Prevention and treatment of the consequences of head and neck radiotherapy. *Crit Rev Oral Biol Med.* 2003;14(3):213-225.

43. Braam PM, Roesink JM, Raaijmakers CP, Busschers WB, Terhaard CH. Quality of life and salivary output in patients with head-and-neck cancer five years after radiotherapy. *Radiation oncology.* 2007;2:3.

44. Hutcheson KA, Lewin JS, Barringer DA, et al. Late dysphagia after radiotherapy-based treatment of head and neck cancer. *Cancer.* 2012;118(23):5793-5799.

45. Alterio D, Gerardi MA, Cella L, et al. Radiation-induced acute dysphagia : Prospective observational study on 42 head and neck cancer patients. *Strahlentherapie und Onkologie : Organ der Deutschen Rontgengesellschaft [et al].* 2017;193(11):971-981.

46. Elgestad Stjernfeldt P, Sjogren P, Wardh I, Bostrom AM. Systematic review of measurement properties of methods for objectively assessing masticatory performance. *Clinical and experimental dental research.* 2018;5(1):76-104.

47. Vermaire JA, Weinberg FM, Raaijmakers CPJ, Verdonck-de Leeuw IM, Terhaard CHJ, Speksnijder CM. Reliability of the mixing ability test testing masticatory performance in patients with head and neck cancer and healthy controls. *Journal of oral rehabilitation.* 2020.

48. Patterson JM, Hildreth A, McColl E, Carding PN, Hamilton D, Wilson JA. The clinical application of the 100mL water swallow test in head and neck cancer. *Oral oncology.* 2011;47(3):180-184.

49. Nathadwarawala KM, Nicklin J, Wiles CM. A timed test of swallowing capacity for neurological patients. *J Neurol Neurosurg Psychiatry.* 1992;55(9):822-825.

50. Roesink JM, Moerland MA, Battermann JJ, Hordijk GJ, Terhaard CH. Qualitative dose-volume response analysis of changes in parotid gland function after radiotherapy in the head-and-neck region. *Int J Radiation Oncology Biol Phys.* 2001;51(4):938–946.

51. Dijkema T, Raaijmakers CP, Ten Haken RK, et al. Parotid gland function after radiotherapy: the combined michigan and utrecht experience. *International journal of radiation oncology, biology, physics.* 2010;78(2):449-453.

52. Scholtes VA, Terwee CB, Poolman RW. What makes a measurement instrument valid and reliable? *Injury.* 2011;42(3):236-240.

53. van der Veen J, Nuyts S. Can Intensity-Modulated-Radiotherapy Reduce Toxicity in Head and Neck Squamous Cell Carcinoma? *Cancers.* 2017;9(12):135.

54. Singer S, Arraras JI, Chie WC, et al. Performance of the EORTC questionnaire for the assessment of quality of life in head and neck cancer patients EORTC QLQ-H&N35: a methodological review. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation.* 2013;22(8):1927-1941.

55. Bjordal K, de Graeff A, Fayers PM, et al. A 12 country field study of the EORTC QLQ-C30 (version 3.0) and the head and neck cancer specific module (EORTC QLQ-H&N35) in head and neck patients. EORTC Quality of Life Group. *European journal of cancer.* 2000;36(14):1796-1807.

56. Singer S, Araujo C, Arraras JI, et al. Measuring quality of life in patients with head and neck cancer: Update of the EORTC QLQ-H&N Module, Phase III. *Head & Neck.* 2014.

57. Bogaardt HC, Speyer R, Baijens LW, Fokkens WJ. Cross-cultural adaptation and validation of the Dutch version of SWAL-QoL. *Dysphagia.* 2009;24(1):66-70.

58. Rinkel RN, Verdonck-de Leeuw IM, Langendijk JA, van Reij EJ, Aaronson NK, Leemans CR. The psychometric and clinical validity of the SWAL-QOL questionnaire in evaluating swallowing problems experienced by patients with oral and oropharyngeal cancer. *Oral oncology.* 2009;45(8):e67-71.

59. Beetz I, Burlage FR, Bijl HP, et al. The Groningen Radiotherapy-Induced Xerostomia questionnaire: development and validation of a new questionnaire. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology.* 2010;97(1):127-131.

Chapter 2

Mastication in health-related quality of life in patients treated for oral cancer: a systematic review

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Submitted

Abstract

Background

Treatment for oral cancer can impair oral functions such as mastication, which may negatively affect Quality of Life (QoL). In this review, an overview is provided of masticatory ability in patients treated for oral cancer.

Methods

The PubMed (MEDLINE), Embase and Cochrane databases were systematically searched for scientific literature on masticatory ability in relation to QoL in patients treated for oral cancer. Studies were included when oral cancer treatment was given, and the University of Washington Quality of Life questionnaire (UW-QoL) was used. Risk of bias (MINORS) was independently assessed by two authors.

Results

The PubMed (MEDLINE), Embase and Cochrane search yielded 575 unique records of which 111 were assessed full text, and 27 studies were included. The UW-QoL mastication scores ranged from 31.9 to 97.4. There was a wide variety in methodology, patient groups, tumor site, treatment, and assessment moment, to such a degree that outcome scores are difficult to compare.

Conclusion

The wide variety in studies exploring Health Related QoL in relation to mastication in oral cancer patients prevents the identification of possible relations between treatment, masticatory ability and QoL. Our findings underline the limitations in currently available literature and indicate the necessity for more comparable research.

Introduction

Oral cancer is currently in the top ten most common cancers worldwide.[1] More insight into oral cancer and advancement in procedures have contributed to a more effective treatment. However, tumor eradication is not the only outcome that should be included in the evaluation of treatment success. Quality of life (QoL) of patients after cancer treatment has become more significant in the past decade.[2] A patient's self-reported Health Related QoL (HR-QoL) contributes to a better understanding of the range of health challenges patients with cancer may encounter.[3] Those issues may continue long after initial curative treatment, and can be easily overlooked without adequate follow-up and assessment of HR-QoL.

Primary curative treatment for oral cancer is mostly surgical ablation of the tumor, which can be followed by (chemo)radiotherapy, depending on affected regional lymph nodes (N-stage), extent of radical resection, and tumor specific growth factors.[4,5] The sequelae of curative treatment can temporarily or permanently impair oral functions, because treatment may affect vital structures for mastication, such as dentition, musculature, and nerves.[3,6] This is one of the considerations for the multidisciplinary team regarding cancer treatment.[7,8]

Masticatory performance depends on maximum bite force, tongue function, maximum mouth opening and dental status.[9,10] Ideally, to prevent loss of masticatory function, early identification of a lesion and referral to a head and neck cancer (HNC) specialist for further examination is preferred. Early-stage oral cancers with a relatively small affected area are less likely to drastically impact oral function after treatment. However, treatment of advanced tumors will include a larger area and more likely involve multiple structures, thus having a higher risk of impacting speech, mastication and swallowing.[11,12] Post-surgery deformities may occur, depending on resection procedure. Aesthetics can be (partially) restored by reconstructing the affected site. Unfortunately, reconstruction has its limitations. For example, soft tissue reconstruction following a glossectomy can replace the missing part of the tongue with a free flap such as the radial forearm flap.[13] Although the result can be aesthetically acceptable, this is not necessarily equivalent to adequate oral function. Tongue function will mostly depend on the remaining tongue structures after resection.[13,14] After segmental mandibulectomy, loss of vital structures is linked to the location and extent of the resection.[11] Nonetheless, fibula reconstruction in combination with implant rehabilitation in larger resections can give adequate oral function, provided that there is no tongue impairment, resulting in less impact on masticatory functioning.[15] In addition, (chemo)radiotherapy may be indicated during treatment with concomitant oral complications such as trismus, xerostomia, mucositis, dyspepsia and increased risk of infectious disease.[16-18]

Although the importance and value of HR-QoL studies is widely acknowledged, there is little standardization in these studies.[2] Use of different HR-QoL questionnaires makes it difficult to compare obtained data. One of the most frequently used questionnaires that specifically focuses on mastication is the university of Washington quality of life (UW-QoL) questionnaire.[3] The UW-QoL is a brief and self-administered multi-factorial questionnaire, with questions specific to head and neck cancer (HNC), and reflects the QoL as indicated by the patient.[19]

To our knowledge, no overview is available regarding QoL based on UW-QoL outcomes in patients treated for oral cancer with an emphasis on masticatory ability. Therefore, this systematic review was conducted, to provide an overview of the available scientific literature on masticatory ability in relation to QoL in patients treated for oral cancer. This will provide insight into the effect of masticatory ability on HR-QoL in oral cancer patients after primary curative treatment.

Methods

This systematic review was conducted according to the preferred reporting item for systematic reviews and meta-analyses (PRISMA) guidelines.[20]

Eligibility criteria

Studies that were eligible were full text articles focusing on HR-QoL and masticatory ability in oral cancer patients after primary curative treatment using the validated UW-QoL.[3,19,21] There were no restrictions in year of publication or use of a translated version of the UW-QoL. Exclusion criteria were: (1) studies that did not differentiate between different types of HNC; (2) inclusion of the oropharynx; (3) inclusion of the base of the tongue; (4) ameloblastoma or other benign tumors; (5) case reports, reviews, comments or ongoing trials; (6) and studies written in a language other than English.

Information sources

Studies were retrieved by searching the following electronic databases: PubMed, Embase and Cochrane. No limits were applied in the search. The final search was conducted on 2 November 2021.

Search

The search strategies terms were synonyms, variations and associated terms with regard to the following keywords: “head and neck neoplasms”, “mastication” and “quality of life”.

In PubMed, combinations of MeSH Terms and title/abstract were used. Embase and Cochrane had adapted search strategies based on the PubMed search strategy. Grey literature was not included. The full strategies for each database are presented in Appendix A.

Study selection

All records were imported in reference manager Endnote X9 (Clarivate Analytics 2013). After manual removal of duplicates, the eligibility assessment based on title and abstract was independently conducted by two authors (JV and AP). Afterwards, disagreements between reviewers were resolved by discussion. Full-text articles were obtained and independently assessed on inclusion and exclusion criteria. Conflicts between reviewers were resolved in all cases. If needed, a third author (CS) was available to resolve any disagreements.

Data collection process, data items and summary measures

A data extraction sheet was used, which included clinical and demographic characteristics of patients as well as study related details relevant to our review. One author (AP) extracted the data from included studies and the other author (JV) verified the extracted data. Any seemingly incorrect data were discussed. If needed, a third author (CS) was available to resolve any disagreements. The following information was extracted from each included study: (1) study characteristics (study design, number of included patients); (2) patients characteristics (sex, age, tumor site, tumor stage); (3) type of cancer treatment; (4) assessment (evaluation frequency, assessment moment, follow-up); and (5) UW-QoL outcome regarding masticatory ability (mean with standard deviation (SD) or standard error (SE)). When authors clearly defined different subgroups in their study, composed data as well as specified data were extracted.

Risk of bias in individual studies

The risk of bias was evaluated with the validated methodological index for non-randomized studies (MINORS).[22] This instrument contains eight items for non-comparative studies and four additional items for comparative studies. The grading of each item is done by appointing one of three grades: not reported (0); reported but inaccurate (1); reported and adequate (2). The studies were independently assessed by two authors (JV and AP). Criteria for scoring each item were discussed by the two reviewers before as well as during the assessment of the publications. Any disagreements were resolved by discussion. A third

author (CS) was consulted in case of doubt. The ideal score for non-comparative studies is 16 and 24 for comparative studies.

Synthesis of results and additional analyses

The ability of MINORS to differentiate between poor or excellent quality studies has not been validated.[22] Thus, rating the methodological quality as 'poor' or 'excellent' based on MINOR scores cannot be done. However, the scores can be displayed as a fraction of the ideal score and corresponding percentage.

Results

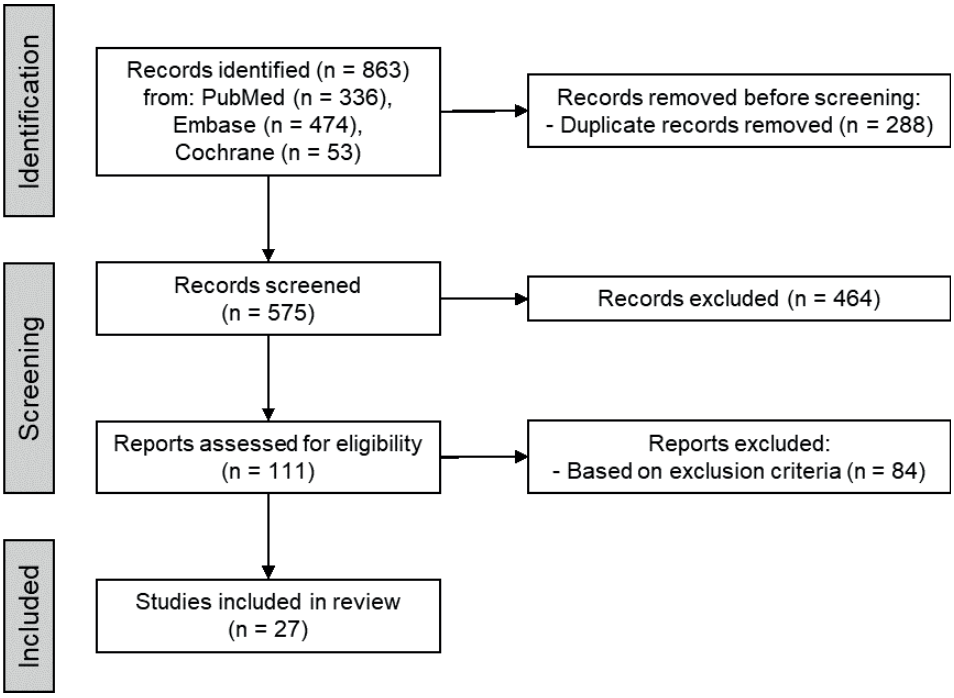
The search of PubMed (n=336), Embase (n=474) and Cochrane (n=53) provided a total of 863 records. After duplicate deletion, 575 unique records remained. After title and abstract were screened and consensus was reached between authors on all records, 464 studies were discarded. Of the 111 records that were read full text, a total of 27 studies were identified for inclusion in the review. No meta-analysis was performed in this study. An overview of the study selection process is shown in Figure 1.

Study characteristics

The studies selected for this review were 20 cross-sectional studies and 7 longitudinal studies, of which 11 were prospective, 10 were retrospective and 6 did not report prospective or retrospective data collection. The included studies involved a total of 1849 oral cancer patients of which at least 1308 were male, as one study did not report sex of patients.[23] Eleven studies only reported mean or median age with SD and did not mention range.[24-34] One study did not mention age of patients,[23] and 3 studies categorized patients in age groups without further details about mean and SD.[31,34,35] Studies were mainly conducted in China,[28,33-44] followed by India,[24,45-47] the United Kingdom,[25,27,31,48] Brazil,[26,32] the United States,[30,49] Germany,[29] and Pakistan.[23]

Tumor sites included: tongue, buccal mucosa, gingiva, floor of mouth (FOM), palate, retromolar region, lip, alveolar process, and gum. Tumor stage was reported in all studies, except one.[48] All studies included patients with curative intended treatment, as mentioned in the inclusion criteria. However, the type of primary treatment differed: besides primary surgery (tumor resection), a (selective/functional) neck dissection was performed in some studies.[24,25,32,33,35-37,39,42,45,48,49] Most surgical treatments included reconstruction.[26-31,33-35,37-40,42-48] Only two studies did not apply or mention adjuvant therapy.[42,49] One study did not report any treatment details.[23]

Figure 1. PRISMA flowchart of the literature search and study selection



Summarized literature search methodology, in accordance to the PRISMA Statement[20]

As stated in the inclusion criteria, HR-QoL outcomes were assessed in all studies by using the UW-QoL questionnaire. In addition, some studies also used the Oral Health Impact Profile (OHIP-14 or OHIP-49) questionnaire,[34,38,40,42,43] and one study used the European Organization for Research and Treatment of Cancer Head and Neck Cancer module (EORTC QLQ-H&N35).[43] Evaluation of HR-QoL outcomes was performed at different moments in time. In some studies, patients administered the questionnaire at least once pre- and post-treatment.[24,41] Patients in other studies administered the questionnaire only once post-treatment.[23,25,26,28,30,32-38,40,42,44-49] The questionnaire was administered twice post-treatment in two studies.[31,43] The follow-up time between treatment and assessment of HR-QoL varied from less than 3 months[46] to 10 years.[31] Characteristics and assessment details are presented in Table 1.

Risk of bias within studies

The methodological quality of all studies was assessed and is presented in Table 2. The MINORS quality scores of non-comparative studies ranged from 44%[23] to 69%,[34,36,46] with an average of 60%. The MINORS quality scores of comparative studies ranged from 54%[45,49] to 75%,[28,33,34,41,44,47] with an average of 67%.

Results of individual studies

Detailed outcome scores of each study are presented in Table 1. HR-QoL masticatory ability scores clustered by time are presented in Figure 2.

Vakil et al. did not report any specific data to compare with other studies included in the present review.[23] Agarwal et al. showed that the ability to chew solid food at baseline reduced to only semisolids and liquids post-treatment.[24] Li et al. followed 47 hemiglossectomy patients and reported that only 7 patients complained about a negative effect on chewing ability.[39] Rogers et al. stated that chewing scores were maintained over time.[27] An 8-year longitudinal study by Yan et al. showed the worst QoL-scores for mastication 3 months post-treatment.[41] The scores improved at the 1-year assessment and remained the same at the 8-year assessment. Nonetheless, overall, the problems with chewing significantly worsened between time of diagnosis and 8 years after treatment. Rogers et al. showed an improvement from 2 years to 10 years post treatment.[31] Bekiroglu et al. reported a mean decline in chewing of 25 points after 1 year for patients treated with a combination of surgery and RT, and a mean decline of 7 points for those treated with surgery without RT.[25]

The percentage of patients considering chewing as one of the 3 most important domains of the UW-QoL differed between 33.3% (2nd rank)[36] and 94.1% (1st rank).[38] Other studies only reported the rank of the chewing domain: 1st rank,[35,40,46] 2nd rank,[45] and 3rd rank.[45] Soares et al. used an alternative way to present outcomes. At 41.5 months, patients scored as follows: cannot chew anything (n=26), chews light food (n=20) and chews light food and solids (n=1). There were no significant associations between chewing scores and demographic or clinical variables.[26] Ochoa et al. reported patients scores as follows: I cannot even chew soft solids (n=0), I can eat soft solids but cannot chew some foods (n=2), I can chew as well as ever (n=37). Chewing was one of the worst scoring domains in this study.[49] Vakil et al. also presented their findings in a slightly different manner. A score from 1 to 3 was used, where 1 indicated no change in chewing function and 3 indicated that patients could not chew soft food. In this study, the most frequently occurring value was 2 with a standard deviation of 0.7.[23]

Table 1. Demographic, tumor and treatment related details of reviewed

Author	Location	Type	Sub-groups	n (%male)	Age mean (SD) (range) in y	Site (n)	T stage (n)	N stage (n)	Treatment (n)	Timing of assessment in m (range)	Outcome mean (SD)
1. Argawal et al. (2014)	IN	L, P	N/A	39 (87)	51.62 (21.23)	T(39)	T1-2: 39	N0	Wide local excision, HG with SND, FPND, RT	12	Pre-Tx: 76.9 (25.3) Post-Tx: 52.6 (16.0) p<0.001
2. Bekiroglu et al. (2011)	UK	L, R	*I*: no RT *II*: RT	*I*:69 (38) *II*:60 (43)	*I*:61 (11) *II*:60 (12)	B(23), FOM(40), G(24), T(29), other(13)	T3-T4: *I*:44, *II*:38	N0: *I*:53, *II*:41 N1: *I*:10, *II*:9 N2+: *I*:6, *II*:10	SND, soft FF (*I*:39, *II*:32), composite FF (*I*:25, *II*:23), adj. RT	*I*:16 (IQR 12-23) & 28 (IQR 23-35) *II*:15 (IQR 12-20) & 26 (IQR 22-33)	±1 year: *I*:62 (SE 5), *II*:44 (SE 6), p=0.01 ±2 years: *I*:59 (SE 5), *II*:43 (SE 5), p=0.03
3. Devine et al. (2001)	UK	C, P	*I*: LSM *II:* V/MLR	20 (70) *I*:10 (70) *II*:10 (70)	55.6 (43-72) *I*:59.3 (45-72) *II*:51.9 (43-65)	Anterior FOM (*I*:5, *II*:4), B and FOM and G and T(*I*:5, *II*:6)	N/A	N/A	Mandible res. (*I*:3, *II*:3), FPND, soft tissue radial rec.(RFFF(20)), adj. RT(*I*:4, *II*:5)	*I*:40.6 (10-60) *II*:27.9 (8-54)	*I*:65 (24.2), *II*:40 (21.1), p=0.024
4. Fang et al. (2013)	CHN	C, P	N/A	21 (100)	53.1 (41-69)	FOM(8),T(13)	T2: 5 T3: 5 T4: 11	N/A	Partial mandible res. (10), segm. res. (1), PG and limited FOM res. (12), SG and total FOM excision (9), uni- or bilateral ND (SND(18), MRND(3)), PORT(6)	64.3 (20-93)	57.1 (17.9)
5. Fang et al. (2014)	CHN	C, R	*I:* FF rec. *II:* no FF rec.	49 (78) *I*:20 (75) *II*:29 (79)	*I*:73.8 (70-83) *II*:73.5 (70-89)	B(*I*:2, *II*:4), FOM(*I*:4, *II*:6), G(*I*:8, *II*:8), *L*(*I*:2, *II*:6), T(*I*:4, *II*:5)	T2: *I*:1, *II*:4 T3: *I*:7, *II*:12 T4: *I*:12, *II*:13	N/A	No or marginal mandibulectomy (*I*:18, *II*:19), segm. Mandibulectomy (*I*:2, *II*:10), PORT (*I*:10, *II*:17)	≥12	*I*:69 (18.3), *II*:57 (19.3), p=0.039
6. Ghai et al. (2021)	IN	C	*I:*T1 without RT *II:*T2 without RT *III:*T1 and T2 with RT	54 (87) *I*:26 *II*:15 *III*:13	44 (11) (18-70)	B(54)	T1: 29 T2: 25	N0: 54	Res. with SOND, local flap, FF or PMMF, free fibula bone graft, PORT (13)	8.5 (IQR 4-13.5)	75 (32) *I*:75 (35), *II*:80 (32), *III*:69 (25)
7. Gu et al. (2021)	CHN	C, R	*I:*ND with submandibular gland preservation *II:* conventional ND	*I*:36 (63.9) *II*:131 (76.3)	*I*:48.6 *II*:53.4	T(*I*:15, *II*:51), B(*I*:9, *II*:35), G(*I*:7, *II*:23), FOM(*I*:5, *II*:22)	T1: *I*:14, *II*:56 T2: *I*:22, *II*:75	N0: *I*:36, *II*:131	Res. with or without submandibular gland preservation, flap rec. (*I*:2, *II*:12)	12	*I*:86.1 (22.7), *II*:71.0 (24.8), p=0.001
8. Hoene et al. (2021)	G	L, R	N/A	15 (66)	60 (13.2) (46-94)	FOM(4), A(4), B(2), T(3), L(1), P(1)	Tis: 1 T1: 6 T2: 4 T4: 4	N0: 14 N2: 1	Res., rec. with distant (8) or local (7) flap	One day preoperatively, ½, 1, 3, 6, 9, 12	Post-operative: 31.9 (26.9)
9. Larson et al. (2021)	US	C	*I:* lateral FOM *II*: anterior FOM *III*: alveolar ridge with FOM *IV*: No RT *V*: RT	24 (66) *I*:17 (35) *II*:4 (50) *III*:3 (100) *IV*:16 *V*:8	66.8 *I*:65.7 *II*:65.8 *III*:74.3	Lateral FOM (*I*:17), anterior FOM (*II*:4), alveolar ridge with FOM(*III*:3)	T1: *I*:12, *II*:3, *III*:3 T2: *I*:5, *II*:1	N0: *I*:8, *II*:3, *III*:1 N1: *I*:2, *III*:1 N2: *I*:2, *II*:1, *III*:1	FOM res., PG, marginal mandibulectomy, ND, rec. with thigh STSG, adj. RT (*I*:5, *II*:1, *III*:2)	41.1 (6-88) *I*:39.2 *II*:32.5 *III*:63.7	79.2 (25.2) *I*:85.3, *II*:50.0, p=0.01 *IV*:81 (25), *V*:75 (27), p=0.58

Table 1 (*continued*)

Author	Location	Type	Sub-groups	n (%male)	Age mean (SD) (range) in y	Site (n)	T stage (n)	N stage (n)	Treatment (n)	Timing of assessment in m (range)	Outcome mean (SD)
10. W. Li et al. (2013)	CHN	C, R	N/A	51 (80)	Med. 55 (22-75)	B(3), FOM(14), G(6), P(2), T(26)	T1: 3 T2: 16 T3: 24 T4: 8	N0: 38 N1: 8 N2: 4 N3: 1	Res., ALTFF rec., PO(C)RT (33)	(12-84)	42.7 (1.1)
11. W. Li et al. (2016)	CHN	C, P	*I*: PMMF *II:* RFFF	41 (83) *I*:17 (100) *II*:24 (71)	Med. 53.6 (22-65) *I*:82% <50 *II*:63% <50	T(*I*:12, *II*:18), FOM(*I*:5, *II*:6)	T1-2: *I*:8, *II*:10 T3-4: *I*:9, *II*:14	N/A	Res., rec., PO(C)RT (*I*:7, *II*:8)	(13-108)	*I*:43.4 (12.4), *II*:42.5 (6.2), p=0.817
12. X. Li et al. (2016)	CHN	C, P	*I*: RT pre-Tx *II*: RT post-Tx *III*:RT pre- & post-Tx *IV*: no RT	47 (72) *I*:5, *II*:24 *III*:9, *IV*:9	58.4 (44-72)	T(47)	T2:13 T3: 23 T4: 11	N/A	HG, RFFF rec., marginal mandible rec. (9), SND(43), MRND(4), adj. RT(*I*:5, *II*:24, *III*:9)	24	Post-Tx: 92.6 (18) *I*:90, *II*:94, *III*:94, *IV*:89, p>0.05
13. Ochoa et al. (2020)	US	C, R	N/A	39 (54)	64.4 (32-78)	T(39)	Tis: 11 T1: 24 T2: 4	Unknown N: 11, N0: 26, N1: 1, N2: 1	Res., ND (14)	28.7 (6-80.4)	97.4 (11.2)
14. Rogers et al. (2004)	UK	L	*I:* nil *II:* rim res. *III:* segment res.	224 (66) *I*:123 (63) *II*:44 (68) *III*:57 (68)	61 (SD 13), 41% 65+ *I*:37% 65+ *II*:43% 65+ *III*:47% 65+	B(*I*:27, *II*:8, *III*:14), A(*II*:7,*III*:22), FOM(*I*:33, *II*:26, *III*:17), T(*I*:63,*II*:3, *III*:4)	T1-4: 224	N/A	Mandibular res. (*II*:44, *III*:57), soft tissue FF (*I*:74, *II*:37), composite FF rec. (*III*:57), adj. RT (*I*:35, *II*:16, *III*:29)	6 (4.5-9.0) 12 (9.0-18.0) >18	72 (SE 2) *I*:79 (SE 3), *II*:70 (SE 5), *III*:59 (SE 5), KW p=0.002, MW p=0.11
15. Rogers et al. (2020)	UK	L, P	N/A	230(60)	50% <55 40% 55-64 28% 65-74 13% 75+	B(38), gum(24), T(87), FOM(69), other(12)	N/A	N/A	Res.(166), res. with RT(59), only RT(5), rec. with composite FF(45) or soft FF(103)	med.25 (IQR 20-28) med. 121 (IQR 117-124)	2y: 66.2 (SE 2.8) 10y: 71.2 (SE 2.8) p=0.08
16. Sakthivel et al. (2017)	IN	C, R	*I*: surgery *II*: adj. therapy	36 (78) *I*:10 *II*:26	Med. 43 (24-66)	T(36): tip (*I*:1, *II*:2), lateral border(*I*:6, *II*:8), tip with lateral border(*I*:2, *II*:10), lateral border with FOM(*I*:1, *II*:6)	T1: *I*:6, *II*:4 T2: *I*:4, *II*:22	N0: *I*:9, *II*:8 N1: *I*:1, *II*:10 N2: *I*:0, *II*:8	Unilateral extended SOND (*I*:3, *II*:7), bilateral extended SOND(*II*:12), FPND (*I*:1, *II*:7), PORT (26)	45 (14-65) med. 34	*I*:79 (SE 7.3), *II*:43.5 (SE 4.8), p<0.001
17. Seferin et al. (2020)	BR	C	*I*: sentinel lymph node biopsy *II*: cervical ND level I-III	*I*:15 (67) *II*:9 (100)	*I*:62.6 (10) *II*:62.2 (9.3)	RMT(*II*:4), lip(*II*:1), T(*I*:13, *II*:1), hard P(*I*:1), FOM(*I*:1, *II*:3)	T1: *I*:14, *II*:2 T2: *I*:1, *II*:5 T3: *II*:1 T4: *II*:1	N0: *I*:15, *II*:4 N+: *II*:5	Sentinel lymph node biopsy (*I*:15), cervical ND level I-III(*II*:9), adj. RT (*I*:1, *II*:6), concurrent CRT(*II*:1)	*I*:31.7 (SD 7.8) *II*:38.0 (SD 5.9)	*I*:86.7 (22.9), *II*:56.7 (30.0), MW p=0.041
18. Soares et al. (2018)	BR	C	N/A	47 (83)	61.8 (±8.4)	FOM(23), G(16), other(8)	T3: 8 T4: 39	N0: 26 N1: 9 N2: 10 N3: 2	Segm. mandibulectomy, myocutaneous flap (72%), FF rec. (28%), PORT (42), POCRT (3)	41.5	N/A

Table 1 (*continued*)

Author	Location	Type	Sub-groups	n (%male)	Age mean (SD) (range) in y	Site (n)	T stage (n)	N stage (n)	Treatment (n)	Timing of assessment in m (range)	Outcome mean (SD)
19. Vakil et al. (2012)	PK	C	N/A	30	N/A	N/A	N/A	N/A	N/A	N/A	N/A
20. Vora et al. (2017)	IN	C, P	N/A	65 (85)	50.5 (30-60)	A(12), B(42), RMT (4), T(7)	T1: 14 T2: 35 T3: 3 T4: 13	N0: 48 N1: 5 N2: 12	Mandibular res., PMMF rec., PORT(46), POCRT(19)	<3-24, mean 30	46.2 (22.2)
21. Wu et al. (2020)	CHN	C, R	*I*:classic ALTFF *II*:chimeric ALTFF	*I*:27 (96) *II*:21 (95)	*I*:46.9 (9.2) *II*:47.4 (9.8)	B(*I*:27, *II*:21)	T1: *I*:8, *II*:9 T2: *I*:18, *II*:10 T3: *I*:1, *II*:1 T4: *II*:1	N0: *I*:18, *II*:13 N1: *I*:5, *II*:6 N2: *I*:4, *II*:2	Res. with MRND, rec. with classical ALT perforator(*I*:27) or chimerical ALT perforator flap(*II*:21)	6	*I*:68.6 (13.6), *II*:70.7 (15.4), p=0.624
22. Yan et al. (2017)	CHN	L, P	*I*:long-term survivors (8y) *II*:non-survivors (<8y)	*I*:30 (57) *II*:25 (56)	*I*:57.7 (35-81) *II*:59.5 (35-90)	G (*I*:13, *II*:8), T (*I*:7, *II*:13), other (*I*:10, *II*:4)	T1-2: *I*:22, *II*:12 T3-4: *I*:8, *II*:13	N/A	FF rec. (*I*:14, *II*:18), ND (*I*:20, *II*:25), PORT (*I*:9, *II*:16)	3, 12, and 96	At diagnosis: *I*:83.3 (30.3), *II*:78.0 (29.1) 3m: *I*:53.4 (18.6) 1y: *I*:69.0 (24.7), *II*:46.6 (29.1) 8y: *I*:66.7 (24.0)
23. Yang et al. (2014)	CHN	L, R	N/A	34 (74)	Med. 53.4 (28-65)	A(13), B(7), FOM(9), T(5)	T1-2: 10 T3-4: 23	N/A	Mandible res., fibula FF rec.	27.6 (12-48) 1-3 y: 24 >3 y: 10	33.1 (16.1)
24. Yuan et al. (2016)	CHN	L, P	*I*:RFFF *II*:ALTFF	67 (67) *I*:46 (72) *II*:21 (76)	Med. 56.2 (33-74)	T(67)	T1-2: *I*:25, *II*:13 T3-4: *I*:21, *II*:8	N/A	TG(*II*:16), PG (*I*:46, *II*:5), rec.(*I*:46, *II*:21), PO(C)RT(*I*:17, *II*:6)	6 and 12	6m: *I*:64.0 (11.0), *II*:64.0 (10.2) 12m: *I*:68.5 (10.6), *II*:71.0 (9.5), p=0.490 *I*: p=0.004 *II*: p=0.036
25. Yue et al. (2018)	CHN	C, P	*I*:tongue *II*:other *III*:no rec. *IV*:rec	139 (65) *I*:68 (63), *II*:71 (66) T2: *III*:53 (57), *IV*:39 (67) T3-4: *III*:24 (79), *IV*:23 (65)	% under 70: 24% *I*:28%, *II*:20% T2: *III*:85%, *IV*:90% T3-4: *III*:88%, *IV*:83%	B and FOM and RMT and P(71), T(68)	T2: *I*:53, *II*:39 T3-4: *I*:15, *II*:32	N/A	Maxillectomy or mandibulectomy (*I*:30, *II*:42, *III*:36, *IV*:49), ND (*I*:68, *II*:71, *III*:77, *IV*:62), rec. (RFFF(48), ATF(9), FOMF(5)), PORT(*I*:12, *II*:12, *III*:6, *IV*:18), Neo-adj. CRT (47)	>12	*I*:67.3 (16.9), *II*:73.9 (19.6), p=0.036 T2: *III*:72.6 (17.9), *IV*:73.1 (17.6), p=0.888 T3/T4: *III*:57.3 (20.2), *IV*:76.1 (14.1), p=0.001
26. Zhang et al. (2013)	CHN	C	*I*:≤ 40 years *II*:≥ 40 years	*I*:21 (43) *II*:42 (43)	*I*:34.0 (5.2) (22-40) *II*:58.9 (7.4) (42-74)	T(63)	T1-2: *I*:16, *II*:32 T3-4: *I*:5, *II*:10	N0: *I*:16, *II*:32 N1: *I*:3, *II*:6 N2: *I*:2, *II*:4	Res., flap rec. (*I*:6, *II*:12), PO(C)RT(*I*:8, *II*:16)	*I*: med. 44.4 (12-144) *II*: med. 38.4 (24-120)	*I*:87.5 (1.3), *II*:86.7 (1.7), p=0.37

Table 1 (*continued*)

Author	Location	Type	Sub-groups	n (%male)	Age mean (SD) (range) in y	Site (n)	T stage (n)	N stage (n)	Treatment (n)	Timing of assessment in m (range)	Outcome mean (SD)
27. Zhang et al. (2020)	CHN	C,R	N/A	65 (86)	Med. 49 (25-70)	T(65)	T1: 4 T2: 8 T3: 31 T4: 22	N0: 27 N1: 12 N2: 23 N3: 3	Res. with ALTFF rec.	≥12	41.2 (13.2)

Med.=median, m=months, N/A=not applicable, SD=Standard Deviation, SE=Standard Error, Tx=treatment, y=years

Location: BR=Brazil, CHN=China, G=Germany, IN=India, PK=Pakistan, UK=United Kingdom, US=United States of America.

Type: C=cross-sectional study or L=longitudinal study, P=prospective study or R=retrospective study.

Site and treatment: A=alveolus, B=buccal, FOM=floor of mouth, G=gingival, L=lip, P=palate, RMT=retromolar trigone, T=tongue.

Sub-groups and treatment: adj.=adjuvant, ALTFF=anterolateral thigh perforator free flap, ATF=anterolateral thigh flap, CIS=carcinoma in situ, CRT=chemo radiotherapy, DCIA=deep circumflex iliac artery, FF=free flap, FOM=floor of mouth, FOMF=fibular osteomyocutaneous flap, FPND=functional preserving neck dissection, HG=hemiglossectomy, LSM=lip-split mandibulotomy, MRND=modified radical neck dissection, ND=neck dissection, nil=no resection, PG=partial glossectomy, PMMF=pectoralis major myocutaneous flap, PO(C)RT=post-operative (chemo) radiotherapy, rec.=reconstruction, res.=resection, RFFF=radial forearm free flap, RT=radiotherapy, segm.=segmental, SG=subtotal glossectomy, SND=selective neck dissection, SOND=supraomohyoid neck dissection, STSG=split-thickness skin graft, TG=total glossectomy, V/MLR=visor or mandibular lingual release.

Assessment: IQR=Inter Quartile Range, KW=Kruskal Wallis, m=months, MW=Mann Whitney

Table 2. MINORS assessment tool

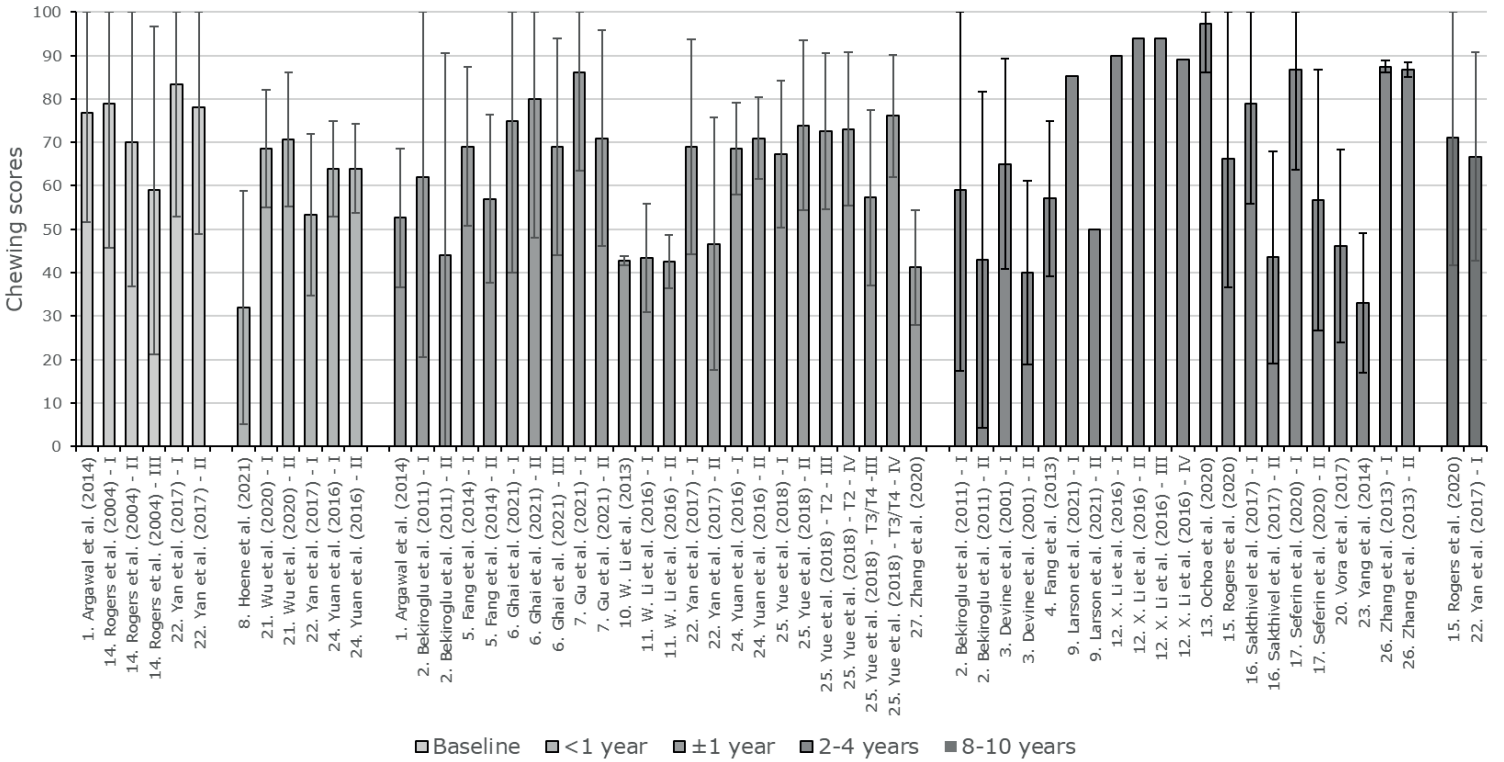
	Items													
Author	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**Total**	**%**
1. Agarwal et al. (2014)	1	2	2	2	0	2	1	0	N/A	N/A	N/A	N/A	10/16	63
2. Bekiroglu et al. (2011)	2	2	1	2	0	2	1	0	1	1	1	2	15/24	63
3. Devine et al. (2001)	2	1	1	2	0	2	1	0	N/A	N/A	N/A	N/A	9/16	56
4. Fang et al. (2013)	2	1	0	2	0	2	1	0	1	2	1	2	14/24	58
5. Fang et al. (2014)	2	2	2	2	0	2	1	0	N/A	N/A	N/A	N/A	11/16	69
6. Ghai et al. (2021)	2	2	2	2	0	2	2	0	1	2	1	2	18/24	75
7. Gu et al. (2021)	2	2	0	2	0	2	2	0	2	2	2	2	18/24	75
8. Hoene et al. (2021)	2	1	0	2	0	2	2	0	N/A	N/A	N/A	N/A	9/16	56
9. Larson et al. (2021)	2	2	1	2	0	2	1	0	1	2	1	2	16/24	67
10. W. Li et al. (2013)	2	2	0	2	0	2	1	0	N/A	N/A	N/A	N/A	9/16	56
11. W. Li et al. (2016)	2	2	2	2	0	2	1	0	1	2	1	2	17/24	71
12. X. Li et al. (2016)	1	2	2	2	0	2	1	0	N/A	N/A	N/A	N/A	10/16	63
13. Ochoa et al. (2020)	1	2	2	2	0	2	1	0	1	0	0	2	13/24	54
14. Rogers et al. (2004)	2	2	2	2	0	2	1	0	1	2	1	2	17/24	71
15. Rogers et al. (2020)	2	2	1	2	0	2	1	0	N/A	N/A	N/A	N/A	10/16	63
16. Sakthivel et al. (2017)	1	1	0	2	0	2	1	0	1	2	1	2	13/24	54
17. Seferin et al. (2020)	2	1	2	2	0	2	1	0	1	2	1	2	16/24	67
18. Soares et al. (2018)	2	1	2	1	0	2	1	0	N/A	N/A	N/A	N/A	9/16	56
19. Vakil et al. (2012)	2	1	1	1	0	2	0	0	N/A	N/A	N/A	N/A	7/16	44
20. Vora et al. (2017)	2	2	2	2	0	1	2	0	N/A	N/A	N/A	N/A	11/16	69
21. Wu et al. (2020)	2	2	0	2	0	2	2	0	2	2	2	2	18/24	75
22. Yan et al. (2017)	2	2	1	2	0	2	2	0	1	2	2	2	18/24	75
23. Yang et al. (2014)	2	1	0	2	0	2	2	0	N/A	N/A	N/A	N/A	9/16	56
24. Yuan et al. (2016)	2	2	2	2	0	2	1	0	1	2	1	2	15/24	63
25. Yue et al. (2018)	2	2	1	2	0	2	0	0	1	2	2	2	16/24	67
26. Zhang et al. (2013)	2	2	2	2	0	2	1	0	1	2	2	2	18/24	75
27. Zhang et al. (2020)	2	2	1	2	0	2	1	0	N/A	N/A	N/A	N/A	10/16	63

Items:
1. A clearly stated aim. **2.** Inclusion of consecutive patients. **3.** Prospective collection of data.
4. Endpoints appropriate to the aim of the study. **5.** Unbiased assessment of the study endpoint.
6. Follow-up period appropriate to the aim of the study. **7.** Loss to follow-up less than 5%.
8. Prospective calculation of the study size.

Additional criteria in case of comparative study:
9. An adequate control group. **10.** Contemporary groups. **11.** Baseline equivalence of groups.
12. Adequate statistical analyses.

The items are scored 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate).
The total ideal score being 16 for non-comparative studies and 24 for comparative studies.
N/A= not applicable

Figure 2. QoL chewing scores clustered by time



QoL Chewing scores (mean ±SD) clustered by time (baseline, ≤1 year, ±1 year, 2-4 years, 8-10 years). In case SE instead of SD was provided, SD scores were calculated as $SD = SE * \sqrt{N}$, where N = the number of participants

Subgroups of studies: 2=Bekiroglu et al. (2011) (*I*:no RT, *II*:RT); 3=Devine et al. (2001) (*I*:LSM, *II*:V/MLR); 5=Fang et al. (2014) (*I*:FF rec., *II*:no FF rec.); 6=Ghai et al. (2021) (*I*:T1 without RT, *II*:T2 without RT, *III*:T1 and T2 with RT); 7=Gu et al. (2021) (*I*:ND with submandibular gland preservation, *II*:conventional ND); 9=Larson et al. (202) (*I*:lateral FOM, *II*:anterior FOM, *III*:alveolar ridge with FOM); 11=W. Li et al. (2016) (*I*:PMMF, *II*:RFFF); 12=X. Li et al. (2016) (*I*:RT pre-Tx, *II*:RT post-Tx, *III*:RT pre- and post-Tx, *IV*:no RT); 14=Rogers et al. (2004) (*I*:nil, *II*:rim res., *III*:segment res.); 16=Sakthivel et al. (2017) (*I*:surgery, *II*:adjuvant therapy); 17=Seferin et al. (2020) (*I*:sentinel lymph node biopsy, *II*:cervical ND level I-III); 21=Wu et al. (2020) (*I*:classic ALTFF, *II*:chimeric ALTFF); 22=Yan et al. (2017) (*I*:long-term survivors, *II*:non-survivors); 24=Yuan et al. (2016) (*I*:RFFF, *II*:ALTFF); 25=Yue et al. (2018) (*I*:tongue, *II*:other, *III*:no rec., *IV*:rec.); 26=Zhang et al. (2013) (*I*:≤ 40 years, *II*:≥ 40 years).

ALTFF=anterolateral thigh perforator free flap, FF=free flap, FOM=Floor of mouth, LSM=lip-split mandibulotomy, ND=neck dissection, nil=no resection, PMMF=pectoralis major myocutaneous flap, rec= reconstruction, RFFF=radial forearm free flap, res=resection, RT=radiotherapy, SD=standard deviation, SE=Standard Error, Tx=Treatment, V/MLR=visor or mandibular lingual release

Discussion

HR-QoL is often impaired in patients with oral cancer,[50] and these patients face challenges in masticatory function caused by the tumor itself or oncological treatment.[51] Therefore, this review described the HR-QoL mastication scores in patients treated for oral cancer, as measured with the UW-QoL questionnaire. The UW-QoL mastication scores ranged from 31.9 to 97.4.[29,49] However, there was a wide variety in methodology (e.g., patient groups, treatment, assessment moment), making it impossible to compare outcome scores.

Strengths and limitations

This review is strengthened by the fact that the PRISMA guidelines were followed. Another strength of this review is the use of the UW-QoL questionnaire. This questionnaire has been extensively researched, developed and validated, and is available in several languages.[52] Studies utilizing the UW-QoL questionnaire have been selected in an attempt to obtain standardized outcome measures. However, our review shows that there is a wide variety in the way the outcomes of the UW-QoL questionnaire are reported, making it difficult to compare data. Another limitation of this review is the overall quality of the included studies. None of the studies had a prospective calculation of the sample size. In addition, some studies had a small number of patients or did not include all eligible patients in their study. Therefore, we cannot exclude a possible bias introduced by differences in patients that participated in the studies. In addition, there was a large heterogeneity between and within studies, both in demographic-, tumor- and treatment details, and in reported outcomes. Tumor site was too heterogeneous for adequate comparison between studies, despite our restriction to oral cancer. Eight studies were restricted to tongue cancer.[24,34,39,40,43,45,49,53] Other studies included several tumor sites within the oral cavity. Due to this heterogeneity, the variation in reported outcomes, and the heterogeneous sub-groups between studies, it was impossible to perform a meta-analysis. Therefore, only a descriptive analysis of the results is provided. In addition, underreporting study details was common across studies, contributing to the inability to compare findings. To quantify this underreporting, the MINORS assessment tool was used.[22] This is the best suitable tool to assess methodological quality of non-randomized surgical studies. However, the combined scores as measured with the MINORS assessment tool did not identify the underreporting in studies as such, despite the noticeable flaws. One problem of the assessment tool is that the scores for each item range from 0 to 2, where a score of 1 indicates that something is reported but inaccurate. When all items are reported but inaccurate, this will therefore lead to a total score of 50%. One improvement could be to further specify missing items, to get a more detailed image of methodological shortcomings.

Another focus of attention is the survey follow-up time. Twenty of the 27 studies had patients complete the questionnaire only once, making it impossible to evaluate changes in chewing capacity.[23,26,28,30,32-40,42,45-49,53] Three of these studies had an assessment range of one year or less.[23,28,33] Patients were asked to complete the questionnaire at baseline in five studies.[24,27,29,39,41] However, one study failed to report the data at baseline[39] and another study did not report follow-up data in a table.[27] Rogers et al. included 230 patients, however, only 111 of them filled in the questionnaires 2 and 10 years after treatment.[31]
As stated in the method section, our literature search for this review was limited by publication language and eligibility criteria, and therefore selection bias might have occurred. Moreover, reporting bias may have occurred as statistically significant studies in general have a higher likelihood of publication.

Future research

There is a need for standardized methodology across studies, enabling comparison of data. For review and comparison purposes, criteria should be narrowed down and limited to a specific type of (oral) cancer. Ideally, HR-QoL questionnaires should be an integrated part of cancer treatment, because they are a non-invasive way to obtain information about the effect of treatment on patients' HR-QoL. In addition, a baseline assessment followed by multiple assessments over time is favored to avoid misinterpretation of HR-QoL by a single outcome measure, and to be able to identify changes in HR-QoL over time. Finally, we recommend a combination of (a) HR-QoL questionnaire(s) with an objective measurement of chewing function in patients treated for oral cancer in future research. This can contribute to a better understanding of differences between objective findings and the patients' subjective perception.

Conclusion

The results of this review provide insight in the available literature regarding HR-QoL in patients treated for oral cancer with an emphasis on masticatory ability after primary curative treatment. Currently, there is a lack of comparable HR-QoL studies regarding mastication in oral cancer patients. This prevents identifying possible relations between oral cancer treatment, masticatory ability and QoL. Our findings underline the flaws in the available literature and highlight the necessity for improvement in future HR-QoL research.

Appendix

Appendix 1. PubMed (MEDLINE), Embase, and Cochrane searches

Search	PubMed 02-11-2021	Result
#1	"Head and Neck Neoplasms"[MeSH] OR "Jaw Neoplasms"[MeSH] OR Gingival cancer*[tiab] OR Gingival carcinom*[tiab] OR Gingival Neoplasm*[tiab] OR Head and Neck Cancer*[tiab] OR Head and Neck Carcinom*[tiab] OR Head and Neck Neoplasm*[tiab] OR Jaw Cancer*[tiab] OR Jaw Carcinom*[tiab] OR Jaw Neoplasm*[tiab] OR Lip Cancer*[tiab] OR Lip carcinom*[tiab] OR Lip Neoplasm*[tiab] OR Mandib* Cancer*[tiab] OR Mandib* Carcinom*[tiab] OR Mandib* Neoplasm*[tiab] OR Maxill* Cancer*[tiab] OR Maxill* Carcinom*[tiab] OR Maxill* Neoplasm*[tiab] OR mouth cancer*[tiab] OR mouth carcinom*[tiab] OR mouth neoplasm*[tiab] OR oral cancer*[tiab] OR oral carcinom*[tiab] OR oral neoplasm*[tiab] OR Palat* Cancer*[tiab] OR Palat* Carcinom*[tiab] OR Palat* Neoplasm*[tiab] OR Tongue Cancer*[tiab] OR Tongue Carcinom*[tiab] OR Tongue Neoplasm*[tiab]	363676
#2	"mastication"[MeSH] OR "Dental Occlusion"[MeSH] OR Bite[tiab] OR Biting[tiab] OR Chew*[tiab] OR Comminut*[tiab] OR Dental occlusion*[tiab] OR Tooth occlusion*[tiab] OR Teeth occlusion*[tiab] OR Masticat*[tiab] OR Occlusal Forc*[tiab] OR Triturat*[tiab]	89165
#3	"Quality of Life"[MeSH] OR Quality of Life[tiab] OR QoL[tiab] OR Health Related Quality of Life[tiab] OR OHRQoL[tiab] OR HRQoL[tiab] OR UW-QOL[tiab] OR EQ-5D[tiab] OR EORTC-QLQ-C30[tiab] OR EORTC-QLQ-HN35[tiab] OR SWAL-QoL[tiab] OR MFIQ[tiab] OR OHIP[tiab] OR LORQ[tiab]	378657
#4	#1 AND #2 AND #3	328

Search	Embase 02-11-2021	Result
#1	'Head and neck tumor'/exp OR ('Gingival cancer*' OR 'Gingival carcinom*' OR 'Gingival neoplasm*' OR 'Head and neck cancer*' OR 'Head and neck carcinom*' OR 'Head and neck neoplasm*' OR 'Jaw cancer*' OR 'Jaw carcinom' OR 'Jaw neoplasm*' OR 'Lip cancer*' OR 'Lip carcinom*' OR 'Lip neoplasm*' OR 'Mandibul* cancer*' OR 'Mandibul* carcinoma*' OR 'Mandibul* neoplasm*' OR 'Maxill* cancer*' OR 'Maxill* carcinoma*' OR 'Maxill* neoplasm*' OR 'Mouth cancer*' OR 'Mouth carcinom*' OR 'Mouth neoplasm*' OR 'Oral cancer*' OR 'Oral carcinom*' OR 'Oral neoplasm*' OR 'Palat* cancer*' OR 'Palat* carcinom*' OR 'Palat* neoplasm*' OR 'Tongue cancer*' OR 'Tongue carcinom*' OR 'Tongue neoplasm*'):ti,ab,kw	363101
#2	'Mastication'/exp OR 'Tooth occlusion'/exp OR ('Bite' OR 'Biting' OR 'Chew*' OR 'Comminut*' OR 'Dental occlusion*' OR 'Tooth occlusion*' OR 'Teeth occlusion*' OR 'Masticat*' OR 'Occlusal Forc*' OR 'Triturat*'):ti,ab,kw	103910
#3	('Quality of Life'/exp OR 'Quality of life assessment'/exp OR ('Quality of Life' OR 'QoL' OR 'Health Related Quality of Life' OR 'OHRQoL' OR 'HRQoL' OR 'UW-QOL' OR 'EQ-5D' OR 'EORTC-QLQ-C30' OR 'EORTC-QLQ-HN35' OR 'SWAL-QoL' OR 'MFIQ' OR 'OHIP' OR 'LORQ'):ti,ab,kw)	704333
#4	#1 AND #2 AND #3	481

Search	Cochrane 02-11-2021	Result
#1	((Gingiva* NEAR cancer*) OR (Gingiva* NEAR carcinom*) OR (Gingiva* NEAR Neoplasm*) OR (Head NEAR Neck NEAR Cancer*) OR (Head NEAR Neck NEAR Carcinoma*) OR (Head NEAR Neck NEAR Neoplasm*) OR (Jaw NEAR Cancer*) OR (Jaw NEAR Carcinom*) OR (Jaw NEAR Neoplasm*) OR (Lip NEAR Cancer*) OR (Lip NEAR carcinom*) OR (Lip NEAR Neoplasm*) OR (Mandib* NEAR Cancer*) OR (Mandib* NEAR Carcinom*) OR (Mandib* NEAR Neoplasm*) OR (Maxill* NEAR Cancer*) OR (Maxill* NEAR Carcinoma*) OR (Maxill* NEAR Neoplasm*) OR (mouth NEAR cancer*) OR (mouth NEAR carcinom*) OR (mouth NEAR neoplasm*) OR (oral NEAR cancer*) OR (oral NEAR carcinom*) OR (oral NEAR neoplasm*) OR (Palat* NEAR Cancer*) OR (Palat* NEAR Carcinom*) OR (Palat* NEAR Neoplasm*) OR (Tongue NEAR Cancer*) OR (Tongue NEAR Carcinom*) OR (Tongue NEAR Neoplasm*)):ti,ab,kw	11049
#2	(Bite OR Biting OR Chew* OR Comminut* OR (Dental NEAR occlusion*) OR (Tooth NEAR occlusion*) OR (Teeth NEAR occlusion*) OR Masticat* OR (Occlusal NEAR Forc*) OR Triturat*):ti,ab,kw	6783
#3	("Quality of Life" OR QoL OR "Health Related Quality of Life" OR OHRQoL OR HRQoL OR UW-QOL OR EQ-5D OR EORTC-QLQ-C30 OR EORTC-QLQ-HN35 OR SWAL-QoL OR MFIQ OR OHIP OR LORQ):ti,ab,kw	127562
#4	#1 AND #2 AND #3	53

Literature

1. Rivera C. Essentials of oral cancer. *Int J Clin Exp Pathol.* 2015.

2. Haraldstad K, Wahl A, Andenæs R, et al. A systematic review of quality of life research in medicine and health sciences. *Quality of Life Research.* 2019;28(10):2641-2650.

3. Valdez JA, Brennan MT. Impact of Oral Cancer on Quality of Life. *Dental clinics of North America.* 2018;62(1):143-154.

4. Deng H, Sambrook PJ, Logan RM. The treatment of oral cancer: an overview for dental professionals. *Aust Dent J.* 2011;56(3):244-252, 341.

5. Kerawala C, Roques T, Jeannon JP, Bisase B. Oral cavity and lip cancer: United Kingdom National Multidisciplinary Guidelines. *J Laryngol Otol.* 2016;130(S2):S83-S89.

6. Kirsch C. Oral cavity cancer. *Top Magn Reson Imaging.* 2007;18(4):269-280.

7. Chandu A, Smith AC, Rogers SN. Health-related quality of life in oral cancer: a review. *Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons.* 2006;64(3):495-502.

8. Taberna M, Gil Moncayo F, Jane-Salas E, et al. The Multidisciplinary Team (MDT) Approach and Quality of Care. *Frontiers in oncology.* 2020;10:85.

9. Buurman DJM, Speksnijder CM, Engelen B, Kessler P. Masticatory performance and oral health-related quality of life in edentulous maxillectomy patients: A cross-sectional study to compare implant-supported obturators and conventional obturators. *Clinical oral implants research.* 2020;31(5):405-416.

10. de Groot RJ, Wetzels JW, Merkx MAW, et al. Masticatory function and related factors after oral oncological treatment: A 5-year prospective study. *Head & neck.* 2019;41(1):216-224.

11. Petrovic I, Rosen EB, Matros E, Huryn JM, Shah JP. Oral rehabilitation of the cancer patient: A formidable challenge. *J Surg Oncol.* 2018;117(8):1729-1735.

12. de Groot RJ, Merkx MAW, Hamann MNS, et al. Tongue function and its influence on masticatory performance in patients treated for oral cancer: a five-year prospective study. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer.* 2020;28(3):1491-1501.

13. Vincent A, Kohlert S, Lee TS, Inman J, Ducic Y. Free-Flap Reconstruction of the Tongue. *Semin Plast Surg.* 2019;33(1):38-45.

14. Ji YB, Cho YH, Song CM, et al. Long-term functional outcomes after resection of tongue cancer: determining the optimal reconstruction method. *European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies.* 2017;274(10):3751-3756.

15. Kumar VV, Srinivasan M. Masticatory efficiency of implant-supported removable partial dental prostheses in patients with free fibula flap reconstructed mandibles: A split-mouth, observational study. *Clinical oral implants research.* 2018;29(8):855-863.

16. Carneiro-Neto JN, de-Menezes JD, Moura LB, Massucato EM, de-Andrade CR. Protocols for management of oral complications of chemotherapy and/or radiotherapy for oral cancer: Systematic review and meta-analysis current. *Medicina oral, patologia oral y cirugia bucal.* 2017;22(1):e15-e23.

17. Mosel DD, Bauer RL, Lynch DP, Hwang ST. Oral complications in the treatment of cancer patients. *Oral Dis.* 2011;17(6):550-559.

18. Wetzels JW, Merkx MA, de Haan AF, Koole R, Speksnijder CM. Maximum mouth opening and trismus in 143 patients treated for oral cancer: a 1-year prospective study. *Head & neck.* 2014;36(12):1754-1762.

19. Hassan SJ, Weymuller EA, Jr. Assessment of quality of life in head and neck cancer patients. *Head & neck.* 1993;15(6):485-496.

20. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med.* 2009;6(7):e1000100.

21. Rogers SN, Gwanne S, Lowe D, Humphris G, Yueh B, Weymuller EA, Jr. The addition of mood and anxiety domains to the University of Washington quality of life scale. *Head & neck.* 2002;24(6):521-529.

22. Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (minors): development and validation of a new instrument. *ANZ J Surg.* 2003;73(9):712-716.

23. Vakil M, Ali A, Shakir MM. Life quality assessment of patients suffering from oral cancer. *Medical Forum Monthly.* 2012;23(1):18-22.

24. Agarwal SK, Munjal M, Koul R, Agarwal R. Prospective evaluation of the quality of life of oral tongue cancer patients before and after the treatment. *Annals of palliative medicine.* 2014;3(4):238-243.

25. Bekiroglu F, Ghazali N, Laycock R, Katre C, Lowe D, Rogers SN. Adjuvant radiotherapy and health-related quality of life of patients at intermediate risk of recurrence following primary surgery for oral squamous cell carcinoma. *Oral oncology.* 2011;47(10):967-973.

26. Soares JRN, Dias FL, Lima R, et al. Assessment of quality of life in patients with advanced oral cancer who underwent mandibulectomy with or without bone reconstruction. *Revista da Associacao Medica Brasileira (1992).* 2018;64(8):710-716.

27. Rogers SN, Devine J, Lowe D, Shokar P, Brown JS, Vaugman ED. Longitudinal health-related quality of life after mandibular resection for oral cancer: a comparison between rim and segment. *Head & neck.* 2004;26(1):54-62.

28. Gu H, Xuan G, Zhou Y, Li M, Chen M, Wang Y. Functional outcomes after submandibular gland-sparing neck dissection in patients with oral squamous cell carcinoma. *International journal of oral and maxillofacial surgery.* 2021.

29. Hoene G, Gruber RM, Leonhard JJ, et al. Combined quality of life and posttraumatic growth evaluation during follow-up care of patients suffering from oral squamous cell carcinoma. *Mol Clin Oncol.* 2021;15(3):189.

30. Larson AR, Han M, Webb KL, et al. Patient-Reported Outcomes of Split-Thickness Skin Grafts for Floor of Mouth Cancer Reconstruction. *ORL; journal for oto-rhino-laryngology and its related specialties.* 2021;83(3):151-158.

31. Rogers SN, Lowe D. Health-related quality of life after oral cancer treatment: 10-year outcomes. *Oral surgery, oral medicine, oral pathology and oral radiology.* 2020.

32. Seferin MR, Pinto FR, Leite AKN, et al. The impact of sentinel lymph node biopsy on the quality of life in patients with oral cavity squamous cell carcinoma. *Brazilian journal of otorhinolaryngology.* 2020.

33. Wu X, Yang R, Yuan Y, et al. Application of a chimeric ALT perforator flap with vastus lateralis muscle mass in the reconstruction of the defects after radical resection of a buccal carcinoma: A retrospective clinical study. *J Surg Oncol.* 2020;122(4):632-638.

34. Zhang S, Wu S, Liu L, Zhu D, Zhu Q, Li W. Assessment of Quality of Life of Free Anterolateral Thigh Flap for Reconstruction of Tissue Defects of Total or Near-Total Glossectomy. *J Oncol.* 2020;2020:2920418.

35. Yue J, Zhuo S, Zhang H, Liu X, Zhang W. Long-term quality of life measured by the University of Washington QoL questionnaire (version 4) in patients with oral cancer treated with or without reconstruction with a microvascular free flap. *The British journal of oral & maxillofacial surgery.* 2018;56(6):475-481.

36. Fang QG, Shi S, Zhang X, Li ZN, Liu FY, Sun CF. Assessment of the quality of life of patients with oral cancer after pectoralis major myocutaneous flap reconstruction with a focus on speech. *Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons.* 2013;71(11):2004.e2001-2004.e2005.

37. Fang QG, Shi S, Li M, Zhang X, Liu FY, Sun CF. Free flap reconstruction versus non-free flap reconstruction in treating elderly patients with advanced oral cancer. *Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons.* 2014;72(7):1420-1424.

38. Li W, Yang Y, Xu Z, et al. Assessment of quality of life of patients with oral cavity cancer who have had defects reconstructed with free anterolateral thigh perforator flaps. *The British journal of oral & maxillofacial surgery.* 2013;51(6):497-501.

39. Li X, Sun Q, Guo S. Functional Assessments in Patients Undergoing Radial Forearm Flap Following Hemiglossectomy. *The Journal of craniofacial surgery.* 2016;27(2):e172-175.

40. Li W, Zhang P, Li R, Liu Y, Kan Q. Radial free forearm flap versus pectoralis major pedicled flap for reconstruction in patients with tongue cancer: Assessment of quality of life. *Medicina Oral, Patologia Oral y Cirugia Bucal.* 2016;21(6):e737-e742.

41. Yan YB, Meng L, Liu ZQ, et al. Quality of life in long-term oral cancer survivors: an 8-year prospective study in China. *Oral surgery, oral medicine, oral pathology and oral radiology.* 2017;123(1):67-75.

42. Yang W, Zhao S, Liu F, Sun M. Health-related quality of life after mandibular resection for oral cancer: reconstruction with free fibula flap. *Medicina oral, patologia oral y cirugia bucal.* 2014;19(4):e414-418.

43. Yuan Y, Zhang P, He W, Li W. Comparison of Oral Function: Free Anterolateral Thigh Perforator Flaps Versus Vascularized Free Forearm Flap for Reconstruction in Patients Undergoing Glossectomy. *Journal of Oral and Maxillofacial Surgery.* 2016;74(7):1500.e1501-1500.e1506.

44. Zhang X, Fang QG, Li ZN, Li WL, Liu FY, Sun CF. Quality of life in patients younger than 40 years treated for anterior tongue squamous cell carcinoma. *The Journal of craniofacial surgery.* 2013;24(6):e558-561.

45. Sakthivel P, DV KI, Singh CA, et al. Quality of life outcome measures using University of Washington questionnaire version 4 in early T1/T2 anterior tongue cancers with and without radiotherapy: A cross-sectional study. *Indian journal of cancer.* 2017;54(2):447-452.

46. Vora D, Shah J, Maharaja B. Quality of life assessment of oral cancer patients after mandibular resections using the University of Washington Quality of Life (Version 4) questionnaire: Reconstruction with pectoralis major myocutaneous flap. *Clinical Cancer Investigation Journal.* 2017;6(2):123-127.

47. Ghai S, Pillai A, Sharma Y, Singh R, Jain N, Sharma S. In spite of successful curative surgery for buccal mucosa carcinoma the health-related quality-of-life continues to remain poor. *Oral and maxillofacial surgery.* 2021.

48. Devine JC, Rogers SN, McNally D, Brown JS, Vaughan ED. A comparison of aesthetic, functional and patient subjective outcomes following lip-split mandibulotomy and mandibular lingual releasing access procedures. *International journal of oral and maxillofacial surgery.* 2001;30(3):199-204.

49. Ochoa E, Larson AR, Han M, et al. Patient-Reported Quality of Life After Resection With Primary Closure for Oral Tongue Carcinoma. *Laryngoscope.* 2020.

50. Lalla RV, Treister N, Sollecito T, et al. Oral complications at 6 months after radiation therapy for head and neck cancer. *Oral Dis.* 2017;23(8):1134-1143.

51. Namaki S, Matsumoto M, Ohba H, Tanaka H, Koshikawa N, Shinohara M. Masticatory efficiency before and after surgery in oral cancer patients: comparative study of glossectomy, marginal mandibulectomy and segmental mandibulectomy. *Journal of oral science.* 2004;46(2):113-117.

52. UW-QOL v4 Translations (2009). http://www.hancsupport.com/professionals/quality-life/qol-questionnaires/uw-qol/uw-qol-v4-translations. 2021.

53. Zhang PP, Meng L, Shen J, et al. Free radial forearm flap and anterolateral thigh flap for reconstruction of hemiglossectomy defects: A comparison of quality of life. *Journal of cranio-maxillo-facial surgery : official publication of the European Association for Cranio-Maxillo-Facial Surgery.* 2018;46(12):2157-2163.

Chapter 3

Reliability of the Mixing Ability Test testing masticatory performance in patients with head and neck cancer and healthy controls

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Abstract

Background

Treatment of patients with head and neck cancer can result in disrupted mastication. To measure masticatory performance in people with compromised mastication, the Mixing Ability Test (MAT) was developed. In this study, the reliability of the MAT was evaluated in patients with head and neck cancer and healthy controls.

Methods

Thirty-four patients with head and neck cancer and 42 healthy controls performed the MAT twice on the same day. To assess reliability, the Intraclass Correlation Coefficient ($ICC_{2,1}$), Standard Error of Measurement (SEM), Smallest Detectable Change (SDC), and Limits of Agreement (LoA) were calculated.

Results

A good (ICC=0.886) and moderate correlation (ICC=0.525) were found for patients and healthy controls, respectively. Patients had a worse mixing ability (mean=19.12, SD=4.56) in comparison to healthy controls (mean=16.42, SD=2.04). The SEM was 0.76 in patients, and 1.45 in healthy controls, with a SDC of 2.12 and 4.02, respectively. The LoA were -4.46 to 4.42 in patients, and -3.65 to 4.59 in healthy controls.

Conclusion

The MAT has a good reliability in patients with head and neck cancer and a moderate reliability in healthy controls.

Introduction

Mastication is a learned automatic complex process involving interaction of hard and soft tissues in order to grind a food bolus prior to swallowing.[1] It involves several nerves, muscles, and connective tissue structures, such as the tongue, masseter, temporalis and pterygoid muscles.[2] Many factors can affect efficient mastication, such as maximal biting force, maximal mouth opening, tongue function, tongue force, and number of occlusal units.[3] Loss of teeth, cavities, inadequate restorations, malocclusion, and periodontal diseases can negatively affect the chewing function.[4,5] In patients with head and neck cancer (HNC), mastication may be disrupted due to HNC or cancer treatment, which can result in affected motor and oral functioning. Because of this compromised mastication, tougher foods are more difficult to process because they require a higher muscle force and more chewing cycles.[6] Therefore, some patients switch their diet to softer foods, because the muscle force needed to break down food is too high.[7]

Treatment for HNC may consist of radiotherapy (RT), chemoradiotherapy (CHT), surgery, or a combination of these. Early-stage cancers are usually treated with either surgery or radiotherapy, while locally advanced cancers are treated with surgery followed by adjuvant radiation or chemoradiotherapy.[8] RT damages all cells receiving a radiation dose, including normal tissue cells surrounding the tumor. This damage to normal tissues can result in acute or long-term damage. Acute effects include pain, mucositis, dermatitis, decreased saliva production, or edema. Long term damage can consist of dysphagia, fibrosis, edema, ulcers, vascular toxicity, or osteoradionecrosis.[1,9,10] One of the most feared complications is osteoradionecrosis of the jaws. In order to prevent this, teeth can be extracted pre-treatment, or hyperbaric oxygen treatment post-treatment can be prescribed. However, this cannot always be achieved, causing serious deterioration in dental health.[1] Chemotherapy may show additional toxicities, for example by the enhancement of radiation-induced fibrosis of the muscles, edema or neuropathy.[9] Surgery may require wide resections of one or multiple sub sites, including tongue, floor of mouth, or lower gingiva.[11] Surgery may be combined with neck dissection or reconstruction of the tumor site by a tissue transfer. Impairments after surgery depend on volume of resection, tumor site and type of reconstruction. Patients may develop defects on soft tissues, bone, or dentition, which can lead to functional deficits in mastication, swallowing and speech. For example, tongue resection compromises lingual mobility and strength, and dental and mandibular surgery affect mastication.[1] Although survival rates have improved over time, morbidity remains high.[1] In order to determine the influence of HNC treatment on oral function, it is important to evaluate the masticatory performance in these patients.[12]

In previous research, different tests have been developed to measure mastication, such as comminution methods, sieve and optical scanning methods, gummy jelly as test food, and mixing ability methods.[13] Construct validity was positive in one method measuring mixing ability to test oral function: the Mixing Ability Test (MAT).[12] The MAT was specifically developed for patients with HNC,[7,12,14] consisting of a relatively soft material (wax), to make sure patients with compromised mastication would still be able to perform this test. This test has proven to be sensitive in measuring mastication in adults with dental deficits, and children with cerebral palsy.[15,16] However, reliability of this test has not been evaluated in patients with HNC yet. The aim of this study was therefore to provide insight in the reliability of the MAT, by investigating test-retest reproducibility, standard error of measurement, smallest detectable change, and limits of agreement in patients with HNC. In order to make a comparison between patients and healthy subjects, reliability of the MAT was tested in healthy controls as well.

Methods

Patients were included when they were 18 years or older, were diagnosed with oral, oropharyngeal, hypopharyngeal, laryngeal, or unknown primary HNC and were treated with a curative intent at the University Medical Center Utrecht (UMCU), the Netherlands between September 2016 and June 2018. Patients with recurrent or residual disease, cognitive impairments, and patients having trouble understanding or reading the Dutch language were excluded. Healthy controls were recruited through a poster at the outpatient clinic, between November 2018 and February 2019. Healthy controls were included when they were 18 years or older. The study protocol for patients with HNC was approved by the Medical Ethics Committee of the Netherlands (NL45051.029.13), which is part of the NET-QUBIC research.[17] The study protocol for healthy controls was approved by the Medical Ethics Committee of the UMCU (18/701). Patient data about age, sex, tumor stage,[18] tumor location, treatment, number of teeth (maximal 32 teeth) and number of occlusal units (maximal 16 units)[19] were collected. In addition, data about age, sex, number of teeth and number of occlusal units were collected for healthy controls. All participants signed informed consent before participation.

Mixing Ability Test

The Mixing Ability Test (MAT) consists of two layers of wax, with the colors red and blue (Plasticine modelling wax, non-toxic DIN EN-71, art. nos. crimson 52801 and blue 52809, Stockmar, Kalten Kirchen, Germany).[7,12,14,20] The total thickness is 3 mm, with a diameter of 30 mm. The outcome variable is called the Mixing Ability Index (MAI), and ranges between 5-30, where a lower MAI score implies a better mixed tablet and better masticatory

performance. A subject was asked to chew on this tablet 20 times in order to mix the two colors. The tablet is then flattened, pressed to a thickness of 2 mm, and scanned on both sides using a high-quality scanner (Epson® V750, Long Beach, CA, USA). The scanned images are then processed using Adobe Photoshop CS3 extended (Adobe, San Jose, CA, USA). The histograms of both sides of the flattened and scanned wax tablet are added to obtain red and blue intensity distributions. The spread of the color intensities is measured.[12] Subjects were instructed to chew 20 times on two different tablets in order to test reliability. The interim period between the two tests was approximately 2 hours for patients with HNC, and 30 minutes for healthy controls, with the same testing conditions for all participants.

Statistical Analyses

Test-retest reproducibility of the MAT was tested by a two-way random, single measurement, absolute agreement, Intraclass Correlation Coefficient ($ICC_{2,1}$), calculated as $\frac{MS_R - MS_E}{MS_R + (k-1)MS_E + \frac{k}{n}(MS_C - MS_E)}$, in which MS_R = mean square of rows; MS_E = mean square for error; MS_C = mean square for columns; k = number of measurements; and n = number of subjects. Cut-off points for the ICC were chosen as poor (<0.5), moderate (0.5 to 0.75), good (0.75 to 0.90), and excellent (>0.90).[21,22] Standard Error of Measurement (SEM) was calculated as $SEM = \mathrm{SD} * \sqrt{(1 - \mathrm{ICC})}$.[23] For the SD, the Standard Deviation of the difference between the two MATs was used. SEM percent change was calculated as $SEM\% = (SEM/\bar{X}) * 100$, in which $\bar{X}$ = the mean of all measurements of test and retest. Smallest detectable change (SDC) was calculated as $SDC = 1.96 * \sqrt{2} * SEM$.[24,25] The SDC percent change was calculated as $SDC\% = (SDC/\bar{X}) * 100$, in which $\bar{X}$ = the mean of all measurements of test and retest. In order to check for systematic bias, variability and agreement, Bland-Altman plots were constructed by plotting the test-retest difference versus the mean value of the test and retest. Agreement between test and retest was summarized using the mean difference and SD of the difference, and the 95% Limits of Agreement (LoA) were calculated as $LoA = Mean \pm 1.96 * SD$.[26]

A power analysis was conducted, in which an ICC of at least 0.7 was expected. A p_1 value of 0.9 was chosen, therefore the sample size had to be at least 18.4.[27] In addition, a comparable study in children with cerebral palsy showed a sample size of 25 to 30 patients,[15] therefore it was chosen to include at least 30 subjects.

Data were tested for normality using a Shapiro-Wilk test. Because data were not normally distributed, a Wilcoxon Signed Ranks test was conducted to examine differences between test and retest for both patients with HNC and healthy controls, and a Kruskal-Wallis test was conducted to examine differences in MAT scores according to age and sex. A Mann-

Whitney U test was run to test for differences between patients and healthy controls regarding age, number of teeth, and number of occlusal units, and a chi-square test was run to test for differences regarding sex. All analyses were performed using Statistical Package for the Social Sciences (SPSS) version 25 (Chicago, IL). A p-value below 0.05 was considered statistically significant.

Results

Thirty-four patients with HNC and 42 healthy controls performed the MAT twice within a time interval of two hours. In the patient group, eleven patients performed the test before HNC treatment, six patients 3 months after treatment, five patients 6 months after treatment, five patients 12 months after treatment, and seven patients 24 months after treatment. No missing data were reported. In Table 1, subject characteristics are depicted for both patients with HNC and healthy controls.

Table 1. Characteristics of patients with head and neck cancer and healthy controls

Characteristics	Patients (n = 34)	Healthy controls (n = 42)	p-value
Age (median, IQR)	64 (9)	31 (27)	<0.001*†
Sex			
Male	29 (85%)	20 (48%)	0.001*‡
Female	5 (15%)	22 (52%)	
Number of teeth (median, IQR)	30 (16)	30 (4)	0.968†
Number of occlusal units (median, IQR)	12 (16)	12 (4)	0.641†
Tumor site			
Oropharynx	16 (47%)	NA	-
Larynx	10 (29%)		
Oral cavity	5 (15%)		
Hypopharynx	2 (6%)		
Unknown primary tumor	1 (3%)		
Tumor Stage			
I	7 (20.5%)	NA	-
II	7 (20.5%)		
III	5 (15%)		
IV	15 (44%)		
Primary Treatment			
RT	15 (44%)	NA	-
CRT	13 (38%)		
Surgery	4 (12%)		
Surgery with PORT	2 (6%)		

*: p≤0.001, †: Mann-Whitney U test, ‡: Chi-square test
CRT: Chemoradiotherapy, IQR: Interquartile Range, PORT: Post-Operative Radiotherapy, RT: Radiotherapy

As seen in Table 2, the ICC for patients with HNC (0.886; 95% CI=0.784-0.942) showed a good correlation between the test and retest, and a moderate correlation for healthy controls (ICC=0.525; 95% CI=0.272-0.712). The SEM was 0.76 (4.0%) in patients, and 1.45 (9.0%) in healthy controls, with an SDC of 2.12 (11.1%) and 4.02 (24.8%), respectively. The SEM values indicate that there was an expected random variation in all MAT scores of 0.76 points (4.0%) for patients with HNC and 1.45 points (9.0%) for healthy controls.[21] The SDC values indicate that the difference between two tests needs to be at least 2.12 points (11.1%) for patients with HNC and 4.02 points (24.8%) for healthy controls to be considered a true change in masticatory performance which is not caused by a measurement uncertainty. The Bland-Altman plots (Figure 1 and 2) show that 95% of the data lie between the LoA, with a consistent variability, indicating no systematic variation in performance between two measurements.

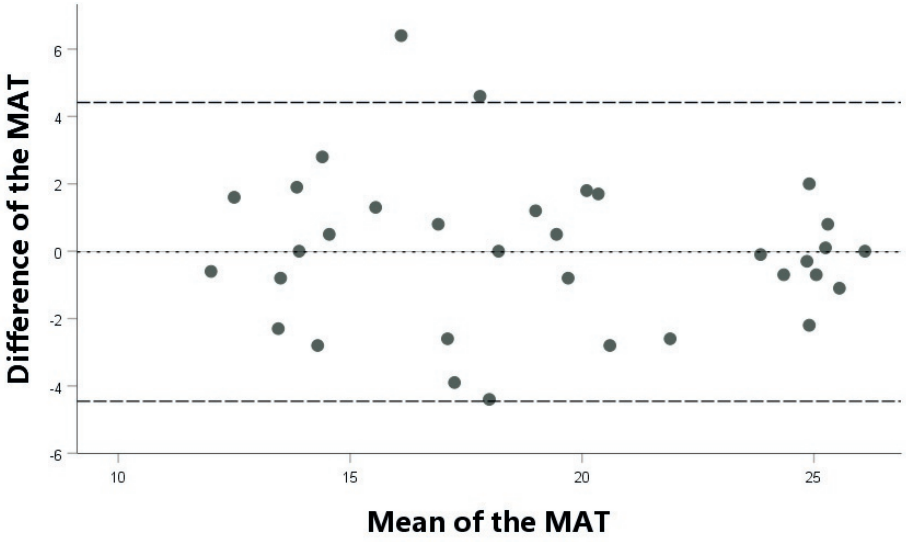
Table 2. Reliability of the Mixing Ability Test for patients with head and neck cancer and healthy controls

	Patients (n = 34)	**Healthy Controls (n = 42)**
Test mean (SD)	19.12 (4.56)	16.42 (2.04)
Test median (IQR)	19.30 (8.68)	15.80 (2.60)
Retest mean (SD)	19.14 (4.80)	15.95 (2.30)
Retest median (IQR)	19.20 (9.58)	15.65 (3.13)
Difference test-retest, mean (SD)	-0.02 (2.26)	0.47 (2.10)
$ICC_{2,1}$	0.886	0.525
95% CI	0.784 - 0.942	0.272 - 0.712
SEM	0.76	1.45
SEM%	4.0%	9.0%
SDC	2.12	4.02
SDC%	11.1%	24.8%
95% LoA	-4.46 to 4.42	-3.65 to 4.59

CI: Confidence Interval, ICC: Intraclass Correlation Coefficient, IQR: Interquartile Range, LoA: Limits of Agreement, SEM: Standard Error of Measurement, SDC: Smallest Detectable Change

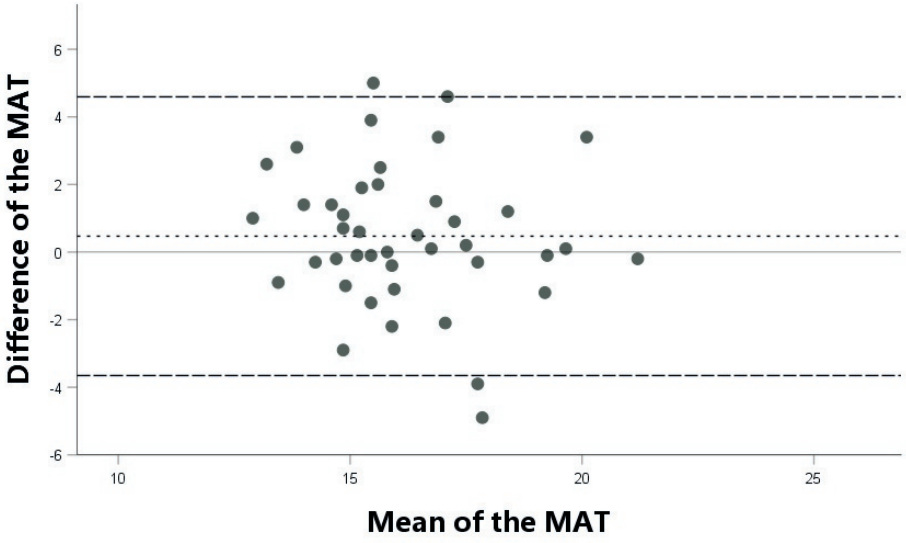
Test and retest showed no significant differences for both patients (Z=-0.206, p=0.837) and healthy controls (Z=-1.406, p=0.160). Age and sex were significantly different between patients and healthy controls (p<0.001 and p=0.001, respectively). A significant effect of age on MAT outcome in both patients and healthy controls was observed (test: $\chi^2(6)=19.812$; p=0.003, retest: $\chi^2(6)=16.127$; p=0.013), in which a higher age leads to a higher MAT score and therefore a lower mixing ability. Sex (test: $\chi^2(1)=0.054$; p=0.815, retest: $\chi^2(1)=0.611$; p=0.434) did not show an effect.

Figure 1. Bland-Altman plot for the difference between test and retest of the Mixing Ability Test (MAT) for patients with head and neck cancer



The dashed line represents the mean difference between test and retest and the striped lines represent the 95% limits of agreement

Figure 2. Bland-Altman plot for the difference between test and retest of the Mixing Ability Test (MAT) for healthy controls



The dashed line represents the mean difference between test and retest and the striped lines represent the 95% limits of agreement

Discussion

The aim of this study was to determine the reliability of the MAT for patients with HNC and healthy controls. The results showed a good reliability in patients with HNC and a moderate reliability in healthy controls. In addition, healthy controls showed a higher SEM and SDC in comparison to patients with HNC, indicating a greater difference between test and retest.

In patients with HNC, an ICC of 0.886 was found, indicating a good reliability. In comparison, previous research tested the reproducibility in children with cerebral palsy and healthy children,[15] in which a moderate ICC of 0.69 was found. The higher ICC in patients with HNC in comparison to children indicates that this MAT is more suitable to use in (older) patients with HNC. In comparison, a moderate correlation between test and retest was found for healthy controls (ICC=0.525), indicating that this MAT is less suitable for healthy subjects.

Healthy controls displayed a better retest result in comparison to the test result, indicating a learning effect (Table 2). This effect was not visible in patients with HNC. In previous research, no learning effect or apparent optimization of jaw muscle activity was induced by a 1-hour training task.[28] Therefore it is unlikely that the second MAT shows a better result caused by a learning effect in masticatory performance after just 20 chewing strokes and with at least half an hour time difference. The variability between test and retest can be influenced by natural individual variability, unfamiliarity with the wax tablet, or adjustment to the taste and structure.[4,15] In addition, healthy controls have no problems regarding masticatory performance and oral functioning. They need less monitoring and regulating of their movements in comparison to patients, because their movements occur implicitly,[29] which may lead to more variation in chewing outcome. Patients are more aware of their chewing ability, due to for example pain or reduced oral sensibility, and therefore perform their movements more consciously (explicitly).[30] Healthy controls can show more variation in their chewing pattern, whereas patients already reached a ceiling effect.

Significant differences were found between patients with HNC and healthy controls for age and sex; significantly more people were male in the patient group, with a higher age in comparison to the healthy control group. Age had a significant effect on MAT outcome. Previous research showed that age has a negative influence on mastication, because total body muscle mass and muscle mechanical performance decrease, indicating that elderly persons need more time and more chewing strokes before food can be safely swallowed.[31] In addition, younger people may automatically chew food without additional effort for monitoring or regulating their movement.[29] Older people have a more distinct experience in chewing, where they monitor their oral status continually. This can also be caused by

poorer oral conditions such as fewer teeth or occlusal units.[29] However, no significant differences were found between patients with HNC and healthy controls for number of teeth or number of occlusal units, indicating that these oral conditions were similar.

Strengths and limitations

The Consensus-based Standards for the selection of health Measurement INstruments (COSMIN) checklist was followed to reduce bias and ensure methodological and statistical quality.[32] Reliability was tested in a large research population. Data were collected by the same authors (JAV and FMW) and the MAT score was calculated by the same observer (CMS). However, no inter-rater reliabilities were tested, because this was believed to be too time consuming for patients with HNC. In addition, significant differences were found between patients and healthy controls for age and sex, causing the groups to be non-comparable.

Future research

The results of the test-retest reliability can be used in future research to provide insight in differences over time and differences between different treatment modalities for patients with HNC. Because the ICC showed a good reproducibility, we expect the outcomes of the MAT to be of good reliability for future research. The SEM and SEM% values can be used as an indication for the expected random variation of a MAT score at any given time. The SDC and SDC% values can be used to describe minimal changes needed over time in order to be clinically significant. When values between different measurements are larger than the SDC, these changes are not caused by measurement uncertainty, and are actual changes over time.[22] The SEM% and SDC% values generate a fair comparison between different measures, and indicate that only small changes are needed to indicate a real change in mixing ability over time for patients with HNC. In healthy controls, bigger changes are needed to determine if performance has truly changed over time.

In conclusion, the MAT has a good reliability in patients with head and neck cancer and a moderate reliability in healthy controls.

References

1. Pace-Balzan A, Shaw RJ, Butterworth C (2011) Oral rehabilitation following treatment for oral cancer. *Periodontology 2000* 57 (1):102-117. doi:10.1111/j.1600-0757.2011.00384.x

2. Teguh DN, Levendag PC, Voet P, van der Est H, Noever I, de Kruijf W, van Rooij P, Schmitz PI, Heijmen BJ (2008) Trismus in patients with oropharyngeal cancer: relationship with dose in structures of mastication apparatus. *Head & neck* 30 (5):622-630. doi:10.1002/hed.20760

3. van der Bilt A, Engelen L, Pereira LJ, van der Glas HW, Abbink JH (2006) Oral physiology and mastication. *Physiology & behavior* 89 (1):22-27. doi:10.1016/j.physbeh.2006.01.025

4. Pereira LJ, van der Bilt A (2016) The influence of oral processing, food perception and social aspects on food consumption: a review. *Journal of oral rehabilitation* 43 (8):630-648. doi:10.1111/joor.12395

5. Pedroni-Pereira A, Marquezin MCS, Araujo DS, Pereira LJ, Bommarito S, Castelo PM (2018) Lack of agreement between objective and subjective measures in the evaluation of masticatory function: A preliminary study. *Physiology & behavior* 184:220-225. doi:10.1016/j.physbeh.2017.12.001

6. van der Bilt A, Abbink JH (2017) The influence of food consistency on chewing rate and muscular work. *Archives of oral biology* 83:105-110. doi:10.1016/j.archoralbio.2017.07.011

7. de Groot RJ, Rosenberg AJWP, van der Bilt A, Aalto D, Merkx MAW, Speksnijder CM (2019) The association between a mixing ability test and patient reported chewing ability in patients treated for oral malignancies. *Journal of oral rehabilitation* 46 (2):140-150. doi:10.1111/joor.12734

8. Mendenhall WM, Dagan R, Bryant CM, Fernandes RP (2019) Radiation Oncology for Head and Neck Cancer: Current Standards and Future Changes. *Oral and maxillofacial surgery clinics of North America* 31 (1):31-38. doi:10.1016/j.coms.2018.08.003

9. Nemeth D, Zaleczna L, Huremovic A, Engelmann J, Poeschl PW, Strasz M, Holawe S, Kornek G, Laskus A, Sacher C, Erovic BM, Perisanidis C (2017) Importance of chewing, saliva, and swallowing function in patients with advanced oral cancer undergoing preoperative chemoradiotherapy: a prospective study of quality of life. *International journal of oral and maxillofacial surgery* 46 (10):1229-1236. doi:10.1016/j.ijom.2017.05.005

10. Owosho AA, Pedreira Ramalho LM, Rosenberg HI, Yom SK, Drill E, Riedel E, Tsai CJ, Lee NY, Huryn JM, Estilo CL (2016) Objective assessment of trismus in oral and oropharyngeal cancer patients treated with intensity-modulated radiation therapy (IMRT). *Journal of cranio-maxillo-facial surgery : official publication of the European Association for Cranio-Maxillo-Facial Surgery* 44 (9):1408-1413. doi:10.1016/j.jcms.2016.06.008

11. Ohkoshi A, Ogawa T, Nakanome A, Ishida E, Ishii R, Kato K, Katori Y (2018) Predictors of chewing and swallowing disorders after surgery for locally advanced oral cancer with free flap reconstruction: A prospective, observational study. *Surgical oncology* 27 (3):490-494. doi:10.1016/j.suronc.2018.05.029

12. Speksnijder CM, Abbink JH, van der Glas HW, Janssen NG, van der Bilt A (2009) Mixing ability test compared with a comminution test in persons with normal and compromised masticatory performance. *Eur J Oral Sci* 117 (5):580-586. doi:10.1111/j.1600-0722.2009.00675.x

13. Elgestad Stjernfeldt P, Sjogren P, Wardh I, Bostrom AM (2018) Systematic review of measurement properties of methods for objectively assessing masticatory performance. *Clinical and experimental dental research* 5 (1):76-104. doi:10.1002/cre2.154

14. Speksnijder CM, van der Bilt A, Abbink JH, Merkx MA, Koole R (2011) Mastication in patients treated for malignancies in tongue and/or floor of mouth: A 1-year prospective study. *Head & neck* 33 (7):1013-1020. doi:10.1002/hed.21573

15. Remijn L, Vermaire JA, Nijhuis-van de Sanden MWG, Groen BE, Speksnijder CM (2018) Validity and reliability of the mixing ability test as masticatory performance

outcome in children with spastic cerebral palsy and children with typical development: A pilot study. *Journal of oral rehabilitation* 45 (10):790-797. doi:10.1111/joor.12690

16. Weinberg FM, Vermaire JA, Forouzanfar T, Rosenberg A, Speksnijder CM (2019) Reproducibility and construct validity of the Utrecht Mixing Ability Test to obtain masticatory performance outcome in patients with condylar mandibular fractures. *Journal of oral rehabilitation*. doi:10.1111/joor.12917

17. Verdonck-de Leeuw IM, Jansen F, Brakenhoff RH, Langendijk JA, Takes R, Terhaard CHJ, Baatenburg de Jong RJ, Smit JH, Leemans CR (2019) Advancing interdisciplinary research in head and neck cancer through a multicenter longitudinal prospective cohort study: the NETherlands QUality of life and BIomedical Cohort (NET-QUBIC) data warehouse and biobank. *BMC Cancer* 19 (1):765. doi:10.1186/s12885-019-5866-z

18. Paleri V, Mehanna H, Wight RG (2010) TNM classification of malignant tumours 7th edition: what's new for head and neck? *Clin Otolaryngol* 35 (4):270-272. doi:10.1111/j.1749-4486.2010.02141.x

19. Gotfredsen K, Walls AW (2007) What dentition assures oral function? *Clinical oral implants research 18 Suppl 3* (3):34-45. doi:10.1111/j.1600-0501.2007.01436.x

20. van der Bilt A, Speksnijder CM, de Liz Pocztaruk R, Abbink JH (2012) Digital image processing versus visual assessment of chewed two-colour wax in mixing ability tests. *Journal of oral rehabilitation* 39 (1):11-17. doi:10.1111/j.1365-2842.2011.02229.x

21. Portney L, Watkins M (2015) Foundations of Clinical Research. Application to Practice. Upper Saddle River, New Jersey

22. de Vet HCW, Terwee CB, Mokkink LB, Knol DL (2011) Measurement in Medicine; a practical guide. 1st edition. Cambridge University Press, New York

23. Shrout PE, Fleiss JL (1979) Intraclass correlations: uses in assessing rater reliability. *Psychol Bull* 86 (2):420-428. doi:10.1037//0033-2909.86.2.420

24. Weir JP (2005) Quantifying test-retest reliability using the intraclass correlation coefficient and the SEM. *J Strength Cond Res* 19 (1):231-240. doi:10.1519/15184.1

25. Terwee CB, Bot SD, de Boer MR, van der Windt DA, Knol DL, Dekker J, Bouter LM, de Vet HC (2007) Quality criteria were proposed for measurement properties of health status questionnaires. *J Clin Epidemiol* 60 (1):34-42. doi:10.1016/j.jclinepi.2006.03.012

26. Bland JM, Altman DG (1986) Statistical Methods for Assessing Agreement between Two Methods of Clinical Measurement. *Lancet* 1 (8476):307-310. doi:10.1016/S0140-6736(86)90837-8

27. Walter SD, Eliasziw M, Donner A (1998) Sample size and optimal designs for reliability studies. *Stat Med* 17 (1):101-110. doi:10.1002/(sici)1097-0258(19980115)17:1<101::aid-sim727>3.0.co;2-e

28. Kumar A, Svensson KG, Baad-Hansen L, Trulsson M, Isidor F, Svensson P (2014) Optimization of jaw muscle activity and fine motor control during repeated biting tasks. *Archives of oral biology* 59 (12):1342-1351. doi:10.1016/j.archoralbio.2014.08.009

29. Lin CS, Wu CY, Wu SY, Lin HH, Cheng DH, Lo WL (2017) Age-Related Difference in Functional Brain Connectivity of Mastication. *Frontiers in aging neuroscience* 9:82. doi:10.3389/fnagi.2017.00082

30. Kal E, Prosee R, Winters M, van der Kamp J (2018) Does implicit motor learning lead to greater automatization of motor skills compared to explicit motor learning? A systematic review. *PLoS ONE* 13 (9). doi:10.1371/journal.pone.0203591

31. Peyron MA, Woda A, Bourdiol P, Hennequin M (2017) Age-related changes in mastication. *Journal of oral rehabilitation* 44 (4):299-312. doi:10.1111/joor.12478

32. Mokkink LB, de Vet HCW, Prinsen CAC, Patrick DL, Alonso J, Bouter LM, Terwee CB (2018) COSMIN Risk of Bias checklist for systematic reviews of Patient-Reported Outcome Measures. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation* 27 (5):1171-1179. doi:10.1007/s11136-017-1765

Chapter 4

Reliability of the 100 mL Water Swallow Test in patients with head and neck cancer and healthy subjects

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Abstract

Background

Dysphagia may occur in up to 44% of patients with head and neck cancer (HNC) treated with radiotherapy and up to 84% of patients treated with surgery. To test the extent of dysphagia, the 100 mL Water Swallow Test (WST) was developed. In this study, reliability of the 100 mL WST was determined in patients with HNC and healthy subjects.

Methods

Thirty-three patients and 40 healthy subjects performed the WST twice on the same day. To assess reliability, the Intraclass Correlation Coefficient ($ICC_{2,1}$), Standard Error of Measurement (SEM), Smallest Detectable Change (SDC), and Limits of Agreement (LoA) were calculated.

Results

Good to excellent correlations were found for patients with HNC (number of swallows; ICC=0.923, duration; ICC=0.893), and excellent correlations for healthy subjects (number of swallows; ICC=0.950, duration; ICC=0.916).

Conclusion

The 100 mL WST has a good to excellent reliability in patients with HNC and healthy subjects.

Introduction

Swallowing is a physiological process formed by oral, pharyngeal and esophageal phases.[1] It occurs due to neuromuscular actions involving sensitive cranial, motor and parasympathetic nerves.[2] Its purpose is to transport food from the mouth to the stomach, promoting hydration and nutrition. In order to be successful at this, a number of rapid, coordinated and accurate events have to occur, such as soft palate elevation, vocal fold closure, pharyngeal muscle contraction, laryngeal elevation and anteriorization and epiglottis lowering.[3] These mechanisms occur involuntarily after stimulation of sensory receptors, especially located in the oropharyngeal cavity.[2] A lack of onset or delayed onset of these events can be a sign of dysphagia. Dysphagia is a significant toxicity resulting in difficulty in swallowing, caused by abnormalities in structure or function of cartilaginous, bony, muscular or neural anatomy involved in normal swallowing.[4] Complications such as malnutrition, aspiration and subsequent pneumonia can occur.[4] Dysphagia can not only lead to a reduction of intake, but a reduction in peoples' activities and social interactions as well, with corresponding negative changes to quality of life.[5]

Dysphagia may occur in up to 44% of patients with head and neck cancer (HNC) treated with Radiotherapy (RT) and up to 84% of patients treated with surgery.[6,7] In addition, up to 2 out of 3 HNC patients may present with dysphagia at the time of diagnosis, and silent aspiration is present in 14 to 18% of patients pre-treatment.[8] RT related toxicity may consist of dysphagia caused by the irradiation of swallowing related normal tissues, fibrosis, edema, ulcers, vascular toxicity, and osteoradionecrosis.[9,10] Chemotherapy can add to the effects of RT and cause edema, mucositis and fibrosis.[4] Surgical resection of the soft palate, floor of mouth, or base of tongue can cause severe swallowing dysfunction as well,[6] compromising lingual mobility, muscle strength, mastication, muscle action, and muscle coordination.[4,5,8] The most common procedure to evaluate dysphagia, swallowing safety and efficiency in patients with HNC is based on video-endoscopy, such as Fibreoptic Endoscopic Evaluation of Swallowing (FEES).[8,11] However, these procedures are time consuming and require special equipment. Therefore, the 100 mL Water Swallow Test (WST) was developed.[11,12] This test requires minimal equipment, is easily accessed and provides quantitative measures of swallowing performance. It is therefore used as a standardized test for screening dysphagia.[13] In addition, the WST may be better in reflecting swallowing in everyday life in comparison to FEES, because it allows the patients to self-select the size of each bolus swallowed.[11] In previous research, the WST was performed in neurological patients, where it had high inter-rater reliability, a difference on average of 2.4% between two measurements, when assessing videotaped swallowing movies.[12,14] Besides, the WST has been validated using video fluoroscopy in patients with neurogenic dysphagia, with a sensitivity and specificity up to 85.5% and 91.7%.[15] It showed no

significant inter-rater differences or differences between tests over a 48 hour period.[12] The WST has proven to be an excellent test to help identify patients at risk for dysphagia and aspiration, and can be used to monitor swallowing performance over time.[11,16] In order to detect changes that may occur in the WST outcomes after treatment, test-retest reliability is an important test criterion, most often measured with an Intraclass Correlation Coefficient.[17] Besides, to interpret repeated measurement scores, it is important to use the Smallest Detectable Change (SDC) scores to determine whether a change in scores is significant and not a measurement uncertainty. The SDC is crucial for clinicians and researchers to determine the real change in repeated measurements for individual patients.[18] The reliability of the WST has been tested in patients with motor neuron disease, in which a high inter-rater reliability was found.[19] However, to our knowledge, test-retest reliability has not been performed in patients with HNC yet. The purpose of this study was therefore to assess the reliability of the WST in patients with HNC. In order to detect differences in reliability that may occur in a different population, the reliability was tested in healthy subjects as well.

Methods

Patients were included when they had been diagnosed with oral, oropharyngeal, hypopharyngeal, laryngeal, or unknown primary HNC. Patients were included at the University Medical Center Utrecht (UMCU), the Netherlands, and were referred for either RT, chemoradiotherapy, or surgery, with a curative intent, between September 2016 and June 2018. Patients with recurrent or residual disease, cognitive impairments and patients having trouble understanding and reading the Dutch language were excluded. Healthy subjects could respond to a flyer outside the hospital, and were included when they were 18 years or older. The study protocol for patients with HNC is part of the NET-QUBIC research,[20] and was approved by the Medical Ethics Committee of the Netherlands (NL45051.029.13). A random selection of the total NET-QUBIC research (n=154) was taken, and patients were asked before the start of the measurements if they would want to perform the WST twice. The study protocol for healthy subjects was approved by the Medical Ethics Committee of the UMCU (18/701). General information about age, sex, tumor site, tumor stage, and treatment were collected for patients with HNC, and about age and sex for healthy subjects. Before participating, all subjects received oral and written information about the study, before signing written informed consent.

100 mL Water Swallow Test

During the 100 mL WST, a subject was asked to drink 100 mL of water as quickly as is comfortably possible. The time to swallow this 100 mL (in seconds) and the number of swallows were counted. The researcher counted the number of swallows by touching the larynx, and the subject was asked to count the number of swallows simultaneously, as a control reference. Timing started when the water touched the bottom lip, and stopped when the larynx came to rest after the last swallow.[14] From these measurements, the following parameters could be calculated: the swallowing volume (the amount of mL per swallow), the swallowing capacity (the amount of mL per second) and the swallowing speed (the time per swallow). Swallowing volume was calculated by dividing the number of mL by the number of swallows. Swallowing capacity was calculated by dividing the number of mL by the duration. Swallowing speed was calculated by dividing the duration by the number of swallows. Subjects failed the test when they coughed or choked post swallow, had a wet voice quality post swallow, or were unable to drink the whole 100 mL.[11] When a person was unable to drink the 100 mL, the residual water was measured and noted. Subjects were instructed to perform the WST two times, with an interim period between 15 minutes and two hours, with the same rater and testing conditions for all subjects.

Statistical analyses

Test-retest reproducibility of the WST outcomes was tested by a two-way random, single measurement, absolute agreement, intra class correlation coefficient ($ICC_{2,1}$) calculated as $\frac{MS_R - MS_E}{MS_R + (k-1)MS_E + \frac{k}{n}(MS_C - MS_E)}$, in which MS_R = mean square of rows; MS_E = mean square for error; MS_C = mean square for columns; k = number of measurements; and n = number of subjects. Cut-off points for the ICC were chosen as poor (<0.5), moderate (0.5 to 0.75), good (0.75 to 0.90), and excellent (>0.90).[21,22] The Standard Error of Measurement (SEM) was calculated as $\mathrm{SD} * \sqrt{(1 - \mathrm{ICC})}$.[23] For the SD, the Standard Deviation of the difference between the two WSTs was used. The SEM percent change (SEM%) was calculated as $(SEM/\bar{X}) * 100$, in which $\bar{X}$ = the mean of all measurements of test and retest. The Smallest Detectable Change (SDC) was calculated as $1.96 * \sqrt{2} * SEM$.[24,25] The SDC percent change (SDC%) was calculated as $(SDC/\bar{X}) * 100$, in which $\bar{X}$ = the mean of all measurements of test and retest.

In order to check for systematic bias, variability and agreement, Bland-Altman plots were constructed by plotting the test-retest difference versus the mean value of the test and retest. The agreement between the two tests was summarized using the mean difference and SD of the difference, and the 95% Limits of Agreement (LoA) were calculated as $Mean \pm 1.96 * SD$.[26]

A power analysis was conducted, with an expected ICC of at least 0.7. A p_1 value of 0.9 was chosen, therefore the sample size had to be at least 18.4.[27] Data were tested for normality using a Shapiro-Wilk test. Because data were not normally distributed, a Wilcoxon Signed Ranks test was conducted to examine differences between the test outcomes of the WST for both patients with HNC and healthy subjects. A paired samples t-test was conducted to examine differences between the number of swallows reported by the researcher in comparison to the number of swallows reported by the patient or healthy subject. A Kruskal-Wallis test was conducted to examine differences in WST outcomes according to sex and age. All analyses were performed using Statistical Package for the Social Sciences (SPSS) version 25 (Chicago, IL). A p-value below 0.05 was considered statistically significant.

Results

Thirty-three patients with HNC and 40 healthy subjects performed the WST twice on the same day. In Table 1, subject characteristics are depicted for patients with HNC and healthy subjects.

The median age for patients with HNC was 65 years (91% male), and 31 years (50% male) for healthy subjects. All subjects were able to drink the 100 mL of water, and no missing data were reported. For the patient group, ten patients performed the test before treatment, five patients 3 months after treatment, five patients 6 months after treatment, five patients 12 months after treatment, and eight patients 24 months after treatment. No significant differences ($p=1.00$) were reported between number of swallows reported by the researcher (mean=4.25, SD=2.41) in comparison to the subject (mean=4.25, SD=2.43). Significant differences were found for age and sex between patients with HNC and healthy subjects ($p<0.001$ and $p=0.002$, respectively). Mean and median scores are depicted in Table 2 for patients with HNC and healthy subjects, and for test and retest.

Table 1. Subject characteristics of patients with head and neck cancer and healthy subjects

Characteristics	**Patients (n = 33)**	**Healthy subjects (n = 40)**	**p-value**
Age (median, IQR)	65 (12)	31 (28)	<0.001*†
Sex			
Male	30 (91%)	20 (50%)	0.002**‡
Female	3 (9%)	20 (50%)	
Tumor site			
Oropharynx	15 (46%)	NA	-
Larynx	10 (30%)		
Oral cavity	5 (15%)		
Hypopharynx	2 (6%)		
Unknown primary	1 (3%)		
Tumor Stage			
I	7 (21%)	NA	-
II	9 (27%)		
III	2 (6%)		
IV	15 (46%)		
Primary Treatment			
RT	17 (52%)	NA	-
CRT	11 (33%)		
Surgery	3 (9%)		
Surgery with PORT	2 (6%)		

CRT: Chemoradiotherapy, IQR: Interquartile Range, PORT: Post-Operative Radiotherapy, RT: Radiotherapy

*: p<0.001, **: p<0.05, †: Mann-Whitney U test; ‡: Chi-square test

All swallowing parameters (number of swallows, duration, swallowing volume, swallowing capacity, and swallowing speed) showed good to excellent test-retest correlations for patients with HNC (ICC>0.75), and moderate to excellent correlations for healthy subjects (ICC>0.70) (Table 3). The SEM values indicated that there is an expected random variation in the different parameters of 5.9-19.1% for patients with HNC, and of 4.0-13.8% for healthy subjects. The SDC values indicated that the difference between two tests needs to be higher than this SDC value to be considered a true change in swallowing, which is not caused by a measurement uncertainty. Therefore, the difference for the different parameters needs to be higher than 16.5-52.8% for patients with HNC, and 11.1-38.2% for healthy subjects. The Bland-Altman plots (Figure 1 and 2) showed that 95% of the data lie between the Limits of Agreement, indicating no systematic variation in performance between two measurements.

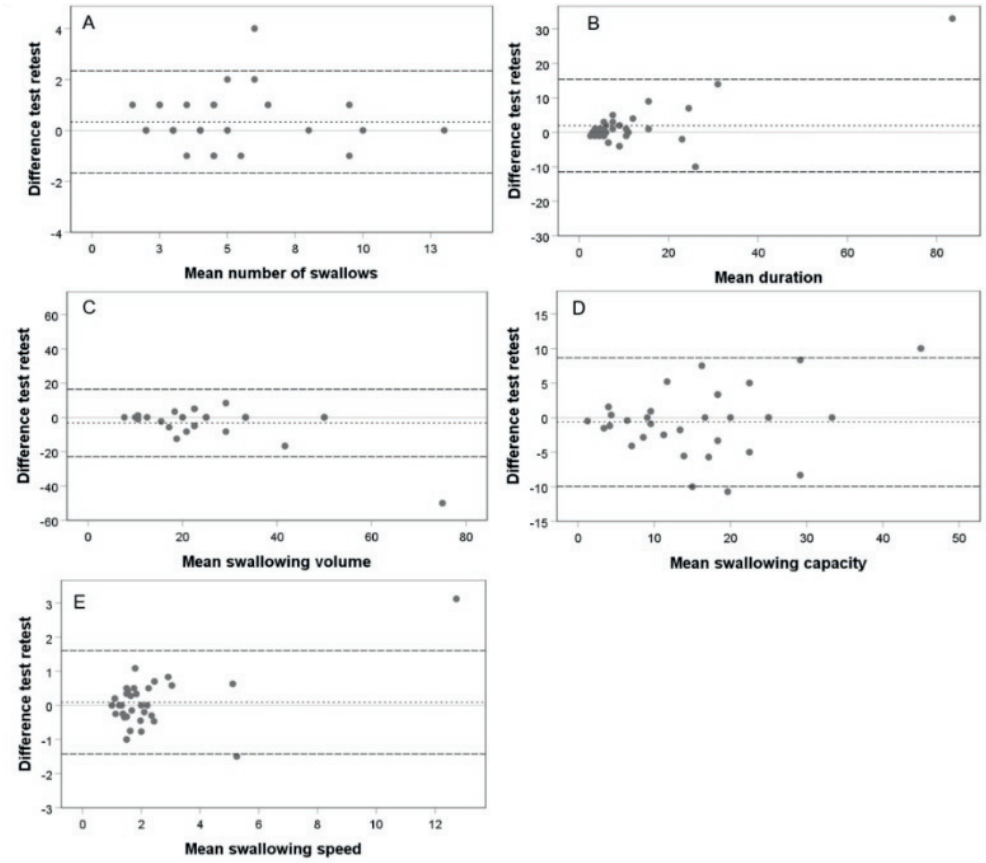
The Wilcoxon Signed Ranks test showed no significant differences between test and retest for all swallowing parameters except swallowing volume in patients with HNC. The Kruskal-Wallis test showed a significant effect for age for all parameters (number of swallows, $p<0.001$, duration, $p<0.001$, swallowing volume, $p=0.001$, swallowing capacity, $p<0.001$, swallowing speed, $p=0.005$). Number of swallows and duration increase with age, and swallowing volume, swallowing capacity, and swallowing speed decrease with increasing age. In addition, a significant effect was found for sex for number of swallows ($p=0.033$) and swallowing volume ($p=0.044$). Women need a higher number of swallows and have a lower swallowing volume in comparison to men. Duration ($p=0.257$), swallowing capacity ($p=0.257$) and swallowing speed ($p=0.373$) did not show an affect for sex.

Table 2. WST characteristics of patients with head and neck cancer and healthy subjects. Differences between test and retest outcome for patients with HNC and healthy subjects are depicted

	Patients (n = 33)					**Healthy subjects (n = 40)**				
	Test		**Retest**		**p-value‡**	**Test**		**Retest**		**p-value‡**
	Mean (SD)	*Median (IQR)*	*Mean (SD)*	*Median (IQR)*		*Mean (SD)*	*Median (IQR)*	*Mean (SD)*	*Median (IQR)*	
Number of swallows	4.94 (2.69)	4.00 (3.50)	4.61 (2.68)	4.00 (2.00)	0.069	3.68 (2.02)	3.00 (2.75)	3.70 (2.11)	3.00 (2.75)	0.808
Duration (s)	12.73 (17.57)	7.00 (7.50)	10.76 (12.18)	6.00 (6.50)	0.080	5.69 (5.19)	3.90 (3.91)	5.28 (4.01)	4.11 (3.38)	0.089
Swallowing volume (mL)	25.78 (12.14)	25.00 (17.86)	29.08 (17.66)	25.00 (13.33)	0.046*	36.96 (24.09)	33.33 (28.75)	36.21 (22.09)	33.33 (28.75)	0.875
Swallowing capacity (mL/s)	15.44 (10.53)	14.29 (11.88)	16.09 (9.41)	16.67 (13.41)	0.336	26.29 (14.03)	25.71 (19.88)	26.28 (13.24)	24.33 (17.63)	0.371
Swallowing speed (s)	2.37 (2.35)	1.75 (1.02)	2.28 (1.89)	1.75 (0.96)	0.509	1.49 (0.62)	1.35 (0.58)	1.42 (0.43)	1.34 (0.55)	0.446

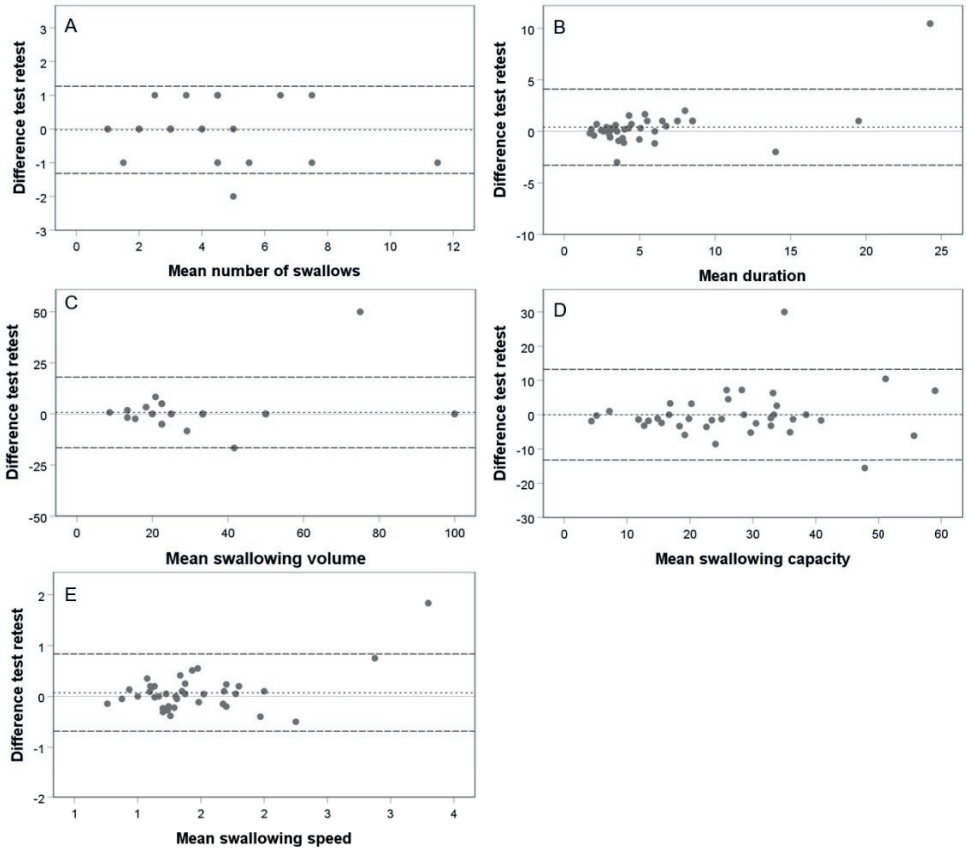
IQR: Interquartile range
*: $p<0.05$, ‡: Wilcoxon Signed Ranks test

Figure 1. Bland-Altman plots for patients with head and neck cancer for the number of swallows (A), duration (B), swallowing volume (C), swallowing capacity (D), and swallowing speed (E)



The dashed line represents the mean difference between test and retest and the striped lines represent the 95% Limits of Agreement

Figure 2. Bland-Altman plots for healthy subjects for the number of swallows (A), duration (B), swallowing volume (C), swallowing capacity (D), and swallowing speed (E)



The dashed line represents the mean difference between test and retest and the striped lines represent the 95% Limits of Agreement

Table 3. Reliability of the WST for the parameters number of swallows, duration, swallowing volume, swallowing capacity, and swallowing speed. Both patients with head and neck cancer and healthy subjects are depicted

	Diff. test-retest Mean (SD)	95% LoA	$ICC_{2,1}$ (95% CI)	SEM	SEM%	SDC	SDC%
Patients (n = 33)							
Number of swallows	0.33 (1.02)	2.33 to -1.67	0.923 (0.846 to 0.962)	0.28	5.9%	0.79	16.5%
Duration (s)	1.97 (6.84)	15.38 to -11.44	0.893 (0.793 to 0.946)	2.24	19.1%	6.21	52.8%
Swallowing Volume (mL)	-3.30 (10.02)	16.34 to -22.94	0.768 (0.577 to 0.879)	4.83	17.6%	13.38	48.8%
Swallowing capacity (mL/s)	-0.65 (4.74)	8.64 to -9.94	0.888 (0.787 to 0.943)	1.59	10.1%	4.40	27.9%
Swallowing speed (s)	0.09 (0.77)	1.61 to -1.43	0.935 (0.873 to 0.967)	0.20	8.5%	0.55	23.6%
Healthy subjects (n = 40)							
Number of swallows	-0.03 (0.66)	1.27 to -1.32	0.950 (0.908 to 0.973)	0.15	4.0%	0.41	11.1%
Duration (s)	0.40 (1.89)	4.11 to -3.29	0.916 (0.847 to 0.954)	0.55	10.0%	1.52	27.6%
Swallowing Volume (mL)	0.75 (8.83)	18.06 to -16.56	0.928 (0.869 to 0.961)	2.37	6.5%	6.57	18.0%
Swallowing capacity (mL/s)	0.01 (6.75)	13.23 to -13.21	0.880 (0.785 to 0.935)	2.34	8.9%	6.48	24.6%
Swallowing speed (s)	0.07 (0.39)	0.84 to -0.69	0.733 (0.551 to 0.849)	0.20	13.8%	0.56	38.2%

CI: Confidence Interval, ICC: Intraclass Correlation Coefficient, LoA: Limits of Agreement, SEM: Standard Error of Measurement, SDC: Smallest Detectable Change

Discussion

The aim of this study was to determine the reliability of the WST for patients with HNC and healthy subjects. The results showed moderate to excellent reliability for all measures (ICC>0.70). The SEM values for patients with HNC were 0.28 (number of swallows), 2.24 (duration (s)), 4.83 (swallowing volume (mL)), 1.59 (swallowing capacity (mL/s)), and 0.20 (swallowing speed (s)), which are small considering the range of outcome possibilities. The SDC values were 0.79 (number of swallows), 6.21 (duration), 13.38 (swallowing volume), 4.40 (swallowing capacity), and 0.55 (swallowing speed), indicating that the outcomes of the WST have to change with at least these values before the observed change over time can be considered a true change in swallowing function and not potentially the result of a measurement uncertainty. The Bland-Altman plots show that 95% of the measures lie between the upper and lower LoA with a consistent variability. In all measures except swallowing speed, the SEM% and SDC% values were lower in healthy subjects in comparison to patients with HNC, indicating the importance of calculating these values for a specific population.

In previous research, no significant differences were found in swallowing speed between the first and fourth test over a 48-hour period.[12] This is in correspondence to the results found in this research, where there is a high reliability between the first and second test, over a 2-hour period. Swallowing speed is correlated with age, as found in this research.[12,14,19] However, previous research is inconclusive about the correlation between swallowing speed and sex: although most research found a correlation,[12,14,19] this was not always the case (including this research).[13] With increasing age,[13] speed decreases while time per swallow increases, and speed is most often lower in women in comparison to men. In addition, volume per swallow and swallowing capacity are greater in men.[19] This is in correspondence to the results found in this research, where swallowing volume is correlated to sex. In addition, in this research, a significant effect for age on number of swallows, duration, and swallowing capacity was found, and an effect for sex on number of swallows.

Strengths and limitations

This study followed the COSMIN checklist (Consensus-based Standards for the selection of health Measurement INstruments) to ensure methodological and statistical quality, and to reduce bias.[28] A large research population was used to test the reliability, and data were collected by the same author (JAV). However, only 3 female patients with HNC were tested, making it possible to have missed sex effects in this population. Therefore, the results found on sex differences between men and women should be tested again in a larger population. Because there were significant differences in age and sex between patients with HNC and

healthy subjects, these groups are not comparable. Therefore, results should be interpreted separately and can only be applied to subjects with the same sex and age distribution.
Although both patients and healthy subjects performed different tests and filled in questionnaires between test and retest, it is possible that the time between test and retest of approximately 15 minutes (healthy subjects) to 2 hours (patients) has caused some recall bias, because previous research used a 48 hour time frame.[12] However, no response shift was found between the second and first test; the second test did not always show an improvement compared to the first test, which otherwise would have been visible in the Bland Altman plots in Figure 1. Therefore, it is believed that this possible bias is negligible. No inter-rater reliabilities were tested, because this was believed to be too time consuming for patients with HNC.

In this study, all patients passed the WST and thus showed no signs of dysphagia nor aspiration. This contradicts previous results, which show that up to 84% of patients suffer from dysphagia post-treatment,[6] and that the WST has a good sensitivity for the detection of aspiration.[13,16] One explanation could be that the WST missed latent or silent aspiration in patients.[11,13] In addition, a random selection was made of different patients with HNC before treatment up to two years after treatment. It may be possible to have missed patients with severe dysphagia, because dysphagia is mainly seen 3 and 6 months after treatment,[11] and in patients with pharyngeal cancer.[14] However, the swallowing speed calculated from the WST provides an effective tool for screening for FEES referral,[15] in which dysphagia can be further evaluated.[8]

Future research

The 100 mL WST has been validated using video fluoroscopy in patients with neurogenic dysphagia with a sensitivity and specificity up to 85.5% and 91.7%.[15] In patients with motor neuron disease, the WST had a high inter-rater reliability, with bigger differences between subjects due to the effects of age and sex.[19] The high sensitivity, specificity and inter-rater reliability indicate that the WST is an excellent test to use when measuring swallowing performance. These findings are equally important as the reliability testing performed in this research, and should be taken into account as well when reporting outcome measures on swallowing performance.

The results of the test-retest reliability can be used in future research to provide insight into differences over time and differences between different treatment modalities for patients with HNC. Swallowing volume was significantly different between test and retest for patients with HNC. In addition, swallowing speed in healthy subjects had a moderate reliability while all other ICCs show a good to excellent reliability, and duration had a

relatively high SEM% and SDC% value. We therefore recommend especially using the parameter number of swallows in future research, instead of the derivatives swallowing volume, swallowing capacity, and swallowing speed. The SEM and SEM% values can be used to indicate the expected random variation in WST outcomes at any given time point before and after treatment for HNC. The SDC and SDC% can be used to describe minimal changes needed between measurements over time in order to be clinically significant.[22]

In conclusion, this study displays a good to excellent reliability of the WST for the parameters number of swallows, duration, swallowing volume, swallowing capacity, and swallowing speed for both patients with HNC, and moderate to excellent reliability for healthy subjects. We recommend especially using the parameter number of swallows in future research, because this parameter showed an excellent reliability and displayed the smallest SEM% and SDC%. Based on the results found in this study, we expect the results of the WST to be of good reliability, and therefore reliable conclusions can be made in future research using the WST.

References

1. Costa MMB. Neural Control of Swallowing. *Arquivos de gastroenterologia.* 2018;55Suppl 1(Suppl 1):61-75.
2. Zancan M, Luchesi KF, Mituuti CT, Furkim AM. Onset locations of the pharyngeal phase of swallowing: meta-analysis. *CoDAS.* 2017;29(2).
3. Almeida RCA, Haguette RCB, de Andrade ISN. Swallowing with and without verbal commands: videofluroscopic findings. *Rev Soc Bras Fonoaudiol.* 2011;16(3):291-297.
4. Riffat F, Gunaratne DA, Palme CE. Swallowing assessment and management pre and post head and neck cancer treatment. *Current opinion in otolaryngology & head and neck surgery.* 2015;23(6):440-447.
5. Perry A, Lee SH, Cotton S, Kennedy C. Therapeutic exercises for affecting post-treatment swallowing in people treated for advanced-stage head and neck cancers. *Cochrane Db Syst Rev.* 2016(8).
6. Kreeft AM, van der Molen L, Hilgers FJ, Balm AJ. Speech and swallowing after surgical treatment of advanced oral and oropharyngeal carcinoma: a systematic review of the literature. *Eur Arch Oto-Rhino-L.* 2009;266(11):1687-1698.
7. van der Veen J, Nuyts S. Can Intensity-Modulated-Radiotherapy Reduce Toxicity in Head and Neck Squamous Cell Carcinoma? *Cancers.* 2017;9(12):135.
8. Russi EG, Corvo R, Merlotti A, et al. Swallowing dysfunction in head and neck cancer patients treated by radiotherapy: Review and recommendations of the supportive task group of the Italian Association of Radiation Oncology. *Cancer treatment reviews.* 2012;38(8):1033-1049.
9. Hutcheson KA, Lewin JS, Barringer DA, et al. Late dysphagia after radiotherapy-based treatment of head and neck cancer. *Cancer.* 2012;118(23):5793-5799.
10. Alterio D, Gerardi MA, Cella L, et al. Radiation-induced acute dysphagia: Prospective observational study on 42 head and neck cancer patients. *Strahlentherapie und Onkologie : Organ der Deutschen Rontgengesellschaft [et al].* 2017;193(11):971-981.
11. Patterson JM, Hildreth A, McColl E, Carding PN, Hamilton D, Wilson JA. The clinical application of the 100mL water swallow test in head and neck cancer. *Oral oncology.* 2011;47(3):180-184.
12. Nathadwarawala KM, Nicklin J, Wiles CM. A timed test of swallowing capacity for neurological patients. *J Neurol Neurosurg Psychiatry.* 1992;55(9):822-825.
13. Osawa A, Maeshima S, Tanahashi N. Water-swallowing test: screening for aspiration in stroke patients. *Cerebrovasc Dis.* 2013;35(3):276-281.
14. Patterson JM, McColl E, Carding PN, Kelly C, Wilson JA. Swallowing performance in patients with head and neck cancer: a simple clinical test. *Oral oncology.* 2009;45(10):904-907.
15. Wu MC, Chang YC, Wang TG, Lin LC. Evaluating swallowing dysfunction using a 100-ml water swallowing test. *Dysphagia.* 2004;19(1):43-47.
16. Patterson JM, McColl E, Carding PN, Hildreth AJ, Kelly C, Wilson JA. Swallowing in the first year after chemoradiotherapy for head and neck cancer: clinician- and patient-reported outcomes. *Head & neck.* 2014;36(3):352-358.
17. Brennan P, Silman A. Statistical methods for assessing observer variability in clinical measures. *BMJ.* 1992;304:1491-1494.
18. Kovacs FM, Abraira V, Royuela A, et al. Minimum detectable and minimal clinically important changes for pain in patients with nonspecific neck pain. *BMC Musculoskelet Disord.* 2008;9:43.
19. Hughes TAT, Wiles CM. Clinical measurement of swallowing in health and in neurogenic dysphagia. *Qjm-Mon J Assoc Phys.* 1996;89(2):109-116.
20. Verdonck-de Leeuw IM, Jansen F, Brakenhoff RH, et al. Advancing interdisciplinary research in head and neck cancer through a multicenter longitudinal prospective cohort study: the NETherlands QUality of life and BIomedical Cohort (NET-QUBIC) data warehouse and biobank. *BMC Cancer.* 2019;19(1):765.

21. Portney L, Watkins M. *Foundations of Clinical Research. Application to Practice.* Upper Saddle River, New Jersey2015.

22. de Vet HCW, Terwee CB, Mokkink LB, Knol DL. *Measurement in Medicine; a practical guide.* New York: Cambridge University Press; 2011.

23. Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. *Psychol Bull.* 1979;86(2):420-428.

24. Terwee CB, Bot SD, de Boer MR, et al. Quality criteria were proposed for measurement properties of health status questionnaires. *J Clin Epidemiol.* 2007;60(1):34-42.

25. Weir JP. Quantifying test-retest reliability using the intraclass correlation coefficient and the SEM. *J Strength Cond Res.* 2005;19(1):231-240.

26. Bland JM, Altman DG. Statistical Methods for Assessing Agreement between Two Methods of Clinical Measurement. *Lancet.* 1986;1(8476):307-310.

27. Walter SD, Eliasziw M, Donner A. Sample size and optimal designs for reliability studies. *Stat Med.* 1998;17(1):101-110.

28. Mokkink LB, de Vet HCW, Prinsen CAC, et al. COSMIN Risk of Bias checklist for systematic reviews of Patient-Reported Outcome Measures. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation.* 2018;27(5):1171-1179.

Chapter 5

Mastication, swallowing and salivary flow in patients with head and neck cancer; objective tests versus patient-reported outcomes

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Abstract

Background

Before and after treatment for head and neck cancer (HNC), many patients have problems with mastication, swallowing, and salivary flow. The aim of this study was to investigate the association between objective test outcomes of mastication, swallowing and salivary flow versus patient-reported outcomes (PROs) measuring mastication, swallowing and salivary flow related quality of life.

Methods

Data of the prospective cohort 'Netherlands Quality of Life and Biomedical Cohort Study' was used as collected before treatment, and 3 and 6 months after treatment. Spearman's rho was used to test the association between objective test outcomes of the Mixing Ability Test (MAT) for masticatory performance, the Water Swallowing Test (WST) for swallowing performance and the salivary flow test versus PROs (subscales of the EORTC QLQ-H&N35, Swallow Quality of Life questionnaire (SWAL-QOL) and Groningen Radiation-Induced Xerostomia (GRIX)).

Results

Data of 142 patients were used, and in total, 285 measurements were performed. No significant correlations were found between the MAT or WST and subscales of the EORTC QLQ-H&N35. Significant but weak correlations were found between the MAT or WST and 4 subscales of the SWAL-QOL. Weak to moderate correlations were found between the salivary flow test and GRIX at 3 and 6 months after treatment, with the highest correlation between salivary flow and xerostomia during the day (Spearman's rho=-0.441, p=0.001).

Conclusion

The association between objective test outcomes and PROs is weak, indicating that these outcome measures provide different information about masticatory performance, swallowing and salivary flow in patients with HNC.

Introduction

Head and neck cancer (HNC) is the seventh most common cancer worldwide, most often caused by alcohol and tobacco use, or the human papilloma virus (HPV).[1] Treatment options for HNC (e.g., oral, pharyngeal or laryngeal cancer) include surgery, radiotherapy (RT) and chemoradiotherapy (CRT). After treatment, patients may suffer from tissue fibrosis, osteoradionecrosis, xerostomia, or dysphagia. Deterioration in oral functioning (such as mastication, swallowing, saliva production, taste, dental condition, and speech) can result in complications such as malnutrition, dehydration, aspiration and subsequent pneumonia. Within the first year after radiotherapy, approximately half of the HNC survivors experience difficulties with oral functioning, and unmet survivorship needs are common.[2] HNC survivors may experience psychosocial problems such as social isolation and depression, which decreases a person's quality of life (QoL).[3-5]

To determine oral functioning before and after treatment, objective and subjective measures can be used. Objective measurements are based on how well a person can perform a task, irrespective of what they experience while performing the task. They are based upon an accurate representation of the world, and are therefore unbiased because they record only what is observed, without adding or taking away from the observation.[6,7] A person's subjective evaluation depends on individual values and priorities, which may differ between persons and even within persons. This subjective evaluation, or patient-reported outcome measure (PRO), is based on what people actually experience, and is increasingly being integrated in routine clinical practice.[8,9] It has shown to contribute to improved communication, patient satisfaction, earlier detection of problems and subsequently earlier referral, and more efficient use of health services.[8] In order to develop strategies to reduce side-effects of oncological treatment, it is important to know the relation between the patients' subjective evaluation of his/her oral functioning and the objective function of the various organs involved. In previous research, multiple studies looked at this relation between objective and subjective measurements, especially comparing swallowing outcomes.[10-13] However, many different measures have been used, and there is a lack of consensus about a preferred method to measure swallowing performance.[10] In addition, most studies focus only on one part of oral functioning, or at one point in time. Therefore, in this paper, objective measures and PROs are compared for three main oral functions (mastication, swallowing, and salivary flow), using the same methodology in a large group of patients at different time points.

To measure more aspects of oral functioning in time, and in particular masticatory performance, dysphagia and xerostomia, different tests can be used. Objective masticatory performance can be measured with, for example, comminution methods, sieving and optical

scanning methods, gummy jelly as test food, and mixing ability methods.[14] One method using the mixing ability method (the Mixing Ability Test (MAT)) has proven to be highly reliable in patients with HNC.[15] Objective swallowing performance can be measured with, for example, Fibreoptic Endoscopic Evaluation of Swallowing (FEES), or in a non-invasive and fast manner with minimal equipment using a 100 mL Water Swallow Test (WST).[16,17] Measures of objective salivary flow rate from parotid and submandibular glands have been used for years to determine the dose response relationship between RT dose and degree of hyposalivation or sticky saliva.[18]

Subjective oral functioning can be measured with several validated questionnaires.[19] The European Organization for Research and Treatment of Cancer Quality of Life core Questionnaire, Head and Neck module (EORTC QLQ-H&N35) was especially developed to measure HNC specific problems and addresses different items of oral functioning.[20] The Dutch version of the Swallow Quality of Life questionnaire (SWAL-QOL-NL) was developed to address swallowing specific problems.[21] The Groningen Radiation-Induced Xerostomia (GRIX) questionnaire was developed to observe xerostomia and sticky saliva during day and night.[22]

Before creating prediction models that show patients at risk for developing mastication, dysphagia or xerostomia related problems after treatment, it is important to get insight in the association between objective and subjective measures to get a total image of oral functioning. Therefore, the aim of this study was to determine the association between the MAT, WST or salivary flow test and the EORTC QLQ-H&N35, SWAL-QOL or GRIX, before treatment, and 3 and 6 months after treatment.

Methods

Data of the prospective cohort study Netherlands Quality of Life and Biomedical Cohort (NET-QUBIC) Study were used.[23] Patients were recruited between 2014 and 2018 and included when they were 18 years or older, diagnosed with oral, oropharyngeal, hypopharyngeal, laryngeal, or unknown primary HNC. Patients with recurrent or residual disease, cognitive impairments, and patients having trouble understanding or reading the Dutch language were excluded. The study protocol was approved by the Medical Ethics Committee (NL45051.029.13). In the present study, the study population consisted of patients with data on MAT, WST and salivary flow test. These tests were only performed in one single center (University Medical Center Utrecht (UMCU)). Sociodemographic and clinical data about age, sex, tumor stage, tumor location, and treatment were collected from medical records. All participants signed informed consent. Data from objective tests and subjective questionnaires were used as collected before primary treatment (baseline,

M0), 3 months after treatment (M3), and 6 months after treatment (M6). Patients that did not perform both objective and subjective measures at one time point were excluded. A comparison between objective and subjective data was based on assumptions regarding best fit of subjective data to objective data.

Mixing Ability Test

The MAT consists of two layers of wax, with the colors red and blue (Plasticine modelling wax, non-toxic DIN EN-71, art. nos. crimson 52801 and blue 52809, Stockmar, Kalten Kirchen, Germany).[24] The total thickness is 3 mm, with a diameter of 30 mm. The outcome variable ranges between 5-30, where a lower score implies a better mixed tablet and better masticatory performance. A subject was asked to chew on this tablet 20 times in order to mix the two colors. The tablet is then flattened, pressed to a thickness of 2 mm, and scanned on both sides using a high-quality scanner (Epson® V750, Long Beach, CA, USA). The scanned images are then processed using Adobe Photoshop CS3 extended (Adobe, San Jose, CA, USA). The histograms of both sides of the flattened and scanned wax tablet are added to obtain red and blue intensity distributions. The spread of the color intensities is measured.[24] In previous research, this test has proven to be highly reliable in patients with HNC (ICC = 0.886).[15]

100 mL Water Swallow test

During the WST, a subject was asked to drink 100 mL of water as quickly as is comfortably possible. The time to swallow this 100 mL (in seconds) and the number of swallows were counted, both by the subject and the researcher. Timing started when the water touched the bottom lip, and stopped when the larynx came to rest after the last swallow.[25] Persons failed the test when they coughed or choked post swallow, had a wet voice quality post swallow, or were unable to drink the whole 100 mL.[17] When a person was unable to drink the 100 mL, the residual water was measured and noted. In previous research, this test has proven to be highly reliable in patients with HNC (ICC=0.923 for number of swallows, and ICC=0.893 for duration).[26]

Saliva collection

Salivary flow was collected simultaneously from the floor of mouth (mainly submandibular gland) using a pipette, and from the left and right parotid gland using Lashley cups, as first described in 1981.[18] The cups were placed over the orifice of the Stenson's duct. Stimulation of the glands was achieved by applying one drop of citric acid to the mobile part of the tongue every minute, and collection was carried out for 10 minutes. The volume of saliva was measured as collected in tubes by weight, assuming the density of saliva 1 g/ml. The

flow rate was expressed in milliliters per 10 minutes (ml/10 min) for both parotid glands and the submandibular gland. In the present study, we used the total amount of saliva by adding up the saliva of both parotid glands and the submandibular gland. No oral stimulus was permitted for at least 30 minutes before saliva collection, including the WST and MAT.[27] In previous research, this test scored an ICC of 0.66 and 0.63 for the left and right parotid flow glands, indicating moderate test-retest reliability.[28]

EORTC QLQ-H&N35

The EORTC QLQ-H&N35 is an additional questionnaire to the EORTC QLQ-C30 (core instrument), and widely used to measure QoL in patients with HNC.[20] It consists of 7 subscales: pain in the mouth (4 items), problems with swallowing (4 items), senses (2 items), speech (3 items), social eating (4 items), social contact (5 items), sexuality (2 items), and eleven single items which address problems with teeth, opening mouth, dry mouth, sticky saliva, coughing, feeling ill, painkillers, nutritional supplements, feeding tube, weight loss, and weight gain.[29] The scores are transformed to a scale of 0 to 100, with a higher score on the symptom scales implying a higher level of symptoms or problems.[20] In the present study, we used the subscales 'pain in mouth' and 'social eating', and the single items 'teeth', 'opening mouth', 'weight loss', and 'weight gain' to explore the association between these PROs and the MAT. The subscales 'pain in mouth' and 'problems with swallowing', and the single items 'dry mouth', 'coughing', and 'feeding tube' were used to explore the association between these PROs and the WST. The single items 'dry mouth' and 'sticky saliva' were used to explore the association between these PROs and the salivary output. This questionnaire performs well on internal consistency and construct validity, and is able to differentiate between diverse groups of patients regarding treatment, tumor size, time elapsed since treatment, and age.[30] In patients with HNC, Cronbach's α range from 0.75 to 0.93 for most scales, indicating satisfactory internal consistency.[20,31]

SWAL-QOL

The SWAL-QOL consists of 39 items on 8 subscales: general burden, food selection, eating duration, eating desire, fear of eating, mental health, social functioning, and symptoms.[21,29] After completing, a total SWAL-QOL score could be calculated based on 23 items (item 1-9 and 12-25). The scores range from 0 to 100, with a higher score indicating more impairment.[29] In the present study we used the subscales 'food selection', 'eating duration', 'eating desire', 'fear of eating', and the total score to explore the association between these PROs and the MAT. We used the subscales 'general burden', 'symptoms', and the total score to explore the association between these PROs and the WST. Cronbach's α ranges from 0.79 to 0.95 in patients with oropharyngeal dysphagia, and intraclass correlations range from 0.59 to 0.91, indicating excellent scale reliability.[32]

GRIX

The GRIX consists of 14 questions and four subscales: xerostomia during day and night, and sticky saliva during day and night.[22] The scores were transformed to a scale from 0 to 100, with a higher score indicating more problems regarding xerostomia or sticky saliva. Total xerostomia and sticky saliva were calculated by adding up the day and night scores to get a score from 0 to 200. In the present study, all subscales were used to explore the association between the PROs and salivary flow. Cronbach's α of these scales ranges between 0.82 and 0.94, and test-retest reliability was between 0.63 and 0.67, indicating moderate correlations.[22]

Statistical analyses

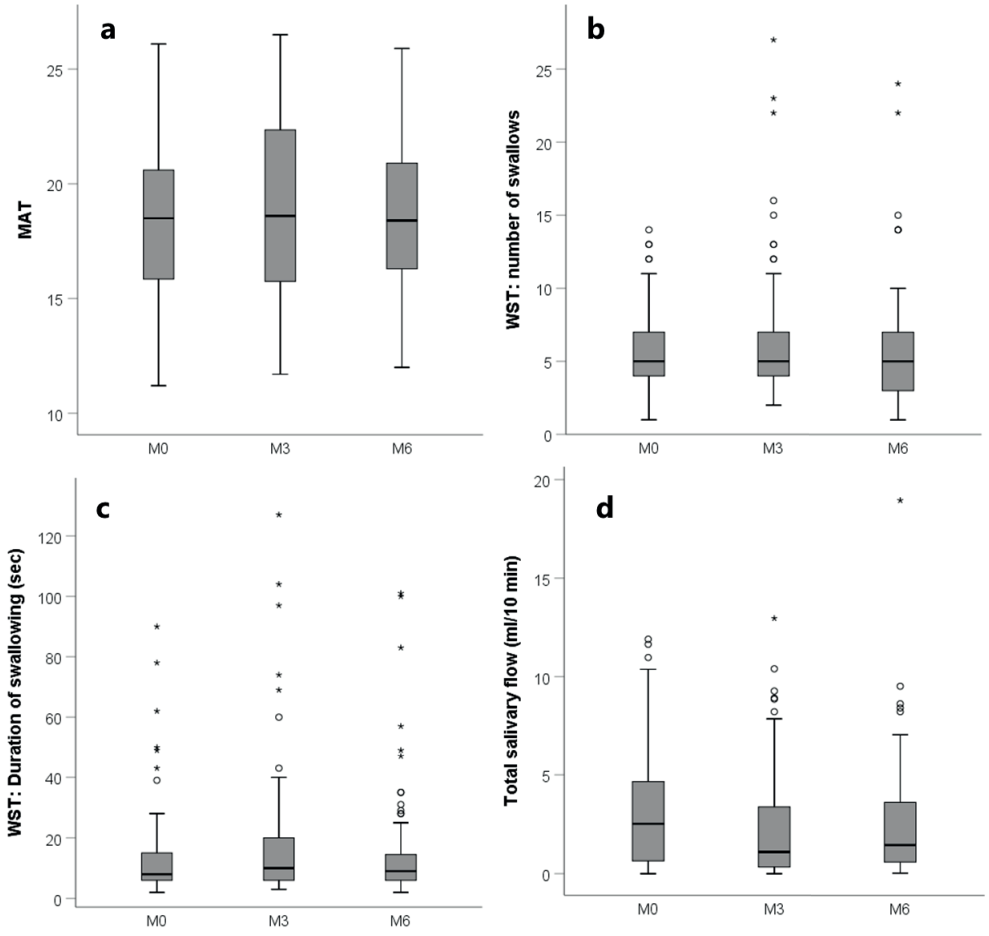
Data were tested for normality using a Shapiro-Wilk test. The associations between the WST, MAT, and salivary flow versus PROs were tested using Spearman's rank correlation coefficient. The spearman correlation coefficient was categorized as very weak (0.0 to 0.1), weak (0.1 to 0.39), moderate (0.4 to 0.69), strong (0.7 to 0.89), and very strong (0.9 to 1.0).[33] Scatterplots were created to visualize the MAT, WST, and salivary flow outcomes that had the highest correlation with one of the PROs. All analyses were performed using Statistical Package for the Social Sciences (SPSS) version 25 (Chicago, IL). A Bonferroni correction was used to account for the number of tests performed, in order to avoid a type I error.[34] This correction was calculated by dividing the p-value by the number of tests performed. The corrected p-value was 0.05/12=0.004 for the MAT, 0.05/8=0.006 for the WST, and 0.05/8=0.006 for the salivary flow. A p-value ≤0.004 or 0.006 was considered statistically significant.

Results

The study cohort consisted of 142 patients out of the total NET-QUBIC cohort in the UMCU (n=154), of which 64 patients had repeated measurements for the MAT and WST at M0, M3, and M6. Twenty of these 142 patients had repeated measurements for the salivary flow measurements at M0, M3, and M6. Characteristics of patients can be found in Table 1a for MAT and WST measures, and Table 1b for salivary flow measures. In total, 285 assessments for the MAT and WST were carried out: 101 at M0, 92 at M3, and 92 at M6. For the salivary flow measurements, 167 assessments were carried out: 45 at M0, 65 and M3, and 57 at M6. All data except the MAT at M0 and M6 were not normally distributed. Boxplots displaying the outcomes of the objective measurements can be found in Figure 1. Regarding WST, there were missing data in 6 patients at M0 (5 patients because they were unable to drink the 100 mL, and 1 patient because of choking or coughing post swallow), in 12 patients at M3 (9 because they choked or coughed post swallow, and 3 because they were unable to

drink the 100 mL), and in 9 patients at M6 (6 because they choked or coughed post swallow, and 3 because they were unable to drink the 100 mL).

Figure 1. Boxplots displaying all objective measurements at M0, M3 and M6 for the MAT (a), number of swallows on the WST (b), duration of swallowing on the WST (c), and total salivary flow (d), respectively



M0: before treatment, M3: 3 months after treatment, M6: 6 months after treatment

Table 1a. Characteristics of patients with HNC for MAT and WST measures

Characteristics	M0 (n = 101)	M3 (n = 92)	M6 (n = 92)	Repeated measurements M0, M3 and M6 (n = 64)
Age (median, IQR)	64.0 (15.5)	64.0 (13.8)	63.5 (13.8)	63.5 (14.0)
Sex				
Male	77 (76.2%)	72 (78.3%)	69 (75%)	49 (76.6%)
Female	24 (23.8%)	20 (21.7%)	23 (25%)	15 (23.4%)
Tumor site				
Oropharynx	36 (35.6%)	37 (40.2%)	34 (37.0%)	27 (42.2%)
Larynx	29 (28.7%)	24 (26.1%)	25 (27.2%)	16 (25.0%)
Oral cavity	27 (26.7%)	24 (26.1%)	26 (28.3%)	17 (26.6%)
Hypopharynx	3 (3.0%)	0 (0.0%)	3 (3.3%)	0 (0%)
Unknown primary	6 (5.9%)	7 (7.6%)	4 (4.3%)	4 (6.3%)
Tumor Stage				
I	27 (26.7%)	22 (23.9%)	24 (26.1%)	16 (25.0%)
II	20 (19.8%)	17 (18.5%)	20 (21.7%)	15 (23.4%)
III	13 (12.9%)	13 (14.1%)	12 (13.0%)	6 (9.4%)
IV	41 (40.6%)	40 (43.5%)	36 (39.1%)	27 (42.2%)
Primary Treatment				
RT	44 (43.6%)	42 (45.7%)	41 (44.6%)	30 (46.9%)
CRT	27 (26.7%)	25 (27.2%)	23 (25.0%)	18 (28.1%)
Surgery	20 (19.8%)	16 (17.4%)	19 (20.7%)	11 (17.2%)
Surgery with PO(C)RT	10 (9.9%)	9 (9.8%)	9 (9.8%)	5 (7.8%)

M0: before treatment, M3: 3 months after treatment, M6: 6 months after treatment
CRT: Chemoradiotherapy, IQR: Interquartile Range, PO(C)RT: Post-Operative (Chemo) Radiation, RT: Radiotherapy

MAT versus PROs

The associations between MAT and subscales of the EORTC QLQ-H&N35 were not statistically significant at M0, M3, and M6 (Table 2). The association between the MAT and subscales of the SWAL-QOL showed weak significant correlations at M0 for the items food selection (Spearman's ρ=0.347, p=0.001), eating duration (Spearman's ρ=0.361, p<0.001), fear of eating (Spearman's ρ=0.336, p=0.001), and total SWAL-QOL score (Spearman's ρ=0.310, p=0.002). No significant correlations were found at M3 and M6. As example, Figure 2a displays the MAT versus the eating duration at M0. Correlations between the MAT and all items of the EORTC-QLQ-H&N35, SWAL-QOL, and GRIX are shown in Appendix 1, 2, and 3, respectively.

Table 1b. Characteristics of patients with HNC for salivary flow measures

Characteristics	M0 (n = 45)	M3 (n = 65)	M6 (n = 57)	Repeated measurements M0, M3 and M6 (n = 20)
Age (median, IQR)	61.8 (16.0)	63.2 (15.0)	62.1 (13.5)	64.0 (11.0)
Sex				
Male	34 (75.6%)	55 (84.6%)	45 (78.9%)	15 (75.0%)
Female	11 (24.4%)	10 (15.4%)	12 (21.1%)	5 (25.0%)
Tumor site				
Oropharynx	14 (31.1%)	26 (40.0%)	23 (40.4%)	6 (30.0%)
Larynx	15 (33.3%)	18 (27.7%)	14 (24.6%)	6 (30.0%)
Oral cavity	11 (24.4%)	16 (24.6%)	16 (28.1%)	6 (30.0%)
Hypopharynx	1 (2.2%)	0 (0.0%)	1 (1.8%)	0 (0.0%)
Unknown primary	4 (8.9%)	5 (7.7%)	3 (5.3%)	2 (10.0%)
Tumor Stage				
I	16 (35.6%)	16 (24.6%)	15 (26.3%)	6 (30.0%)
II	8 (17.8%)	15 (23.1%)	12 (21.1%)	3 (15.0%)
III	3 (6.7%)	7 (10.8%)	5 (8.8%)	2 (10.0%)
IV	18 (40.0%)	27 (41.5%)	25 (43.9%)	9 (45.0%)
Primary Treatment				
RT	21 (46.7%)	31 (47.7%)	24 (42.1%)	8 (40.0%)
CRT	12 (26.7%)	17 (26.2%)	16 (28.1%)	7 (35.0%)
Surgery	8 (17.8%)	12 (18.5%)	10 (17.5%)	4 (20.0%)
Surgery with PO(C)RT	4 (8.9%)	5 (7.7%)	7 (12.3%)	1 (5.0%)

M0: before treatment, M3: 3 months after treatment, M6: 6 months after treatment
CRT: Chemoradiotherapy, IQR: Interquartile Range, PO(C)RT: Post-Operative (Chemo) Radiation, RT: Radiotherapy

WST versus PROs

The association between the PROs and the WST was calculated for both the number of swallows and swallowing duration (Table 3). The association between the number of swallows and subscales of the EORTC QLQ-H&N35 showed no significant correlations at M0, M3, and M6. The association between the number of swallows and subscales of the SWAL-QOL showed no significant correlations at M0 and M3. Weak significant correlations were found at M6 for the item total SWAL-QOL score (Spearman's ρ=0.335, p=0.001). The association between swallowing duration and subscales of the EORTC QLQ-H&N35 showed no significant correlations at M0, M3 and M6. The association between duration and subscales of the SWAL-QOL showed no significant correlations at M0. At M3, weak significant correlations were found for the items food selection (Spearman's ρ=0.332, p=0.001) and total SWAL-QOL score (Spearman's ρ=0.353, p=0.001). At M6, weak

significant correlations were found for the item total SWAL-QOL score (Spearman's ρ=0.398, p<0.001). As example, Figure 2b displays the total score on the SWAL-QOL questionnaire versus the number of swallows of the WST, and Figure 2c displays the total score on the SWAL-QOL questionnaire versus the duration of the WST, both at M6. Correlations between the WST and all items of the EORTC-QLQ-H&N35, SWAL-QOL, and GRIX are shown in Appendix 4, 5, and 6, respectively.

Table 2. Spearman correlation coefficients of the MAT versus the EORTC QLQ-H&N35 and SWAL-QOL

MAT	**M0 (n = 101)**		**M3 (n = 92)**		**M6 (n = 92)**	
EORTC QLQ-H&N35	Spearman's ρ	p-value	Spearman's ρ	p-value	Spearman's ρ	p-value
Pain in mouth	0.082	0.417	0.066	0.541	-0.014	0.896
Trouble with social eating	0.141	0.166	0.276	0.009*	0.201	0.054
Teeth	-0.004	0.972	0.097	0.368	0.106	0.313
Opening mouth	0.026	0.803	0.211	0.048*	-0.028	0.792
Feeding tube	-0.102	0.319	0.146	0.173	-0.040	0.703
Weight loss	-0.119	0.247	-0.004	0.968	-0.009	0.936
Weight gain	0.058	0.571	0.004	0.970	0.086	0.412
SWAL-QOL						
Food selection	0.347	0.001*†	0.227	0.034*	0.232	0.026*
Eating duration	0.361	<0.001*†	0.154	0.152	0.185	0.078
Eating desire	0.167	0.105	0.014	0.900	0.211	0.043*
Fear of eating	0.336	0.001*†	0.172	0.108	0.163	0.119
Total score	0.310	0.002*†	0.165	0.124	0.222	0.033*

*: p<0.05, †: p≤0.004 (Bonferroni correction), M0: before treatment, M3: 3 months after treatment, M6: 6 months after treatment

Table 3. Spearman correlation coefficients of the WST versus the EORTC QLQ-H&N35 and SWAL-QOL

WST	**Number of swallows**						**Duration**					
	M0 (n = 101)		**M3 (n = 92)**		**M6 (n = 92)**		**M0 (n = 101)**		**M3 (n = 92)**		**M6 (n = 92)**	
EORTC QLQ-H&N35	*Spearman' s ρ*	*p-value*	*Spearman' s ρ*	*p-value*	*Spearman' s ρ*	*p-value*	*Spearman' s ρ*	*p-value*	*Spearman' s ρ*	*p-value*	*Spearman' s ρ*	*p-value*
Pain in mouth	0.088	0.378	0.175	0.094	-0.009	0.936	0.125	0.205	0.253	0.015*	-0.075	0.479
Swallowing	0.145	0.145	0.201	0.055	-0.009	0.295	0.172	0.082	0.260	0.012*	0.176	0.094
Dry mouth	0.052	0.603	0.053	0.616	-0.085	0.422	0.013	0.897	0.177	0.091	-0.022	0.832
Coughing	-0.018	0.859	0.035	0.741	-0.056	0.595	0.090	0.364	0.092	0.385	0.018	0.866
SWAL-QOL												
General burden	0.175	0.084	0.156	0.135	0.083	0.430	0.026	0.806	0.205	0.049*	0.162	0.123
Food selection	0.106	0.292	0.226	0.029*	0.244	0.020*	0.110	0.299	0.332	0.001*†	0.265	0.011*
Symptoms	0.248	0.013*	0.172	0.101	0.142	0.179	0.138	0.193	0.268	0.010*	0.255	0.015*
Total score	0.201	0.046*	0.238	0.023*	0.335	0.001*†	0.194	0.064	0.353	0.001*†	0.398	<0.001

*: $p<0.05$, †: $p\leq0.006$ (Bonferroni correction), M0: before treatment, M3: 3 months after treatment, M6: 6 months after treatment

Salivary flow versus PROs

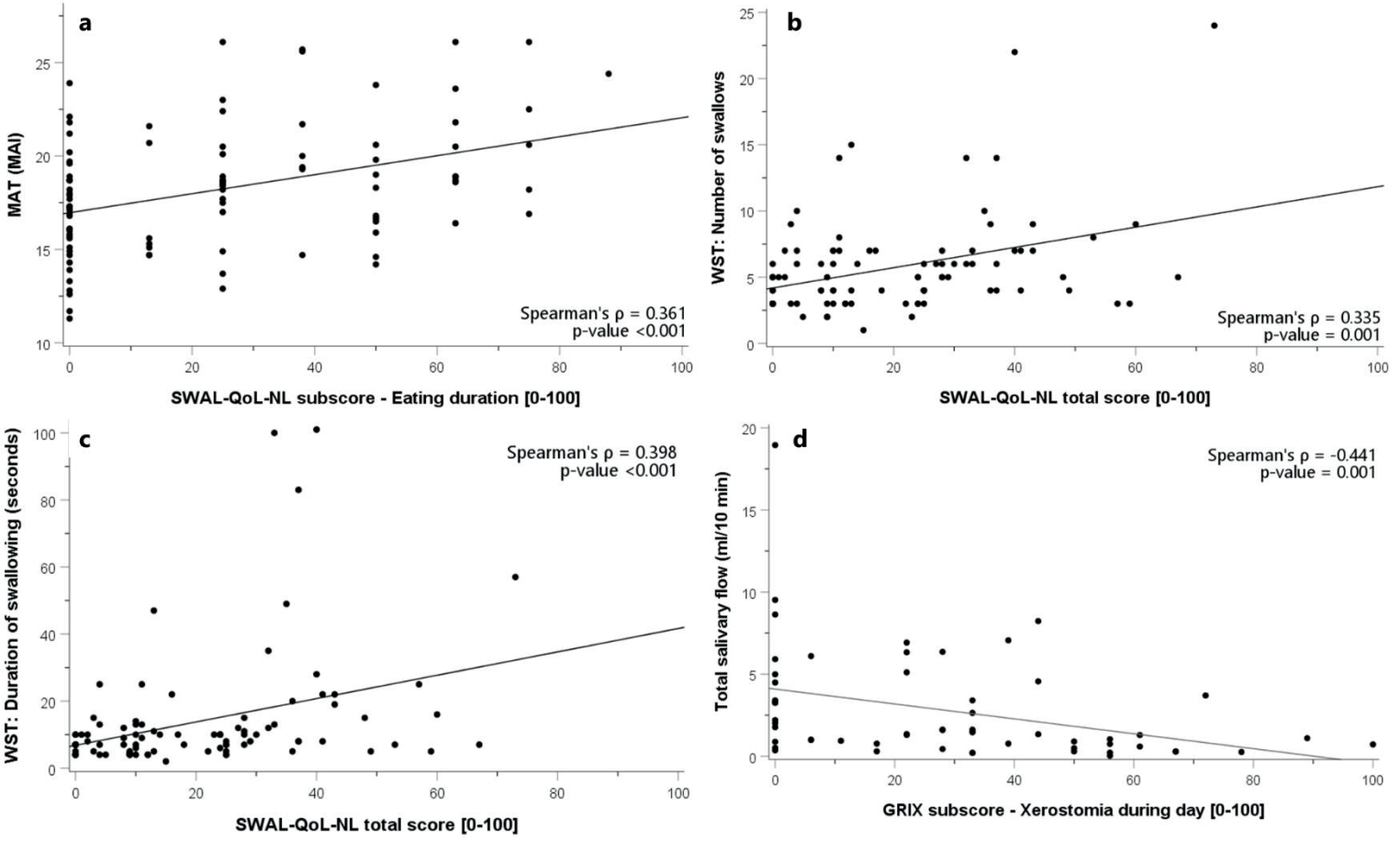
The association between total salivary flow and subscales of the EORTC QLQ-H&N35 and GRIX showed no significant differences at M0 (Table 4). At M3, weak significant differences were found for dry mouth (Spearman's ρ=-0.339, p=0.004) and sticky saliva (Spearman's ρ=-0.321, p=0.006) on the EORTC QLQ-H&N35, and for xerostomia during the day (Spearman's ρ=-0.332, p=0.006) on the GRIX questionnaire. At M6, weak significant differences were found for the item sticky saliva (Spearman's ρ=-0.350, p=0.006) on the EORTC QLQ-H&N35 and for the item sticky saliva during the day (Spearman's ρ=-0.348, p=0.006) on the GRIX questionnaire. A moderate correlation was found for the item xerostomia during the day (Spearman's ρ=-0.441, p=0.001) on the GRIX questionnaire. As example, Figure 2d displays xerostomia during the day versus total saliva at M6. Correlations between total salivary flow and all items of the EORTC QLQ-H&N35 and SWAL-QOL can be found in Appendices 7 and 8, respectively.

Table 4. Spearman correlation coefficients of salivary flow versus the EORTC QLQ-H&N35 and GRIX

Total salivary flow	**M0 (n = 45)**		**M3 (n = 65)**		**M6 (n = 57)**	
EORTC QLQ-H&N35	Spearman's ρ	p-value	Spearman's ρ	p-value	Spearman's ρ	p-value
Dry mouth	-0.227	0.126	-0.339	0.004*†	-0.279	0.031*
Sticky saliva	-0.217	0.143	-0.321	0.006*†	-0.350	0.006*†
GRIX						
Xerostomia during day	-0.254	0.092	-0.332	0.006*†	-0.441	0.001*†
Xerostomia during night	-0.147	0.329	-0.225	0.063	-0.099	0.450
Xerostomia total score	-0.182	0.232	-0.327	0.008*	-0.320	0.015*
Sticky saliva during day	-0.218	0.151	-0.282	0.019*	-0.348	0.006*†
Sticky saliva during night	-0.299	0.044*	-0.192	0.115	-0.128	0.331
Sticky saliva total score	-0.271	0.072	-0.274	0.023*	-0.256	0.048*

*: p<0.05, †: p≤0.006 (Bonferroni correction), M0: before treatment, M3: 3 months after treatment, M6: 6 months after treatment

Figure 2. Scatterplots displaying the highest correlation for each objective measure; the eating duration on the SWAL-QOL versus the MAT at M0 (a), the total score on the SWAL-QOL questionnaire versus the number of swallows on the WST at M6 (b) and duration at M6 (c), and the xerostomia by day versus the total amount of saliva at M6 (d), respectively



Discussion

This study investigated associations between objective tests of mastication, swallowing, and salivary production and patients reported outcomes. The associations between objective tests and PROs were weak (correlation below 0.40) for all items, except one: a moderate correlation between xerostomia during the day versus total salivary flow at M6 (Spearman's ρ=-0.441, p=0.001). In addition, none of the items on the EORTC QLQ-H&N35 questionnaire showed a significant correlation to the MAT nor WST. Even when focusing on patients with the highest 10% scores on the MAT or WST, indicating worst masticatory or swallowing performance (see the top part in Figure 2a-c), there was still a large variation of scores on the PROs taking up almost the entire scale. These findings indicate that the objective tests used in this research do not measure the same construct as the used PROs.

Comparison with literature

Our findings are in line with previous research in patients with HNC that showed that clinical measures and PROs generally correlate poorly.[10,12,35] For example, swallowing research showed weak to strong associations between the 100 mL WST and the MD Anderson Dysphagia Inventory (MDADI) questionnaire (a questionnaire similar to the SWAL-QOL).[10] Research about salivary measurements found weak associations between salivary flow and xerostomia scores.[36] Other research stated that the EORTC quality of life questionnaire provided valuable data on subjective complaints, but that these complaints are not closely correlated with specific objective changes.[37]

Previous research in patients with Parkinson's disease and patients with schizophrenia showed that objective and subjective measures were not interchangeable and each has a unique contribution to the problems assessed.[38,39] Both objective and subjective measures may predict QoL in these patients.[38] Using PROs alone does not seem to measure function the same way functional tests do, and therefore should be combined with other data sources.[9] PROs are designed to assess how a patient evaluates his or her functioning rather than actual performance.[40] In addition, functional disorders measured via instrumental assessments by clinicians may not have a strong relationship with how patients perceive this disorder. Patients are more likely to rate their symptoms more severely than do clinicians, which can lead to an underestimation of side effects post-treatment.[41] Before selecting a measurement method, it is therefore important to identify the purpose of the measurement. For instance, when the effect of swallowing muscle sparing with RT is assessed, it is important to objectively test swallowing function. Whereas when the goal is to evaluate the effect of swallowing muscle sparing RT on perceived swallowing function of patients, it is important to use PROs. When only PROs are measured, it can be difficult to

determine the cause of the reduced swallowing sensation. Individuals differ in what they find important, and expectations about one's progress after treatment may change over time and in response to personal circumstances. Patients may develop a degree of adaptation over time, in which their PRO outcomes improve, but swallowing dysfunction stays the same or worsens.[11] Their subjective feeling of QoL also depends on satisfaction with, physical, material, emotional, and social wellbeing, and their development and activity. Objective observations record only what is observed; they are a representation of how something is.[42] The MAT, for example, reflects a complex process of oral muscle movements and coordination, which is difficult to answer with one single question in a questionnaire. Unfortunately, the loss of teeth, dental decay and periodontal health were not assessed in this research, and may play an important role in oral functioning as well.[37]

Strengths and limitations

A limitation of this study was that the number of salivary flow measurements performed was smaller in comparison to the masticatory performance and swallowing measurements. Therefore, it is possible that these measurements are less reliable due to insufficient power. The salivary flow measurements were much more time consuming, and difficulties occurred with the attachment of the Lashley cups. Therefore, it was chosen to combine the submandibular flow with the parotid flow, and use the total flow to determine the associations between objective and subjective measures. Although these associations regarding xerostomia were higher in comparison to those of masticatory performance and swallowing measurements, a prerequisite should be that the objective test is easy and fast to perform, in order to be a valuable addition to PROs. A recommendation would therefore be to use an easy and fast test for measuring saliva flow, for example by spitting saliva produced over a period of time in a plastic tube, with and without stimulation.[43]

The SWAL-QOL questionnaire is especially designed to detect swallowing problems. However, there is a close relationship between swallowing and mastication, as seen in multiple items such as 'food selection', 'eating duration', 'eating desire', and 'fear of eating'. This relationship also comes across in many items of, e.g., the MDADI questionnaire.[44] When the focus is on swallowing specific problems, it is therefore recommended to use swallowing specific questions only, in combination with an objective swallowing test.

As shown in previous research, the reliability of the MAT, WST, EORTC QLQ-H&N35, and SWAL-QOL was high, with a reliability of 0.886 for the MAT, and 0.893 and 0.923 for the WST. The reliability of the questionnaires was between 0.75 and 0.95, indicating that all measures are reliable to use in patients with HNC.[15,20,26,31,32] This study provides insight in the (weak) association between these objective and subjective measures. The results are

important to take into account when developing prediction models to identify patients at risk for developing mastication, dysphagia, or xerostomia problems after treatment. Consistent with previous research, the results in this paper show that objective and subjective measures do not seem to measure the same construct, and therefore separate prediction models with objective and subjective outcomes should be created, depending on the aim of the model.

Conclusion

This study showed significant but weak associations between objective tests of masticatory performance, swallowing, and salivary performance and patient-reported outcomes. It is therefore important to measure mastication, dysphagia and xerostomia related problems in patients with HNC both objectively and subjectively. This will acquire unique information and will help create the complete picture of a patients' perspective and functioning.

Appendix

Appendix 1. Spearman correlation coefficients of the MAT versus the EORTC QLQ-H&N35

MAT	**M0**		**M3**		**M6**	
EORTC QLQ-H&N35	**(n = 101)**		**(n = 92)**		**(n = 92)**	
	Spearman's ρ	p-value	Spearman's ρ	p-value	Spearman's ρ	p-value
Pain in mouth	0.082	0.417	0.066	0.541	-0.014	0.896
Swallowing	0.103	0.312	0.123	0.253	0.245	0.018*
Senses problems	0.120	0.238	0.198	0.065	0.101	0.337
Speech problems	0.009	0.929	0.200	0.062	0.156	0.135
Trouble with social eating	0.141	0.166	0.276	0.009*	0.201	0.054
Trouble with social contact	0.029	0.778	0.295	0.005*	0.209	0.045*
Less sexuality	-0.048	0.642	0.084	0.447	0.187	0.078
Teeth	-0.004	0.972	0.097	0.368	0.106	0.313
Opening mouth	0.026	0.803	0.211	0.048*	-0.028	0.792
Dry mouth	-0.035	0.734	-0.032	0.766	-0.122	0.243
Sticky saliva	-0.053	0.605	-0.001	0.995	-0.073	0.487
Coughing	0.102	0.317	0.186	0.083	0.143	0.171
Feeling ill	0.013	0.903	0.113	0.296	0.104	0.324
Pain killers	0.135	0.186	0.068	0.530	0.069	0.510
Nutritional supplements	0.163	0.109	0.214	0.045*	0.089	0.395
Feeding tube	-0.102	0.319	0.146	0.173	-0.040	0.703
Weight loss	-0.119	0.247	-0.004	0.968	-0.009	0.936
Weight gain	0.058	0.571	0.004	0.970	0.086	0.412

*: $p<0.05$, M0: before treatment, M3: 3 months after treatment, M6: 6 months after treatment

Appendix 2. Spearman correlation coefficients of the MAT versus the SWAL-QOL

MAT SWAL-QOL	M0 (n = 101)		M3 (n = 92)		M6 (n = 92)	
	Spearman's ρ	p-value	Spearman's ρ	p-value	Spearman's ρ	p-value
General burden	0.264	0.010*	0.032	0.767	0.150	0.151
Food selection	0.347	0.001*	0.227	0.034*	0.232	0.026*
Eating duration	0.361	<0.001*	0.154	0.152	0.185	0.078
Eating desire	0.167	0.105	0.014	0.900	0.211	0.043*
Fear of eating	0.336	0.001*	0.172	0.108	0.163	0.119
Mental health	0.323	0.001*	0.112	0.299	0.204	0.051
Social functioning	0.247	0.016*	0.225	0.035*	0.202	0.052
Symptoms	0.385	<0.001*	0.239	0.025*	0.292	0.005*
Total score	0.310	0.002*	0.165	0.124	0.222	0.033*

*: p<0.05, M0: before treatment, M3: 3 months after treatment, M6: 6 months after treatment

Appendix 3. Spearman correlation coefficients of the MAT versus the GRIX

MAT GRIX	M0 (n = 93)		M3 (n = 82)		M6 (n = 89)	
	Spearman's ρ	p-value	Spearman's ρ	p-value	Spearman's ρ	p-value
Xerostomia during day	0.008	0.936	-0.022	0.843	-0.065	0.548
Xerostomia during night	0.126	0.223	0.041	0.705	0.091	0.386
Xerostomia total score	0.089	0.398	0.007	0.949	0.026	0.809
Sticky saliva during day	0.260	0.010*	-0.104	0.339	0.006	0.959
Sticky saliva during night	0.244	0.016*	-0.038	0.729	0.007	0.947
Sticky saliva total score	0.301	0.003*	-0.093	0.392	0.008	0.943

*: p<0.05, M0: before treatment, M3: 3 months after treatment, M6: 6 months after treatment

Appendix 4a. Spearman correlation coefficients of the WST versus the EORTC QLQ-H&N35 for the number of swallows

WST	**Number of swallows**					
EORTC QLQ-H&N35	**M0 (n = 101)**		**M3 (n = 92)**		**M6 (n = 92)**	
	Spearman's ρ	p-value	Spearman's ρ	p-value	Spearman's ρ	p-value
Pain in mouth	0.088	0.378	0.175	0.094	-0.009	0.936
Swallowing	0.145	0.145	0.201	0.055	0.110	0.295
Senses problems	0.056	0.575	0.055	0.601	-0.030	0.774
Speech problems	-0.043	0.667	0.173	0.099	0.110	0.295
Trouble with social eating	0.126	0.206	0.113	0.285	0.279	0.007*
Trouble with social contact	0.050	0.615	0.135	0.201	0.156	0.138
Less sexuality	0.152	0.128	-0.003	0.981	-0.017	0.877
Teeth	-0.072	0.472	-0.013	0.903	0.024	0.819
Opening mouth	0.114	0.253	0.067	0.525	0.073	0.489
Dry mouth	0.052	0.603	0.053	0.616	-0.085	0.422
Sticky saliva	-0.121	0.227	0.107	0.308	-0.037	0.724
Coughing	-0.018	0.859	0.035	0.741	-0.056	0.595
Feeling ill	0.082	0.413	0.169	0.108	0.161	0.127
Pain killers	0.003	0.975	0.037	0.728	-0.109	0.303
Nutritional supplements	0.052	0.607	0.086	0.417	0.156	0.137
Feeding tube	-0.106	0.289	-0.044	0.680	0.144	0.172
Weight loss	-0.120	0.234	0.043	0.683	0.004	0.973
Weight gain	-0.087	0.388	-0.170	0.108	0.108	0.306

*: $p<0.05$, M0: before treatment, M3: 3 months after treatment, M6: 6 months after treatment

Appendix 4b. Spearman correlation coefficients of the WST versus the EORTC QLQ-H&N35 for the swallowing duration

WST	**Duration**					
EORTC QLQ-H&N35	**M0 (n = 101)**		**M3 (n = 92)**		**M6 (n = 92)**	
	Spearman's ρ	p-value	Spearman's ρ	p-value	Spearman's ρ	p-value
Pain in mouth	0.125	0.205	0.253	0.015*	-0.075	0.479
Swallowing	0.172	0.082	0.260	0.012*	0.176	0.094
Senses problems	0.064	0.523	0.177	0.091	0.051	0.629
Speech problems	0.070	0.482	0.291	0.005*	0.187	0.074
Trouble with social eating	0.178	0.072	0.277	0.008*	0.302	0.003*
Trouble with social contact	0.104	0.297	0.274	0.008*	0.196	0.062
Less sexuality	0.166	0.096	-0.022	0.837	0.106	0.322
Teeth	0.015	0.883	0.085	0.421	0.098	0.359
Opening mouth	0.004	0.964	0.163	0.121	-0.047	0.656
Dry mouth	0.013	0.897	0.177	0.091	-0.022	0.832
Sticky saliva	0.015	0.879	0.238	0.022*	0.077	0.467
Coughing	0.090	0.364	0.092	0.385	0.018	0.866
Feeling ill	0.029	0.775	0.282	0.007*	0.112	0.291
Pain killers	0.047	0.637	0.020	0.847	-0.087	0.408
Nutritional supplements	0.093	0.348	0.192	0.067	0.151	0.150
Feeding tube	-0.073	0.461	0.030	0.775	0.117	0.266
Weight loss	-0.024	0.810	0.053	0.618	0.031	0.773
Weight gain	-0.103	0.303	0.065	0.539	0.030	0.777

*: $p<0.05$, M0: before treatment, M3: 3 months after treatment, M6: 6 months after treatment

Appendix 5a. Spearman correlation coefficients of the WST versus the SWAL-QOL for the number of swallows

WST	**Number of swallows**					
SWAL-QOL	**M0 (n = 101)**		**M3 (n = 92)**		**M6 (n = 92)**	
	Spearman's ρ	p-value	Spearman's ρ	p-value	Spearman's ρ	p-value
General burden	0.175	0.084	0.156	0.135	0.083	0.430
Food selection	0.106	0.292	0.226	0.029*	0.244	0.020*
Eating duration	0.172	0.087	0.204	0.051	0.336	0.001*
Eating desire	0.024	0.814	0.140	0.183	0.282	0.006*
Fear of eating	0.222	0.026*	0.217	0.038*	0.281	0.007*
Mental health	0.123	0.226	0.196	0.061	0.242	0.021*
Social functioning	0.159	0.118	0.214	0.041*	0.231	0.027*
Symptoms	0.248	0.013*	0.172	0.101	0.142	0.179
Total score	0.201	0.046*	0.238	0.023*	0.335	0.001*

*: p<0.05, M0: before treatment, M3: 3 months after treatment, M6: 6 months after treatment

Appendix 5b. Spearman correlation coefficients of the WST versus the SWAL-QOL for the swallowing duration

WST	**Duration**					
SWAL-QOL	**M0 (n = 101)**		**M3 (n = 92)**		**M6 (n = 92)**	
	Spearman's ρ	p-value	Spearman's ρ	p-value	Spearman's ρ	p-value
General burden	0.026	0.806	0.205	0.049*	0.162	0.123
Food selection	0.110	0.299	0.332	0.001*	0.265	0.011*
Eating duration	0.222	0.034*	0.315	0.002*	0.364	<0.001*
Eating desire	0.171	0.104	0.322	0.002*	0.338	0.001*
Fear of eating	0.210	0.044*	0.316	0.002*	0.399	<0.001*
Mental health	0.143	0.175	0.211	0.044*	0.296	0.004*
Social functioning	0.106	0.314	0.280	0.007*	0.254	0.014*
Symptoms	0.138	0.193	0.268	0.010*	0.255	0.015*
Total score	0.194	0.064	0.353	0.001*	0.398	<0.001*

*: p<0.05, M0: before treatment, M3: 3 months after treatment, M6: 6 months after treatment

Appendix 6a. Spearman correlation coefficients of the WST versus the GRIX for the number of swallows

WST	**Number of swallows**					
GRIX	**M0**		**M3**		**M6**	
	(n = 97)		**(n = 85)**		**(n = 87)**	
	Spearman's ρ	p-value	Spearman's ρ	p-value	Spearman's ρ	p-value
Xerostomia during day	0.081	0.428	-0.071	0.513	-0.056	0.605
Xerostomia during night	0.115	0.257	0.095	0.374	-0.036	0.734
Xerostomia total score	0.098	0.341	0.025	0.820	-0.077	0.476
Sticky saliva during day	0.082	0.420	0.059	0.584	-0.048	0.652
Sticky saliva during night	0.103	0.307	-0.101	0.342	-0.066	0.529
Sticky saliva total score	0.075	0.459	-0.009	0.931	-0.107	0.315

*: p<0.05, M0: before treatment, M3: 3 months after treatment, M6: 6 months after treatment

Appendix 6b. Spearman correlation coefficients of the WST versus the GRIX for the swallowing duration

WST	**Duration**					
GRIX	**M0**		**M3**		**M6**	
	(n = 97)		**(n = 85)**		**(n = 87)**	
	Spearman's ρ	p-value	Spearman's ρ	p-value	Spearman's ρ	p-value
Xerostomia during day	0.103	0.307	0.060	0.584	0.022	0.843
Xerostomia during night	0.190	0.058	0.155	0.145	0.042	0.691
Xerostomia total score	0.137	0.180	0.124	0.257	0.027	0.805
Sticky saliva during day	0.185	0.064	0.149	0.161	0.080	0.453
Sticky saliva during night	0.244	0.014*	0.046	0.665	-0.001	0.990
Sticky saliva total score	0.212	0.034*	0.109	0.306	0.008	0.941

*: p<0.05, M0: before treatment, M3: 3 months after treatment, M6: 6 months after treatment

Appendix 7. Spearman correlation coefficients of salivary flow versus the EORTC QLQ-H&N35

Salivary flow	**M0**		**M3**		**M6**	
EORTC QLQ-H&N35	**(n = 45)**		**(n = 68)**		**(n = 59)**	
	Spearman's ρ	p-value	Spearman's ρ	p-value	Spearman's ρ	p-value
Pain in mouth	-0.100	0.503	-0.171	0.153	-0.048	0.718
Swallowing	-0.050	0.737	-0.167	0.164	0.073	0.579
Senses problems	-0.450	0.002*	-0.272	0.022*	-0.287	0.026*
Speech problems	0.037	0.803	0.057	0.635	0.168	0.199
Trouble with social eating	-0.051	0.735	-0.292	0.014*	-0.238	0.067
Trouble with social contact	-0.179	0.228	-0.102	0.397	-0.008	0.950
Less sexuality	-0.024	0.875	-0.008	0.950	-0.181	0.171
Teeth	0.042	0.778	-0.034	0.775	-0.091	0.493
Opening mouth	-0.188	0.207	-0.174	0.146	0.093	0.479
Dry mouth	-0.227	0.126	-0.339	0.004*	-0.279	0.031*
Sticky saliva	-0.217	0.143	-0.321	0.006*	-0.350	0.006*
Coughing	-0.300	0.040*	-0.022	0.853	-0.074	0.572
Feeling ill	-0.125	0.403	0.024	0.843	0.124	0.351
Pain killers	0.011	0.940	0.056	0.645	-0.133	0.310
Nutritional supplements	-0.390	0.007*	-0.314	0.008*	-0.162	0.215
Feeding tube	-0.196	0.187	-0.189	0.114	NA	NA
Weight loss	-0.038	0.805	-0.105	0.384	-0.267	0.041*
Weight gain	-0.185	0.219	0.059	0.627	-0.127	0.335

*: $p<0.05$, M0: before treatment, M3: 3 months after treatment, M6: 6 months after treatment

Appendix 8. Spearman correlation coefficients of salivary flow versus the SWAL-QOL

Salivary flow	**M0**		**M3**		**M6**	
SWAL-QOL	**(n = 45)**		**(n = 71)**		**(n = 57)**	
	Spearman's ρ	p-value	Spearman's ρ	p-value	Spearman's ρ	p-value
General burden	-0.145	0.347	-0.146	0.220	-0.032	0.810
Food selection	-0.147	0.337	-0.219	0.065	-0.312	0.015*
Eating duration	-0.218	0.150	-0.337	0.004*	-0.122	0.354
Eating desire	-0.182	0.231	-0.393	0.001*	-0.202	0.121
Fear of eating	-0.239	0.114	-0.148	0.218	-0.146	0.266
Mental health	-0.126	0.414	-0.273	0.021*	-0.235	0.070
Social functioning	-0.148	0.342	-0.322	0.006*	-0.224	0.086
Symptoms	-0.155	0.314	-0.194	0.105	-0.157	0.231
Total score	-0.218	0.156	-0.338	0.004*	-0.245	0.059

*: p<0.05, M0: before treatment, M3: 3 months after treatment, M6: 6 months after treatment

Appendix 9. Spearman correlation coefficients of salivary flow versus the GRIX

Salivary flow	**M0**		**M3**		**M6**	
GRIX	**(n = 45)**		**(n = 65)**		**(n = 57)**	
	Spearman's ρ	p-value	Spearman's ρ	p-value	Spearman's ρ	p-value
Xerostomia during day	-0.254	0.092	-0.332	0.006*	-0.441	0.001*
Xerostomia during night	-0.147	0.329	-0.225	0.063	-0.099	0.450
Xerostomia total score	-0.182	0.232	-0.327	0.008*	-0.320	0.015*
Sticky saliva during day	-0.218	0.151	-0.282	0.019*	-0.348	0.006*
Sticky saliva during night	-0.299	0.044*	-0.192	0.115	-0.128	0.331
Sticky saliva total score	-0.271	0.072	-0.274	0.023*	-0.256	0.048*

*: p<0.05, M0: before treatment, M3: 3 months after treatment, M6: 6 months after treatment

References

1. Rettig EM, D'Souza G. Epidemiology of head and neck cancer. *Surgical oncology clinics of North America.* 2015;24(3):379-396.
2. Ringash J, Bernstein LJ, Devins G, et al. Head and Neck Cancer Survivorship: Learning the Needs, Meeting the Needs. *Seminars in radiation oncology.* 2018;28(1):64-74.
3. Riffat F, Gunaratne DA, Palme CE. Swallowing assessment and management pre and post head and neck cancer treatment. *Current opinion in otolaryngology & head and neck surgery.* 2015;23(6):440-447.
4. Kamal M, Rosenthal DI, Volpe S, et al. Patient reported dry mouth: Instrument comparison and model performance for correlation with quality of life in head and neck cancer survivors. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology.* 2018;126(1):75-80.
5. Hamlet S, Faull J, Klein B, et al. Mastication and swallowing in patients with postirradiation xerostomia. *Int J Radiation Oncology Biol.* 1997;37(4):789-796.
6. Buitenweg DC, Bongers IL, van de Mheen D, van Oers HAM, van Nieuwenhuizen C. Subjectively different but objectively the same? Three profiles of QoL in people with severe mental health problems. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation.* 2018;27(11):2965-2974.
7. Mascolo MF. Beyond Objectivity and Subjectivity: The Intersubjective Foundations of Psychological Science. *Integr Psychol Behav Sci.* 2016;50(4):543-554.
8. Papadakos JK, Charow RC, Papadakos CJ, Moody LJ, Giuliani ME. Evaluating cancer patient-reported outcome measures: Readability and implications for clinical use. *Cancer.* 2019;125(8):1350-1356.
9. Wolpert M. Uses and abuses of patient reported outcome measures (PROMs): potential iatrogenic impact of PROMs implementation and how it can be mitigated. *Adm Policy Ment Health.* 2014;41(2):141-145.
10. Pedersen A, Wilson J, McColl E, Carding P, Patterson J. Swallowing outcome measures in head and neck cancer--How do they compare? *Oral oncology.* 2016;52:104-108.
11. Frowen J, Drosdowsky A, Perry A, Corry J. Long-term swallowing after chemoradiotherapy: Prospective study of functional and patient-reported changes over time. *Head & neck.* 2016;38 Suppl 1:E307-315.
12. Hedstrom J, Tuomi L, Finizia C, Olsson C. Correlations Between Patient-Reported Dysphagia Screening and Penetration-Aspiration Scores in Head and Neck Cancer Patients Post-oncological Treatment. *Dysphagia.* 2018;33(2):206-215.
13. Rogus-Pulia NM, Pierce MC, Mittal BB, Zecker SG, Logemann JA. Changes in swallowing physiology and patient perception of swallowing function following chemoradiation for head and neck cancer. *Dysphagia.* 2014;29(2):223-233.
14. Elgestad Stjernfeldt P, Sjogren P, Wardh I, Bostrom AM. Systematic review of measurement properties of methods for objectively assessing masticatory performance. *Clinical and experimental dental research.* 2018;5(1):76-104.
15. Vermaire JA, Weinberg FM, Raaijmakers CPJ, Verdonck-de Leeuw IM, Terhaard CHJ, Speksnijder CM. Reliability of the mixing ability test testing masticatory performance in patients with head and neck cancer and healthy controls. *Journal of oral rehabilitation.* 2020.
16. Nathadwarawala KM, Nicklin J, Wiles CM. A timed test of swallowing capacity for neurological patients. *J Neurol Neurosurg Psychiatry.* 1992;55(9):822-825.
17. Patterson JM, Hildreth A, McColl E, Carding PN, Hamilton D, Wilson JA. The clinical application of the 100mL water swallow test in head and neck cancer. *Oral oncology.* 2011;47(3):180-184.
18. Baum BJ. Evaluation of stimulated parotid saliva flow rate in different age groups. *Journal of dental research.* 1981;60(7):1292-1296.

19. van der Veen J, Nuyts S. Can Intensity-Modulated-Radiotherapy Reduce Toxicity in Head and Neck Squamous Cell Carcinoma? *Cancers.* 2017;9(12):135.

20. Bjordal K, de Graeff A, Fayers PM, et al. A 12 country field study of the EORTC QLQ-C30 (version 3.0) and the head and neck cancer specific module (EORTC QLQ-H&N35) in head and neck patients. EORTC Quality of Life Group. *European journal of cancer.* 2000;36(14):1796-1807.

21. Bogaardt HC, Speyer R, Baijens LW, Fokkens WJ. Cross-cultural adaptation and validation of the Dutch version of SWAL-QoL. *Dysphagia.* 2009;24(1):66-70.

22. Beetz I, Burlage FR, Bijl HP, et al. The Groningen Radiotherapy-Induced Xerostomia questionnaire: development and validation of a new questionnaire. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology.* 2010;97(1):127-131.

23. Verdonck-de Leeuw IM, Jansen F, Brakenhoff RH, et al. Advancing interdisciplinary research in head and neck cancer through a multicenter longitudinal prospective cohort study: the NETherlands QUality of life and BIomedical Cohort (NET-QUBIC) data warehouse and biobank. *BMC Cancer.* 2019;19(1):765.

24. Speksnijder CM, Abbink JH, van der Glas HW, Janssen NG, van der Bilt A. Mixing ability test compared with a comminution test in persons with normal and compromised masticatory performance. *Eur J Oral Sci.* 2009;117(5):580-586.

25. Patterson JM, McColl E, Carding PN, Kelly C, Wilson JA. Swallowing performance in patients with head and neck cancer: a simple clinical test. *Oral oncology.* 2009;45(10):904-907.

26. Vermaire JA, Terhaard CHJ, Verdonck-de Leeuw IM, Raaijmakers CPJ, Speksnijder CM. Reliability of the 100 mL water swallow test in patients with head and neck cancer and healthy subjects. *Head & neck.* 2021;43(8):2468-2476.

27. Houweling AC, Philippens ME, Dijkema T, et al. A comparison of dose-response models for the parotid gland in a large group of head-and-neck cancer patients. *International journal of radiation oncology, biology, physics.* 2010;76(4):1259-1265.

28. Burlage FR, Pijpe J, Coppes RP, et al. Variability of flow rate when collecting stimulated human parotid saliva. *Eur J Oral Sci.* 2005:386–390.

29. Rinkel RN, Verdonck-de Leeuw IM, Langendijk JA, van Reij EJ, Aaronson NK, Leemans CR. The psychometric and clinical validity of the SWAL-QOL questionnaire in evaluating swallowing problems experienced by patients with oral and oropharyngeal cancer. *Oral oncology.* 2009;45(8):e67-71.

30. Singer S, Wollbruck D, Wulke C, et al. Validation of the EORTC QLQ-C30 and EORTC QLQ-H&N35 in patients with laryngeal cancer after surgery. *Head & neck.* 2009;31(1):64-76.

31. Sherman AC, Simonton S, Adams DC, Vural E, Owens B, Hanna E. Assessing quality of life in patients with head and neck cancer: cross-validation of the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Head and Neck module (QLQ-H&N35). *Arch Otolaryngol Head Neck Surg.* 2000;126(4):459-467.

32. McHorney CA, Robbins J, Lomax K, et al. The SWAL-QOL and SWAL-CARE outcomes tool for oropharyngeal dysphagia in adults: III. Documentation of reliability and validity. *Dysphagia.* 2002;17(2):97-114.

33. Schober P, Boer C, Schwarte LA. Correlation Coefficients: Appropriate Use and Interpretation. *Anesthesia and Analgesia.* 2018;126(5):1763-1768.

34. Armstrong RA. When to use the Bonferroni correction. *Ophthalmic Physiol Opt.* 2014;34(5):502-508.

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

36. Eisbruch A, Kim HJ, Terrell JE, Marsh LH, Dawson LA, Ship JA. Xerostomia and its predictors following parotid-sparing irradiation of head-and-neck cancer.

International journal of radiation oncology, biology, physics. 2001;50(3):695-704.

37. Jensen K, Lambertsen K, Torkov P, Dahl M, Jensen AB, Grau C. Patient assessed symptoms are poor predictors of objective findings. Results from a cross sectional study in patients treated with radiotherapy for pharyngeal cancer. *Acta oncologica.* 2007;46(8):1159-1168.

38. Vlagsma TT, Koerts J, Tucha O, et al. Objective Versus Subjective Measures of Executive Functions: Predictors of Participation and Quality of Life in Parkinson Disease? *Arch Phys Med Rehabil.* 2017;98(11):2181-2187.

39. Hayhurst KP, Massie JA, Dunn G, Lewis SW, Drake RJ. Validity of subjective versus objective quality of life assessment in people with schizophrenia. *BMC Psychiatry.* 2014;14:365.

40. Lycke M, Lefebvre T, Pottel L, et al. Subjective, but not objective, cognitive complaints impact long-term quality of life in cancer patients. *J Psychosoc Oncol.* 2019;37(4):427-440.

41. Wilson JA, Carding PN, Patterson JM. Dysphagia after nonsurgical head and neck cancer treatment: patients' perspectives. *Otolaryngol Head Neck Surg.* 2011;145(5):767-771.

42. Felce D, Perry J. Quality of life: its definition and measurement. *Research in Developmental Disabilities.* 1995;16(1):51-74.

43. Lalla RV, Treister N, Sollecito T, et al. Oral complications at 6 months after radiation therapy for head and neck cancer. *Oral Dis.* 2017;23(8):1134-1143.

44. Chen AY, Frankowski R, Bishop-Leone J, et al. The development and validation of a dysphagia-specific quality-of-life questionnaire for patients with head and neck cancer: the M. D. Anderson dysphagia inventory. *Arch Otolaryngol Head Neck Surg.* 2001;127(7):870-876.

5

Chapter 6

Factors associated with masticatory function as measured with the Mixing Ability Test in patients with head and neck cancer before and after treatment: a prospective cohort study

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Abstract

Background

After treatment for head and neck cancer (HNC), patients often experience major problems in masticatory function. The aim of this prospective cohort study among patients with HNC was to investigate which personal and clinical factors are associated with masticatory function from diagnosis up to 2 years after treatment with curative intent.

Methods

Masticatory function was measured using the Mixing Ability Test (MAT) before treatment (baseline), and 3, 6, 12, and 24 months after treatment. A linear mixed-effects model with a random intercept and slope was conducted to investigate changes over time and the association with personal (sex, age) and clinical (tumor site, tumor stage, treatment modality) factors as measured at baseline.

Results

One hundred and twenty-five patients were included. The prevalence of masticatory dysfunction was estimated at 29% at M0, 38% at M3, 28% at M6, 26% at M12, and 36% at M24. A higher (worse) MAT score was associated with age, tumor stage, tumor site, timing of assessment, and the interaction between assessment moment and tumor site.

Conclusion

In patients with HNC, masticatory function changed over time and dysfunction was associated with a higher age, a tumor in the oral cavity, a higher tumor stage, and a shorter time since treatment. The prevalence of masticatory dysfunction ranged from 26%-38%.

Introduction

Following treatment for head and neck cancer (HNC), patients may experience major problems in masticatory function, which may lead to physical and emotional dysfunctioning as well.[1]

Many factors can influence the masticatory process, such as dentition, bite force, amount and composition of saliva, and neuromuscular control of chewing and swallowing.[2] Treatment may result in deterioration of dentition and mastication, which can still be present 5 years after oncological intervention.[3] Deficiencies in masticatory function may lead to changes in diet, because some foods become troublesome to eat. Malnutrition may be associated with dysphagia, and can influence quality of life in those patients.[4] After treatment for HNC, the type of treatment results in different deficiencies in masticatory performance. Surgery can result in disabling alterations of functional components needed for occlusion, such as the mandible, temporomandibular joint (TMJ), muscles of mastication, or teeth.[5] Radiotherapy (RT) often mandates the extraction of teeth, which require replacement after treatment, often resulting in decreased masticatory function. In addition, radiation dose can affect the muscles of mastication and the TMJ by decreasing the range of motion of the mandible, resulting in a decreased mouth opening and restricting the size of the food bolus.[5] When salivary glands are included in the radiation field, varying degrees of xerostomia can be observed, which adversely affect the maintenance of teeth, and the formation and manipulation of the food bolus. Chemotherapy (CT) can cause mucositis, xerostomia, tooth loss, chewing difficulty, and neurotoxicity, which can restrict masticatory function as well.[5,6]

In order to reduce the risk of masticatory dysfunction before and after curative treatment for HNC, it is important to identify factors affecting masticatory performance. With the help of an associative model, patients in potential need of oral rehabilitation during or after treatment for HNC can be identified. Previous studies that focus on masticatory function, use trismus or patient-reported outcomes as outcome measure, or investigate only a sub-group of patients (e.g., patients with oral cancer or patients treated with surgery).[3,7-9] To our knowledge, objective measures in patients with head and neck cancer and with different treatment modalities have not been performed yet. In addition, the course of masticatory function before and after treatment for patients with head and neck cancer has not been described. The aim of this prospective study was therefore to identify personal and clinical factors associated with objective masticatory function in patients with head and neck cancer before, and 3, 6, 12, and 24 months after treatment. In addition, the prevalence of masticatory dysfunction before and after treatment was assessed.

Methods

Patients were included by convenience sampling when they were 18 years or older, were diagnosed with oral, oropharyngeal, hypopharyngeal, or laryngeal cancer, and were treated with a curative intent at the University Medical Center Utrecht (UMCU), the Netherlands, between September 2014 and June 2018. Patients with recurrent or residual disease, cognitive impairments, and patients having trouble understanding or reading the Dutch language were excluded. All patients signed written informed consent before participation. The study protocol of this prospective cohort study was approved by the Medical Ethics Committee of the Netherlands (NL45051.029.13), and is part of the NET-QUBIC research.[10] Patient data about age, sex, tumor stage,[11] tumor site, and treatment were collected. Patients were assessed before primary treatment (baseline, M0), and 3 (M3), 6 (M6), 12 (M12), and 24 months after treatment (M24). At every assessment, the Mixing Ability Test measuring masticatory performance was performed.

Mixing Ability Test

The Mixing Ability Test (MAT) consists of two layers of wax, with the colors red and blue (Plasticine modelling wax, non-toxic DIN EN-71, art. nos. crimson 52801 and blue 52809, Stockmar, Kalten Kirchen, Germany).[3,12-14] The total thickness is 3 mm, with a diameter of 30 mm. The outcome variable is called the Mixing Ability Index (MAI), and ranges between 5-30, where a lower MAI score implies a better mixed tablet and better masticatory performance. A subject was asked to chew on this tablet 20 times in order to mix the two colors. The tablet was then flattened, pressed to a thickness of 2 mm, and scanned on both sides using a high-quality scanner (Epson® V750, Long Beach, CA, USA). The scanned images were processed using Adobe Photoshop CS3 extended (Adobe, San Jose, CA, USA). The histograms of both sides of the flattened and scanned wax tablet were added to obtain red and blue intensity distributions. The spread of the color intensities was measured, and a mixing ability score was calculated.[13] In previous research, this test showed a good reliability (ICC=0.886) when comparing test and retest.[15] To identify patients with masticatory dysfunction, a cut-off value was calculated, based on a value larger than 2 standard deviations from the mean value of healthy subjects, as calculated in previous research. A cut-off value of ≥20.5 indicated masticatory dysfunction.[15]

Statistical Analyses

Descriptive statistics were used to describe the study population. A Kruskal-Wallis H test was performed to examine differences in age between different tumor sites, and a chi-square test was run to test for differences in sex, primary treatment, and tumor stage between tumor sites. A linear mixed-effects model (LMM) with the MAT as dependent

outcome measure was conducted to investigate changes over time and the effect of patient characteristics and clinical parameters on MAT outcome.[16] Akaike's Information Criterion (AIC) was used to select the most appropriate covariance structure to fit the data.[17] To account for within-patient correlations, a random patient factor was added, and a random intercept was used to account for different entry levels of patients. The fixed-effect factors tumor site, treatment modality, tumor stage, timing of assessment, sex, and age, as well as 2-way interactions of the factors tumor site, treatment modality, and tumor stage during the assessment period were assessed using the AR(1) method (first-order autoregressive covariance pattern) for parameter estimation. Tumor site consisted of 3 levels: oral cavity, oropharynx, and hypopharynx and larynx. Treatment modality consisted of 4 levels: RT, chemoradiotherapy (CRT), surgery, and a combination of surgery followed by postoperative RT or CRT. Tumor stage consisted of 4 levels (stage 1 to 4), timing of assessment consisted of 5 levels (M0, M3, M6, M12, and M24), sex consisted of 2 levels (male and female), and age was defined as a continuous variable. The model included a stepwise backward selection of factors, in which factors not significant at a $p<0.10$ level were removed, beginning with the interactions. A hierarchical structure was maintained, meaning that if an interaction was included in the model, the main effects were also represented in the model. Risk factors were reported as estimated unstandardized regression coefficients with 95% confidence intervals (CI) and p-values.

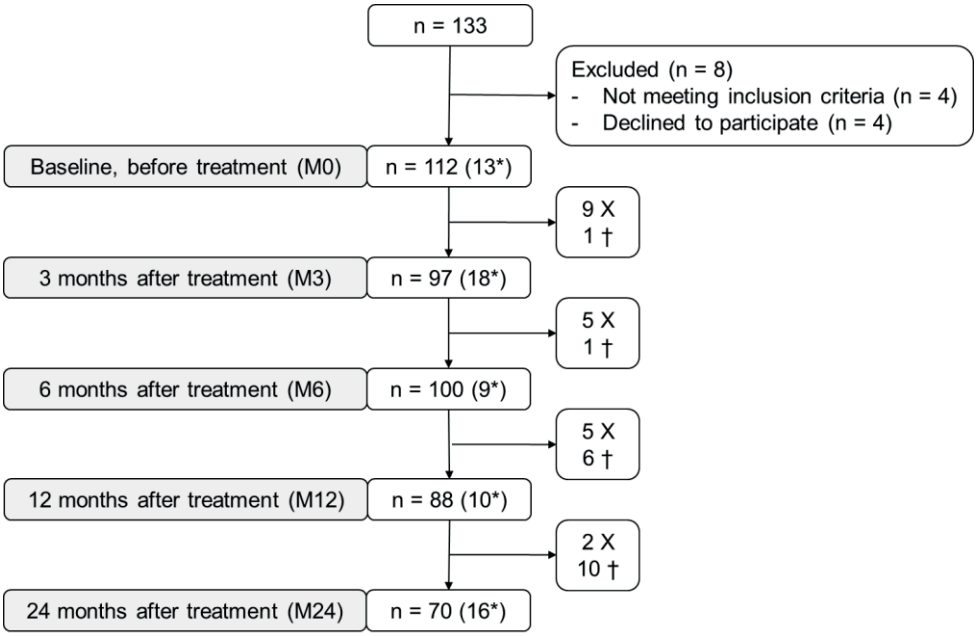
The coefficients of the significant covariates, together with the value of the intercept of the mixed model analysis, were combined into a formula for the estimated MAT. The intercept is the value of the estimated MAT in which all coefficients remain zero. Addition of the coefficients will lead to an increase or decrease of the estimated MAT. For each time point, the formula was filled with average variable values for significant coefficients, as calculated by a restricted maximum likelihood approach (REML). Model assumptions were verified by plotting residuals versus fitted values. All analyses were performed using Statistical Package for the Social Sciences (SPSS) version 25 (Chicago, IL). A p-value below 0.10 was considered statistically significant.

A score above the cut-off value of 20.5 was used to create a Receiver Operating Characteristic (ROC) curve, to help facilitate the use of the linear mixed-effects model in identifying factors associated with swallowing problems in patients with HNC.

Results

Baseline demographics and clinical characteristics are shown in Table 1 for the total patient group, and for subgroups based on tumor site. A total of 125 patients enrolled in this study, of which 112 underwent measurements at M0, 97 at M3, 100 at M6, 88 at M12, and 70 at M24 (Figure 1). During a 2-year follow-up, 18 patients were deceased, and 21 patients dropped out. The mean MAT score was 18.8 (SD=3.6) at M0, 19.2 (SD=4.3) at M3, 19.0 (SD=3.6) at M6, 18.3 (SD=4.0) at M12, and 18.8 (SD=3.7) at M24. The number of patients with masticatory dysfunction (a value above the MAT cut-off score of ≥ 20.5) was 32 at M0 (29%), 37 at M3 (38%), 28 at M6 (28%), 23 at M12 (26%), and 25 at M24 (36%).

Figure 1. Flowchart depicting the number of patients at each time point



X: patients stopped participating; †: patients passed away; *: missing MAT measurement

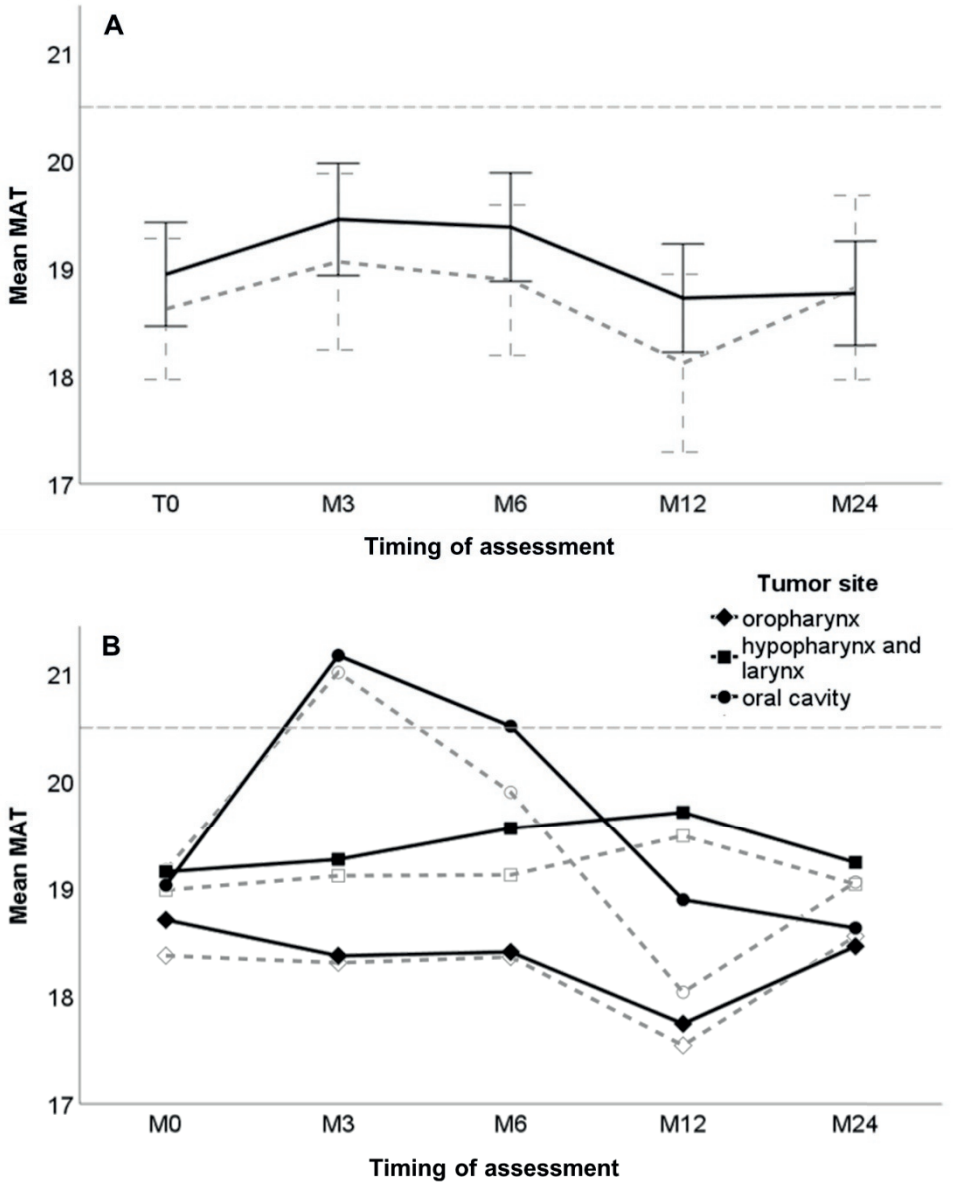
Table 1. Baseline characteristics of patients with HNC that performed the MAT based on all patients, and subgroups of patients based on tumor site

		Tumor site			
	All patients (n = 125)	**Oropharynx (n = 48)**	**Larynx and hypopharynx (n = 42)**	**Oral cavity (n = 35)**	**p-value**
Variable	*median (IQR)*	*median (IQR)*	*median (IQR)*	*median (IQR)*	
Age	63.0 (15.0)	59.0 (14.5)	64 (12.5)	64 (18)	0.142†
Sex	**n (%)**	**n (%)**	**n (%)**	**n (%)**	0.030*‡
Male	97 (77.6)	36 (75.0)	38 (90.5)	23 (65.7)	
Female	28 (22.4)	12 (25.0)	4 (9.5)	12 (34.3)	
Primary treatment					<0.001*‡
RT	55 (44.0)	23 (47.9)	31 (73.8)	1 (2.9)	
CRT	31 (24.8)	24 (50.0)	6 (14.3)	1 (2.9)	
Surgery	25 (20.0)	1 (2.1)	4 (9.5)	20 (57.1)	
Surgery with (C)RT	14 (11.2)	0	1 (2.4)	13 (37.1)	
Tumor stage					0.001*‡
I	34 (27.2)	3 (6.3)	18 (42.8)	13 (37.1)	
II	26 (20.8)	10 (20.8)	7 (16.7)	9 (25.7)	
III	15 (12.0)	6 (12.5)	6 (14.3)	3 (8.6)	
IV	50 (40.0)	29 (60.4)	11 (26.2)	10 (28.6)	
Tumor site					
Oropharynx	48 (38.4)				
Larynx and Hypopharynx	42 (33.6)				
Oral cavity	35 (28.0)				

CRT: Chemoradiotherapy, IQR: Interquartile range, n: number of patients, RT: Radiotherapy
*: p<0.05, †: Kruskal-Wallis H test, ‡: chi-square test

LMM analysis showed that the MAT score increased 3 and 6 months after treatment, indicating a worse masticatory function. The MAT returned to baseline values 12 and 24 months after treatment (Figure 2a). Sex was not associated with the MAT score, and was therefore removed from the model. The MAT score was associated with age, tumor stage, tumor site, and timing of assessment, and the interaction between timing of assessment and tumor site appeared of importance (Table 2). With increasing age, the MAT score increased as well (+0.08 each year, p-value=0.008). Patients with tumor stage 1 and 2 had a lower MAT score in comparison to patients with stage 4 tumors (MAT score=-2.63, p-value=0.001 and MAT score=-1.97, p-value=0.018, respectively). After treatment, the MAT score increased with 2.14 (M3) (p-value=<0.001) and 1.49 (M6) (p-value=0.014), and returned to baseline 1 year after treatment. The longitudinal course of MAT differed between tumor sites (Figure 2b). The cut-off score was used to develop a ROC curve indicating masticatory dysfunction before and after treatment in patients with HNC (appendix 1). The formula for the estimated MAT that was retained in the final model is shown in the footnote of Table 2.

Figure 2. The mean MAT outcome for all patients with corresponding confidence intervals (A) and for patients based on tumor site (B)



The solid lines represent the linear mixed model outcomes of the final model, the striped lines represent the raw data. The mean value of the MAT for healthy subjects is 16.42, and the cut-off score is 20.5 as depicted by the gray line

Table 2. Linear mixed model estimates for the MAT

		Estimate (95% CI)	p-value	Interactions with timing of assessment									
Intercept		15.40		M0	M3		M6		M12		M24		
				Estimate (95% CI)	**Estimate (95% CI)**	**p-value**	**Estimate (95% CI)**	**p-value**	**Estimate (95% CI)**	**p-value**	**Estimate (95% CI)**	**p-value**
Age		0.08 (0.02 to 0.14)	0.008*									
Tumor stage	*1*	-2.63 (-4.23 to -1.03)	0.001*									
	2	-1.97 (-3.59 to -0.35)	0.018*									
	3	0.25 (-1.73 to 2.24)	0.801									
	4	*Reference*										
Timing of assessment	*M0*	*Reference*										
	M3	2.14 (1.08 to 3.21)	<0.001*									
	M6	1.49 (0.31 to 2.67)	0.014*									
	M12	-0.13 (-1.45 to 1.18)	0.840									
	M24	-0.40 (-1.94 to 1.15)	0.613									
Tumor site	*Oral cavity*	*Reference*		*Reference*								
	Oropharynx	-1.21 (-2.94 to 0.51)	0.166	*Reference*	-2.48 (-3.80 to -1.15)	<0.001*	-1.78 (-3.29 to -0.28)	0.020*	-0.83 (-2.49 to 0.83)	0.326	0.15 (-1.74 to 2.04)	0.874
	Hypopharynx and larynx	-0.13 (-1.87 to 1.60)	0.878	*Reference*	-2.03 (-3.45 to -0.61)	0.005*	-1.08 (-2.67 to 0.50)	0.181	0.69 (-1.06 to 2.44)	0.438	0.48 (-1.51 to 2.47)	0.634

*: p<0.10; SE: Standard Error

The following formula for the estimated MAT shows the significant variables and their coefficients that were retained in the model. Factors with a coefficient above 0 will increase the MAT outcome and therefore indicate a worse masticatory performance:

Estimated MAT = 15.40 + 0.08age - 2.63tumorstage1 - 1.97tumorstage2 + 0.25tumorstage3 + 2.14M3 + 1.49M6 - 0.13M12 - 0.40M24 - 1.21oropharynx – 0.13hypopharynx&larynx – 2.48oropharynx*M3 – 2.03hypopharynx&larynx*M3 – 1.78oropharynx*M6 – 1.08hypopharynx&larynx*M6 – 0.83oropharynx*M12 + 0.69hypopharynx&larynx*M12 + 0.15oropharynx*M24 + 0.48hypopharynx&larynx*M24

Discussion

This 2-year prospective study showed that the prevalence of masticatory dysfunction among patients with HNC was estimated at 29% before treatment, 38% at 3 months after treatment, 28% at 6 months, 26% at 12 months, and 36% at 24 months. The mean MAT values indicate a decrease in masticatory function 3 and 6 months after treatment, and a return to baseline values 1 and 2 years after treatment. Masticatory function was associated with age, tumor stage, tumor site, timing of assessment, and the interaction between tumor site and timing of assessment. The masticatory performance decreased with age. Furthermore, a higher tumor stage was associated with a worse masticatory performance. Patients with oral cavity tumors performed worse in comparison to those with oropharynx and hypopharynx and larynx tumors.

Masticatory function worsened in patients with an oral cavity tumor from diagnosis up to 6 months after treatment, and returned to baseline levels 1 and 2 years after treatment. Patients with an oropharynx, hypopharynx or larynx tumor did not show this decrease in function after treatment.

Comparison with literature

The association between age and worse masticatory function is found in previous research as well.[18,19] It was suggested that this association is caused by different mechanisms: fewer contacts between functional units (for example caused by a lower number of teeth), the presence of xerostomia, and/or decreased oral muscle activities.[20] When patients lose their teeth, it is advised to install a suitable dental prosthesis, and to train and exercise the masticatory muscles in order to increase oral motor and sensory functions that are used in mastication.[21] In future research, it is therefore important to measure the number of teeth and number of occlusal units and include these as factors in the LMM.

Previous research on masticatory function as measured with the MAT focused on patients that received surgery for oral cancer, in which measurements were performed before surgery, 4-6 weeks after surgery, 6 months after surgery, and 1 and 5 years after surgery. Masticatory function worsened from baseline to 1 year after treatment, and recovered 5 years after treatment. These changes over time are in line with the results found in this study for patients with oral cancer. Other research in patients with oral cancer found that surgery and surgery followed by RT had a significant impact on oral function, and the recovery was less prominent in patients that received surgery followed by RT in comparison to patients that received surgery only. This was caused by the fact that patients treated with surgery and RT had larger tumors, more extended resections, and received RT which

caused more symptoms.[3] Other research mainly focused on limited mouth opening (trismus) as outcome measure, which is also correlated to mastication.[22] It was found that trismus is significantly related to tumor stage, the use of RT and the use of free tissue reconstruction. Patients with stage 3 and 4 tumors, and patients receiving RT or a reconstruction had a smaller mouth opening.[22] The relation between chewing function and stage 4 tumors was described previously as well.[23] These risk factors are in line with the results found in this research, except for choice of treatment, which was not found in this study.

Strengths and limitations

Strengths of our study were the prospective study design, the use of the LMM checklist with recommendations for reporting multilevel data and analyses,[24] and the high test-retest reliability of the MAT as found in previous research.[15] Limitations were the low number of patients at follow-up, which limited the number of factors that could be explored with the LMM, and the relatively large drop-out and missing values. These missing data might have affected the analyses, because it is unknown how these patients would have performed on the MAT. Although the LMM is better at handling missing values in comparison to other regression analyses, these regression models do not take into account the number of deaths as competing risk.[25]

Although no significant correlations were found between the factors used in the LMM, treatment and tumor stage did differ between different tumor sites, as seen in Table 1: patients with an oropharynx tumor most often received RT or CRT, while patients with an oral cavity tumor most often received surgery or surgery followed by RT or CRT. In addition, oropharynx tumors were most often stage 4 tumors, while hypopharynx and larynx tumors were most often stage 1 tumors. Therefore, the association found between MAT outcome and tumor site is, to a lesser extent, also caused by treatment modality and tumor stage. Because of the low number of patients in this study, no interactions between treatment, tumor stage and tumor site could be explored in the LMM.

The mean values indicate a decrease in masticatory function especially 3 and 6 months after treatment, and a return to baseline at 12 and 24 months after treatment. However, the cut-off values indicate masticatory dysfunction especially 3 and 24 months after treatment. Impairment after treatment varies greatly between patients; it is affected by site and extent of the tumor, age, irradiation site and dose, extent of tumor resection, and reconstruction procedures.[26] Acute toxicity after treatment (e.g., mucositis, xerostomia, tooth loss) causes a decrease in masticatory function, which slowly recovers over time. However, long term treatment effects may persist even beyond 5 years after treatment,[27] which may explain the masticatory dysfunction of 36% at 2 years after treatment. Although

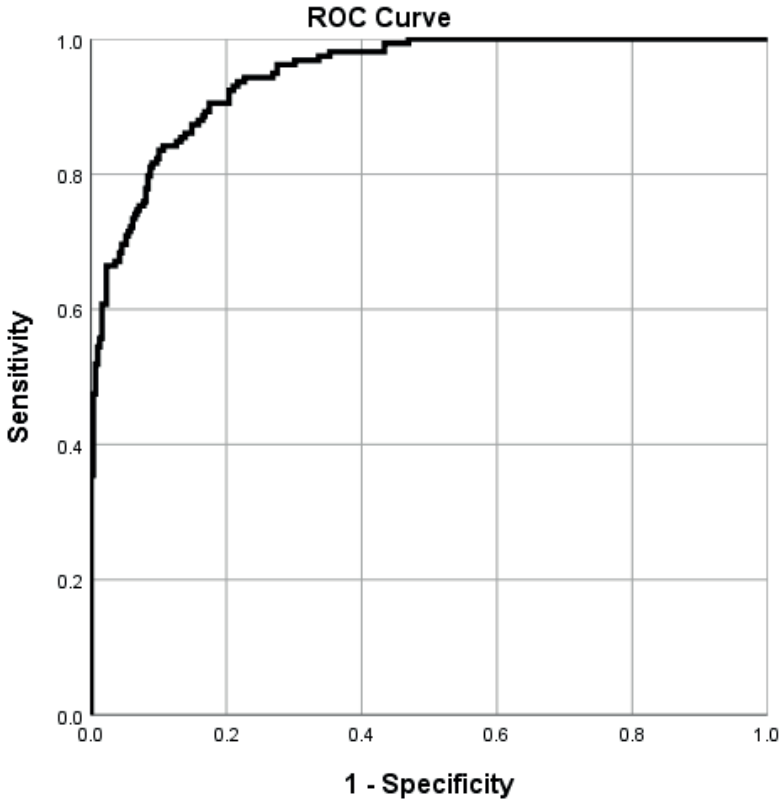
an effort has been made to make a distinction based on tumor site, tumor stage, age, and treatment, future research should aim to investigate the discrepancy between mean values and cut-off values, and why more patients had problems 2 years after treatment in comparison to 1 year after treatment (based on the cut-off value), and why this does not translate to the mean values.

Previous research showed that the objective MAT and subjective patient-reported outcomes related to mastication have a low correlation and can therefore not be used interchangeably.[28] A future study might aim at developing a prediction model with subjective outcomes, to study whether factors found in the current study would be the same when subjective measures are used. A recommendation would be to include a larger study group, to be able to include a larger number of potential predictors in the LMM and thus provide more reliable and focused results.

In conclusion, masticatory function can be influenced by treatment for head and neck cancer. Masticatory dysfunction was associated with a greater age, a tumor in the oral cavity, a higher tumor stage, and a shorter time since treatment. The prevalence of masticatory dysfunction ranged from 26% to 38% before and after treatment. It is important to identify patients at risk for developing masticatory problems, to inform them about possible problems that may occur during and after treatment, and to increase awareness about possibilities for patients regarding rehabilitation.

Appendix

Appendix 1. Receiver operating characteristic (ROC) curve for mastication problems after treatment for head and neck cancer, using the linear mixed model



The area under the curve (AUC) is 0.947. The AUC at the different assessment moments is 0.935 (T0), 0.951 (M3), 0.967 (M6), 0.948 (M12), and 0.953 (M24). The AUC can vary between 0 and 1, where a value of 0 indicated that the model has no diagnostic power, and a value of 1 indicates that the model has a perfect diagnostic accuracy

References

1. Pace-Balzan A, Shaw RJ, Butterworth C. Oral rehabilitation following treatment for oral cancer. *Periodontology 2000.* 2011;57(1):102-117.

2. Pereira LJ, van der Bilt A. The influence of oral processing, food perception and social aspects on food consumption: a review. *Journal of oral rehabilitation.* 2016;43(8):630-648.

3. Speksnijder CM, van der Bilt A, Abbink JH, Merkx MA, Koole R. Mastication in patients treated for malignancies in tongue and/or floor of mouth: A 1-year prospective study. *Head & neck.* 2011;33(7):1013-1020.

4. Schimmel M, Leemann B, Herrmann FR, Kiliaridis S, Schnider A, Muller F. Masticatory function and bite force in stroke patients. *Journal of dental research.* 2011;90(2):230-234.

5. Marunick MT, Mathog RH. Mastication in patients treated for head and neck cancer: a pilot study. *The Journal of prosthetic dentistry.* 1990;63(5):566-573.

6. Caputo JB, Campos SS, Pereira SM, et al. Masticatory performance and taste perception in patients submitted to cancer treatment. *Journal of oral rehabilitation.* 2012;39(12):905-913.

7. Ohkoshi A, Ogawa T, Nakanome A, et al. Predictors of chewing and swallowing disorders after surgery for locally advanced oral cancer with free flap reconstruction: A prospective, observational study. *Surgical oncology.* 2018;27(3):490-494.

8. de Groot RJ, Wetzels JW, Merkx MAW, et al. Masticatory function and related factors after oral oncological treatment: A 5-year prospective study. *Head & neck.* 2019;41(1):216-224.

9. van der Geer SJ, Kamstra JI, Roodenburg JL, et al. Predictors for trismus in patients receiving radiotherapy. *Acta oncologica.* 2016;55(11):1318-1323.

10. Verdonck-de Leeuw IM, Jansen F, Brakenhoff RH, et al. Advancing interdisciplinary research in head and neck cancer through a multicenter longitudinal prospective cohort study: the NETherlands QUality of life and BIomedical Cohort (NET-QUBIC) data warehouse and biobank. *BMC Cancer.* 2019;19(1):765.

11. Paleri V, Mehanna H, Wight RG. TNM classification of malignant tumours 7th edition: what's new for head and neck? *Clin Otolaryngol.* 2010;35(4):270-272.

12. de Groot RJ, Rosenberg AJWP, van der Bilt A, Aalto D, Merkx MAW, Speksnijder CM. The association between a mixing ability test and patient reported chewing ability in patients treated for oral malignancies. *Journal of oral rehabilitation.* 2019;46(2):140-150.

13. Speksnijder CM, Abbink JH, van der Glas HW, Janssen NG, van der Bilt A. Mixing ability test compared with a comminution test in persons with normal and compromised masticatory performance. *Eur J Oral Sci.* 2009;117(5):580-586.

14. van der Bilt A, Speksnijder CM, de Liz Pocztaruk R, Abbink JH. Digital image processing versus visual assessment of chewed two-colour wax in mixing ability tests. *Journal of oral rehabilitation.* 2012;39(1):11-17.

15. Vermaire JA, Weinberg FM, Raaijmakers CPJ, Verdonck-de Leeuw IM, Terhaard CHJ, Speksnijder CM. Reliability of the mixing ability test testing masticatory performance in patients with head and neck cancer and healthy controls. *Journal of oral rehabilitation.* 2020.

16. Bolker BM, Brooks ME, Clark CJ, et al. Generalized linear mixed models: a practical guide for ecology and evolution. *Trends Ecol Evol.* 2009;24(3):127-135.

17. Burnham KP, Anderson DR. Multimodel Inference. *Sociological Methods & Research.* 2016;33(2):261-304.

18. Hirai T, Ishijima T, Koshino H, Anzai T. Age-related change of masticatory function in complete denture wearers: evaluation by a sieving method with peanuts and a food intake questionnaire method. *The*

International journal of prosthodontics. 1994;7(5):454-460.

19. Huckabee ML, McIntosh T, Fuller L, et al. The Test of Masticating and Swallowing Solids (TOMASS): reliability, validity and international normative data. *Int J Lang Commun Disord.* 2018;53(1):144-156.

20. Peyron MA, Woda A, Bourdiol P, Hennequin M. Age-related changes in mastication. *Journal of oral rehabilitation.* 2017;44(4):299-312.

21. Lin CS, Wu CY, Wu SY, Lin HH, Cheng DH, Lo WL. Age-Related Difference in Functional Brain Connectivity of Mastication. *Frontiers in aging neuroscience.* 2017;9:82.

22. Scott B, Butterworth C, Lowe D, Rogers SN. Factors associated with restricted mouth opening and its relationship to health-related quality of life in patients attending a Maxillofacial Oncology clinic. *Oral oncology.* 2008;44(5):430-438.

23. Nemeth D, Zaleczna L, Huremovic A, et al. Importance of chewing, saliva, and swallowing function in patients with advanced oral cancer undergoing preoperative chemoradiotherapy: a prospective study of quality of life. *International journal of oral and maxillofacial surgery.* 2017;46(10):1229-1236.

24. Monsalves MJ, Bangdiwala AS, Thabane A, Bangdiwala SI. LEVEL (Logical Explanations & Visualizations of Estimates in Linear mixed models): recommendations for reporting multilevel data and analyses. *BMC Med Res Methodol.* 2020;20(1):3.

25. Van der Elst W, Molenberghs G, Van Boxtel MP, Jolles J. Establishing normative data for repeated cognitive assessment: a comparison of different statistical methods. *Behav Res Methods.* 2013;45(4):1073-1086.

26. Terada N, Numata T, Kobayashi N, et al. State of mastication affects quality of life in patients with maxillary sinus cancer. *Laryngoscope.* 2003;113(4):729-736.

27. Nilsen ML, Belsky MA, Scheff N, et al. Late and Long-Term Treatment-Related Effects and Survivorship for Head and Neck Cancer Patients. *Curr Treat Options Oncol.* 2020;21(12):92.

28. Vermaire JA, Raaijmakers CPJ, Verdonck-de Leeuw IM, et al. Mastication, swallowing and salivary flow in patients with head and neck cancer; objective tests versus patient reported outcomes. *Supportive care in cancer: official journal of the Multinational Association of Supportive Care in Cancer.* 2021.

Chapter 7

Factors associated with swallowing dysfunction in patients with head and neck cancer

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Abstract

Background

The aim of this prospective cohort study was to investigate swallowing function in relation to personal and clinical factors among patients with head and neck cancer (HNC) from diagnosis up to 2 years after treatment.

Methods

The 100 mL water swallow test was measured before treatment, and 3, 6, 12, and 24 months after treatment. Linear mixed-effects model analysis was conducted to investigate changes over time and the association with personal (sex, age) and clinical (tumor site, tumor stage, treatment modality) factors.

Results

Among 128 included patients, number of swallows increased from baseline to 3 months after treatment and decreased to baseline again at 6 months after treatment. The number of swallows was associated with age and treatment modality.

Conclusion

In patients with HNC, swallowing (dys)function changes over time with the worst score 3 months after treatment. A higher age and being treated with surgery are factors associated with swallowing dysfunction over time.

Introduction

Head and neck cancer (HNC) is the seventh most common cancer worldwide, most often caused by alcohol and/or tobacco use, or the human papilloma virus (HPV).[1] Treatment options for HNC include surgery, radiotherapy (RT) and chemoradiotherapy (CRT). The use of high-intensity radiation treatment regimens have resulted in improved survival, but the prevalence of patients suffering from side effects of treatment has increased as well.[2] Patients may suffer from e.g., tissue fibrosis, osteoradionecrosis, xerostomia, or dysphagia. Dysphagia may occur in up to 44% of patients treated with RT and up to 84% of patients treated with surgery.[3,4] Swallowing function may be impaired due to a number of normal tissue changes such as edema, neuropathy, fibrosis, and mucositis.[5] While edema and mucositis disrupt normal swallowing function during treatment, they substantially improve after treatment in the majority of patients. In contrast, neuropathy and fibrosis of the swallowing musculature may develop or persist long after completion of treatment.[5] Swallowing dysfunction can lead to complications such as malnutrition, aspiration and subsequent pneumonia, which may depend on tumor stage, sub-site of the tumor, age, and treatment modality.[6,7] RT may result in a large dose delivery to critical structures necessary for normal deglutition, such as the base of tongue, supraglottic larynx, soft palate, cricopharyngeal muscles and pharyngeal constrictor muscles.[8] Chemotherapy may also have an effect on swallowing function, and it may lead to various side effects such as nausea, vomiting, neutropenia, generalized weakness and fatigue.[5] Swallowing problems that occur after surgery vary with tumor site and size of resection, and type of reconstruction.[9]

In order to reduce the risk of swallowing dysfunction before and after curative treatment for HNC, it is important to identify factors associated with swallowing dysfunction. Therefore, the aim of this prospective study was to identify factors associated with swallowing dysfunction in patients with HNC, before, and 3, 6, 12, and 24 months after treatment. It was hypothesized that especially treatment modality, tumor site, and tumor stage will have a significant impact on swallowing function after treatment.

Materials and methods

Patients were included by convenience sampling when they were 18 years or older, were diagnosed with oral, oropharyngeal, hypopharyngeal, or laryngeal HNC and were treated with a curative intent at the University Medical Center Utrecht (UMCU), the Netherlands between September 2014 and June 2018. Patients with recurrent or residual disease, cognitive impairments, and patients having trouble understanding or reading the Dutch language were excluded. All patients signed written informed consent before participation.

The study protocol of this prospective cohort study was approved by the Medical Ethics Committee of the Netherlands (2013.301(A2018.307)-NL45051.029.13), and is part of the NET-QUBIC cohort study.[10] Patient data about age, sex, tumor stage,[11] tumor site, and treatment were used. Patients were assessed before primary treatment (baseline, M0), and 3 (M3), 6 (M6), 12 (M12), and 24 months after treatment (M24). At every assessment, the primary outcome measure in the present study (100 mL Water Swallow Test (WST)) was performed.

100 mL Water Swallow Test

During the WST, a subject is asked to drink 100 mL of water as quickly as is comfortably possible. The time to swallow 100 mL (in seconds) and the number of swallows are counted, both by the subject and the researcher. Timing starts when the water touches the bottom lip, and stops when the larynx comes to rest after the last swallow.[12] Persons fail the test when they cough or choke post swallow, have a wet voice quality post swallow, or are unable to drink the whole 100 mL.[13] When a person is unable to drink the 100 mL, the residual water is measured and noted. As shown in previous research, the number of swallows had an excellent reliability (Intraclass correlation coefficient (ICC)=0.923) when comparing test and retest, while the swallowing duration had a slightly lower reliability (ICC=0.893). Swallowing duration needed a larger Smallest Detectable Change (SDC%) and Standard Error of Measurement (SEM%) (16.5% versus 52.8%, and 5.9% versus 19.1%, respectively) in comparison to the number of swallows.[14] Therefore, in the current study, the number of swallows was chosen as primary outcome measure. A higher number of swallows indicates more swallowing problems. Data from previous research was used to calculate a cut-off value.[14] A value larger than two standard deviations from the mean value of healthy subjects was used to indicate swallowing problems in patients with HNC (≥8 swallows needed to drink 100 mL of water).[15] Swallowing dysfunction was defined as a failure on the WST and/or a value above the cut-off value of eight number of swallows needed to swallow 100 mL of water.[15] Apart from the cut-off value, the SDC found in previous research (0.79 swallows) indicates whether the difference between measurements is a real difference and not a measurement error.[14]

Statistical Analyses

Descriptive statistics were used to describe the study population. A Kruskal-Wallis H test was performed to examine differences in age between primary treatment groups, and a chi-square test was run to test for differences in sex, tumor site and tumor stage between primary treatment groups. A linear mixed-effects model (LMM) analysis was conducted to investigate changes over time in number of swallows, and the association with patient and clinical factors.[16] Akaike's Information Criterion (AIC) was used to select the most

appropriate covariance structure to fit the data.[17] To account for within-patient correlations, a random patient factor was added, and a random intercept was used to account for the different entry levels of patients. The fixed-effect factors tumor site, treatment modality, tumor stage, timing of assessment, sex, and age, as well as 2-way interactions of the factors tumor site, treatment modality, and tumor stage during the assessment period were assessed using the AR(1) method (first-order autoregressive covariance pattern) for parameter estimation. Tumor site consisted of 3 levels: oral cavity, oropharynx, or larynx and hypopharynx. Treatment modality consisted of 4 levels: RT, CRT, surgery, or surgery followed by post-operative (C)RT. Tumor stage consisted of 4 levels (stage 1 to 4), timing of assessment consisted of 5 levels (M0, M3, M6, M12, and M24), sex consisted of 2 levels (male or female), and age was defined as a continuous variable. The model included a stepwise backward selection of factors, in which factors that were not significant at a $p<0.10$ level were removed, beginning with the interactions. A hierarchical structure was maintained, meaning that if an interaction was included in the model, the main effects were also represented in the model. Risk factors were reported as estimated unstandardized regression coefficients with 95% confidence intervals (CI) and p-values.

Swallowing dysfunction (a score above the cut-off value of 8 number of swallows) was used to create a Receiver Operating Characteristic (ROC) curve, to help facilitate the use of the linear mixed–effects model in identifying factors associated with swallowing problems in patients with HNC.

The coefficients of the significant covariates, together with the value of the intercept of the mixed model analysis, were combined into a formula for the estimated number of swallows. The intercept is the value of the estimated number of swallows when all coefficients remain zero. Addition of the coefficients will lead to an increase or decrease of the estimated number of swallows. For each time point, the formula was filled with average variable values for significant coefficients, as calculated by a restricted maximum likelihood approach (REML). Model assumptions were verified by plotting the residuals versus the fitted values. All analyses were performed using Statistical Package for the Social Sciences (SPSS) version 25 (Chicago, IL). A p-value <0.10 was considered statistically significant.

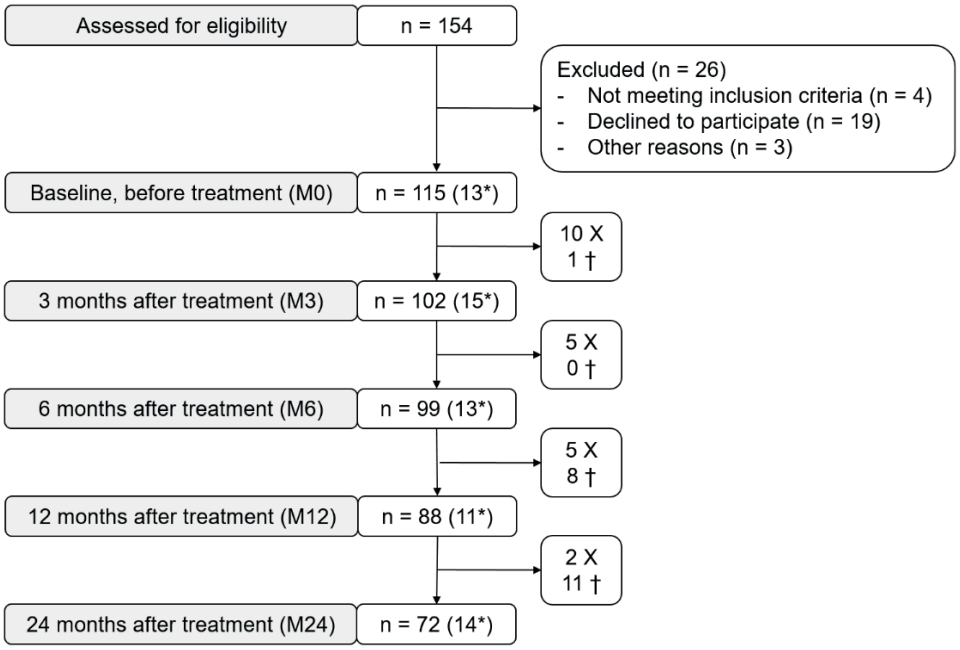
Results

Of 135 patients that met the inclusion criteria, 128 were included and 115 performed baseline measurements. During the study period with 2 years follow-up, 25 patients were deceased, and 24 patients dropped out. In addition, five measurements at M24 could not be performed because of the COVID-19 situation and were indicated as missing. The flow diagram of the study is shown in Figure 1. Personal and clinical characteristics of the study

population are shown in Table 1 for the total patient group, and for subgroups based on treatment.

Of the 41 patients receiving surgery, reconstruction was performed in 16 patients (39%), and neck dissection was performed in 29 patients (71%), of which 24 were elective neck dissection. Radiotherapy most often consisted of a 35 times 2 Gy schedule: of the 103 patients receiving RT, 55 received conventional RT (53%), 32 received accelerated RT (31%), 6 received hyper fractionated RT (6%), and 10 were classified as other. All patients received either intensity-modulated radiation therapy (IMRT) or volumetric modulated arc therapy (VMAT). Of the 43 patients receiving chemotherapy, 32 received cisplatin (74%), 6 received carboplatin (14%), and 5 received cetuximab (12%).

Figure 1. Flowchart depicting the number of patients at each time point



X: patients stopped participating; †: patients passed away; *: missing WST measurement

Table 1. Baseline characteristics of patients with head and neck cancer that performed the 100 mL water swallow test based on all patients, and sub-groups of patients based on primary treatment

Variable	All patients (n = 128)	Primary treatment				p-value
		RT (n = 54)	CRT (n = 33)	Surgery (n = 25)	Surgery with (C)RT (n = 16)	
Age, median (IQR)	61.5 (11.3)	67.0 (15.0)	57.0 (12.5)	64.0 (17.5)	62.5 (16.3)	0.102†
Sex	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	0.090‡
Male	100 (78.1)	45 (83.3)	26 (78.8)	15 (60.0)	14 (87.5)	
Female	28 (21.9)	9 (16.7)	7 (21.2)	10 (40.0)	2 (12.5)	
Tumor stage						<0.001*‡
I	34 (26.6)	16 (29.6)	0	15 (60.0)	3 (18.8)	
II	27 (21.1)	17 (31.5)	0	6 (24.0)	4 (25.0)	
III	15 (11.7)	9 (16.7)	3 (9.1)	2 (8.0)	1 (6.2)	
IV	52 (40.6)	12 (22.2)	30 (90.9)	2 (8.0)	8 (50.0)	
Tumor site						<0.001*‡
Oropharynx	50 (39.1)	23 (42.6)	26 (78.8)	1 (4.0)	0	
Larynx and Hypopharynx	42 (32.8)	31 (57.4)	6 (18.2)	4 (16.0)	1 (6.2)	
Oral cavity	36 (28.1)	0	1 (3.0)	20 (80.0)	15 (93.8)	
Primary treatment						
RT	54 (42.2)					
CRT	33 (25.8)					
Surgery	25 (19.5)					
Surgery with (C)RT	16 (12.5)					

CRT: Chemoradiotherapy, IQR: Interquartile range, n: number of patients, RT: Radiotherapy
*: p<0.05, †: Kruskal-Wallis H test, ‡: chi-square test

Swallowing over time

The mean and standard deviation of the number of swallows needed to drink the 100 mL water at the different times of assessment are shown in Table 2. Linear mixed model analysis showed that the number of swallows increased from baseline to 3 months after treatment and decreased to baseline again at 6 months after treatment and beyond (Figure 2a).

The number of patients with swallowing dysfunction per time of assessment are shown in Table 2 as well, either because of WST failure or because a number above the cut-off value was reached. Both a WST failure and a score above the cut-off value were reported in 16 patients. The prevalence of swallowing dysfunction is estimated to be 19.1% at baseline, 21.6% at M3, 19.2% at M6, 14.8% at M12, and 13.9% at M24.

Factors associated with number of swallows

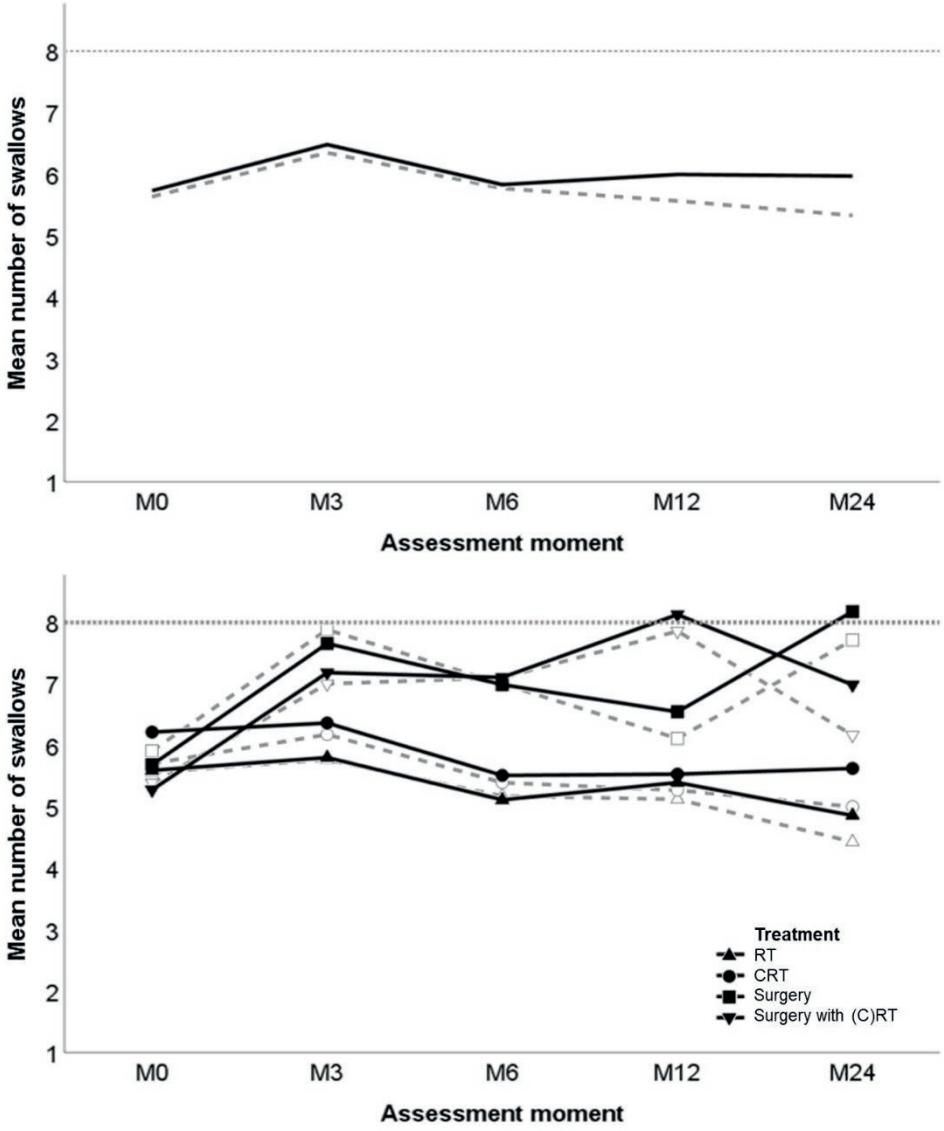
Linear mixed model analysis revealed that tumor site, sex, and tumor stage were not associated with the number of swallows, and were therefore removed from the final model. The course of number of swallows was significantly associated with age, and there was a significant interaction between treatment modality and timing of assessment, as shown in Table 3. Higher age was associated with a higher number of swallows (+0.07 more swallows per increasing year). Number of swallows of patients with surgery alone were comparable to number of swallows of patients that received surgery and adjuvant (C)RT: there was an increase in number of swallows from baseline to 3 months after treatment, which remained high up to 24 months after treatment. In contrast, the number of swallows of patients treated with RT or CRT (without surgery) increased from diagnosis to 3 months after treatment, after which the number of swallows returned to baseline level (Figure 2b). The cut-off score was used to develop a ROC curve indicating swallowing problems before and after treatment in patients with HNC (Appendix 1). The formula for the estimated number of swallows that were retained in the final model is shown in the footnote of Table 3.

Table 2. The mean number of swallows for each timing of assessment, and the total swallowing dysfunction as indicated by the number of failed water swallowing tests and/or the number of patients above the cut-off score

	Timing of assessment				
	M0	**M3**	**M6**	**M12**	**M24**
n patients	115	102	99	88	72
Mean number of swallows (SD)	5.8 (2.6)	6.4 (4.2)	5.8 (3.7)	5.6 (3.4)	5.4 (4.1)
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Swallowing dysfunction*	22 (19.1)	22 (21.6)	19 (19.2)	13 (14.8)	10 (13.9)
Number of patients above cut-off score	16 (13.9)	18 (17.6)	14 (14.1)	13 (14.8)	8 (11.1)
Number of WST failures	6 (5.2)	12 (11.8)	9 (9.1)	4 (4.5)	2 (2.8)
Coughing or choking	1/6 (16.7)	9/12 (75)	6/9 (66.7)	4/4 (100)	2/2 (100)
Not able to drink 100 mL	5/6 (83.3)	3/12 (25)	3/9 (33.3)	0	0

n: number of patients, SD: standard deviation, WST: Water swallow test
*: based on number of swallows above cut-off score and/or WST failure

Figure 2. The mean number of swallows for all patients (A) and for patients based on treatment modality (B)



The black solid lines represent the linear mixed model outcomes of the final model, and the gray striped lines represent the raw data. The mean number of swallows for healthy subjects is 3.68 swallows, and the cut-off value (≥2 times the standard deviation of healthy subjects (8 swallows)) is indicated by the horizontal gray dotted line

Table 3. Linear mixed model estimates for the number of swallows

		Estimate (95% CI)	p-value	Interactions with timing of assessment								
Intercept		1.46 (-2.40 to 5.32)		*M0*	*M3*		*M6*		*M12*		*M24*	
				Estimate (95% CI)	**Estimate (95% CI)**	**p-value**	**Estimate (95% CI)**	**p-value**	**Estimate (95% CI)**	**p-value**	**Estimate (95% CI)**	**p-value**
Timing of assessment	*M0*	*Reference*										
	M3	1.97 (0.47 to 3.48)	0.011*									
	M6	1.30 (0.04 to 2.56)	0.043*									
	M12	0.86 (-0.49 to 2.22)	0.211									
	M24	2.49 (1.03 to 3.95)	0.001*									
Age		0.07 (0.01 to 0.13)	0.021*									
Treatment	*Surgery*	*Reference*		*Reference*								
	RT	-0.33 (-2.09 to 5.32)	0.711	*Reference*	-1.77 (-3.55 to 0.02)	0.052*	-1.78 (-3.29 to -0.27)	0.021*	-1.06 (-2.69 to 0.56)	0.200	-3.23 (-4.96 to -1.49)	<0.001*
	CRT	0.84 (-1.09 to 2.77)	0.392	*Reference*	-1.83 (-3.76 to 0.11)	0.064*	-2.01 (-3.68 to -0.33)	0.019*	-1.55 (-3.32 to 0.23	0.088*	-3.09 (-5.00 to -1.18)	0.002*
	Surgery with (C)RT	-0.36 (-2.72 to 1.99)	0.761	*Reference*	-0.07 (-2.53 to 2.39)	0.956	0.53 (-1.62 to 2.67)	0.630	1.99 (-0.46 to 4.44)	0.112	-0.79 (-3.38 to 1.81)	0.552

*: p<0.10, CI: Confidence interval, CRT: Chemoradiotherapy, SE: Standard Error, RT: Radiotherapy

The following formula for the estimated number of swallows shows the variables and their coefficients. Factors with a positive coefficient will increase the number of swallows and therefore reflect a worse swallowing function:
Estimated number of swallows = 1.46 + 1.97M3 + 1.30M6 + 0.86M12 + 2.49M24 + 0.07age - 0.33RT + 0.84CRT - 0.36surgery with (C)RT - 1.77RT*M3 – 1.83CRT*M3 - 0.07surgery with (C)RT*M3 -1.78RT*M6 – 2.01CRT*M6 + 0.53surgery with (C)RT*M6 - 1.06RT*M12 - 1.55CRT*M12 + 1.99surgery with (C)RT*M12 - 3.23RT*M24 - 3.09CRT*M24 - 0.79surgery with (C)RT*M24

Discussion

Overall, swallowing function as measured by number of swallows needed to drink 100 mL of water, worsened from diagnosis to 3 months after treatment, after which it returned to or below baseline level in patients with head and neck cancer (Table 2). Swallowing dysfunction increased from diagnosis (19%) to 3 months after treatment (22%), after which it returned to or below baseline level (14%). Age and treatment modality were significantly associated with the course of swallowing function. Swallowing function was worse in older patients. Swallowing function of patients receiving surgery as primary treatment in particular was worse 3 months after treatment compared to baseline and remained worse up to 24 months. Patients treated with (C)RT did not show this worsening after treatment. Instead, their swallowing function improved after treatment.

The clinical relevance of the LMM results can be clarified by taking into account the smallest detectable change (SDC) found in previous research. The SDC for the number of swallows was 0.79 points, indicating that the difference between two measurements has to be at least 0.79 points to be a real difference and not a measurement error.[14] When looking at the estimates in Table 3, all results meet this condition except age; one year older does not contribute to a worse swallowing function, however, a difference of more than 11 years will.

Comparison with literature

In previous research, other factors associated with worse swallowing function were sex (female), tumor stage (T3 and T4), the addition of chemotherapy as treatment modality, and oropharynx tumors.[2,18,19] These factors did not contribute to worse swallowing function in our study. In addition, the size of the radiation field, accelerated fractionation, neck irradiation, type of surgery, and normal tissue changes such as edema, neuropathy, fibrosis, and mucositis might influence the WST outcome as well.[2,5,19] The sample size of the current study was too small to also include these factors. For example, only 16 patients received surgery followed by (C)RT. It is therefore recommended to repeat this study with a larger sample size, and include more factors in the LMM analysis.

This study did not find an effect of RT treatment on swallowing function. This might be explained by the fact that patients treated with RT nowadays often receive IMRT, in order to spare the swallowing muscles.[20] The next step should therefore be to investigate the effect of dose to the swallowing organs at risk (OAR) on swallowing function in order to see the effect of OAR sparing.

The number of WST failures increased over time to almost 12% three months after treatment, and the reason for failure changed from 'not being able to drink the 100 mL of water', to 'coughing or choking post swallow'. Coughing or choking post swallow was found to have a specificity of up to 91.7% in predicting aspiration, and the WST is therefore a useful tool for early detection of swallowing dysfunction.[21] Previous research found dysphagia and aspiration rates between 12% to 21%, similar to the results found in this study.[18,22] Especially patients that received surgery with adjuvant treatment have a higher prevalence of dysphagia in comparison to patients that receive RT alone, as also seen in this research by the higher number of swallows.[7] Besides WST failures, between 11% and 18% of patients had a WST score above the cut-off score (>2 standard deviations above the mean of healthy subjects), with the most problems 3 months after treatment.

Previous research showed that the objective WST and subjective patient-reported outcomes measuring swallowing function have a low correlation and can therefore not be used interchangeably.[23] A future study might aim at developing a prediction model with subjective questionnaires, to obtain individual risk scores for swallowing problems in patients with HNC, including a larger number of potential predictors. These predictors could then, apart from the predictors used in this study, also include a larger range of treatment modalities and normal tissue changes. This also makes it possible to study whether the factors found in this study are found with subjective outcome measures as well.

Strengths and limitations

Strengths of our study were the prospective study design, the use of the linear mixed-effects model checklist with recommendations for reporting multilevel data and analyses,[24] and the use of an objective swallowing test with a high test-retest reliability.[14] Limitations were the relatively low number of patients at follow-up, which limited the number of factors that could be explored, and the relative large drop-out and missing values. These missing data may have influenced the results, because it is unknown how these patients would have performed on the WST. Although linear mixed-effects model analysis is especially designed for repeated measurement analyses, and is better at handling missing values in comparison to other regression analyses,[25] these regression models do not take into account the number of deaths as competing risk. Additionally, since the study group was relatively small, it was chosen to only look at interactions between timing of assessment and treatment, location, and tumor stage. Another limitation of this study were the significant differences found between treatment versus tumor stage and tumor site, as seen in Table 1. Patients receiving RT have an oropharynx, hypopharynx or larynx tumor, while patients receiving surgery most often have a tumor in the oral cavity. In addition, patients receiving CRT have larger tumors (stage III and IV), while patients receiving surgery most often have

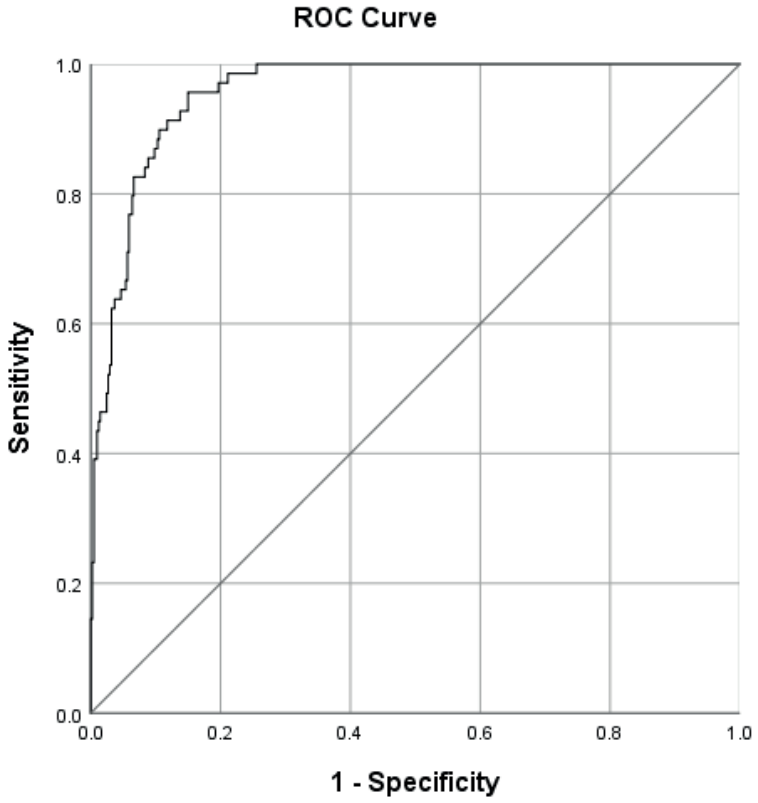
smaller tumors (stage I and II). Therefore, the association found between the WST outcome and treatment is also caused by tumor site and tumor stage. Unfortunately, because of the low number of patients in this study, no interactions between treatment, tumor stage, and tumor site could be explored in the linear mixed-effects model.

Clinical relevance

In order to improve swallowing function, promising results were found using swallowing exercises during the course of radiation treatment.[26] These exercises are designed to improve swallowing safety, i.e., reduce penetration or aspiration, and increase efficiency of swallowing.[27] The results found in the current study suggest that especially older patients and patients after surgery may benefit from preventive swallowing exercises, because they had a worse swallowing function. It is unknown how many patients received swallowing exercises during or after treatment. Especially in patients treated with surgery, performing swallowing exercises before, during and/or after (adjuvant) treatment may prevent dysphagia, or reduce its severity.[28] Also in older patients, who are at a higher risk of aspiration due to a decrease in eating and swallowing function, swallowing exercises can help maintain or improve the oral function.[29-31] In addition to providing swallowing exercises, patients can be informed about expected swallowing difficulties after treatment. It is important to set realistic expectations, so patients can cope with the effects of treatment on daily functioning.[32] Information about expected difficulties can reduce distress and anxiety during treatment, and can increase active patient participation and satisfaction with provided care.[32] In conclusion, in patients with head and neck cancer swallowing function changes over time from diagnosis up to 2 years after treatment, with the worst scores 3 months after treatment. A higher age and being treated with surgery are factors associated with the course of swallowing function over time. It is estimated that swallowing dysfunction occurs in 14-22% of patients with head and neck cancer before or after treatment.

Appendix

Appendix 1. Receiver operating characteristic (ROC) curve for swallowing problems after treatment, using the linear mixed model



The area under the curve (AUC) is 0.957. The AUC for the different timings of assessment is 0.946 (T0), 0.963 (M3), 0.940 (M6), 0.971 (M12), and 0.979 (M24). The AUC can vary between 0 and 1, where a value of 0 indicated that the model has no diagnostic power, and a value of 1 indicates that the model has a perfect diagnostic accuracy

References

1. Rettig EM, D'Souza G. Epidemiology of head and neck cancer. *Surgical oncology clinics of North America.* 2015;24(3):379-396.

2. Langendijk JA, Doornaert P, Rietveld DH, Verdonck-de Leeuw IM, Leemans CR, Slotman BJ. A predictive model for swallowing dysfunction after curative radiotherapy in head and neck cancer. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology.* 2009;90(2):189-195.

3. van der Veen J, Nuyts S. Can Intensity-Modulated-Radiotherapy Reduce Toxicity in Head and Neck Squamous Cell Carcinoma? *Cancers.* 2017;9(12):135.

4. Kreeft AM, van der Molen L, Hilgers FJ, Balm AJ. Speech and swallowing after surgical treatment of advanced oral and oropharyngeal carcinoma: a systematic review of the literature. *Eur Arch Oto-Rhino-L.* 2009;266(11):1687-1698.

5. Hutcheson KA, Lewin JS, Barringer DA, et al. Late dysphagia after radiotherapy-based treatment of head and neck cancer. *Cancer.* 2012;118(23):5793-5799.

6. Riffat F, Gunaratne DA, Palme CE. Swallowing assessment and management pre and post head and neck cancer treatment. *Current opinion in otolaryngology & head and neck surgery.* 2015;23(6):440-447.

7. Hutcheson KA, Nurgalieva Z, Zhao H, et al. Two-year prevalence of dysphagia and related outcomes in head and neck cancer survivors: An updated SEER-Medicare analysis. *Head & neck.* 2019;41(2):479-487.

8. Alterio D, Gerardi MA, Cella L, et al. Radiation-induced acute dysphagia : Prospective observational study on 42 head and neck cancer patients. *Strahlentherapie und Onkologie : Organ der Deutschen Rontgengesellschaft [et al].* 2017;193(11):971-981.

9. Manikantan K, Khode S, Sayed SI, et al. Dysphagia in head and neck cancer. *Cancer treatment reviews.* 2009;35(8):724-732.

10. Verdonck-de Leeuw IM, Jansen F, Brakenhoff RH, et al. Advancing interdisciplinary research in head and neck cancer through a multicenter longitudinal prospective cohort study: the NETherlands QUality of life and BIomedical Cohort (NET-QUBIC) data warehouse and biobank. *BMC Cancer.* 2019;19(1):765.

11. Paleri V, Mehanna H, Wight RG. TNM classification of malignant tumours 7th edition: what's new for head and neck? *Clin Otolaryngol.* 2010;35(4):270-272.

12. Patterson JM, McColl E, Carding PN, Kelly C, Wilson JA. Swallowing performance in patients with head and neck cancer: a simple clinical test. *Oral oncology.* 2009;45(10):904-907.

13. Patterson JM, Hildreth A, McColl E, Carding PN, Hamilton D, Wilson JA. The clinical application of the 100mL water swallow test in head and neck cancer. *Oral oncology.* 2011;47(3):180-184.

14. Vermaire JA, Terhaard CHJ, Verdonck-de Leeuw IM, Raaijmakers CPJ, Speksnijder CM. Reliability of the 100 mL water swallow test in patients with head and neck cancer and healthy subjects. *Head & neck.* 2021;43(8):2468-2476.

15. Thomas FJ, Wiles CM. Dysphagia and nutritional status in multiple sclerosis. *J Neurol.* 1999;246: 677-682.

16. Bolker BM, Brooks ME, Clark CJ, et al. Generalized linear mixed models: a practical guide for ecology and evolution. *Trends Ecol Evol.* 2009;24(3):127-135.

17. Burnham KP, Anderson DR. Multimodel Inference. *Sociological Methods & Research.* 2016;33(2):261-304.

18. Patterson JM, McColl E, Carding PN, Wilson JA. Swallowing beyond six years post (chemo)radiotherapy for head and neck cancer; a cohort study. *Oral oncology.* 2018;83:53-58.

19. Patterson JM, McColl E, Carding PN, Hildreth AJ, Kelly C, Wilson JA. Swallowing in the first year after chemoradiotherapy for head and

neck cancer: clinician- and patient-reported outcomes. *Head & neck.* 2014;36(3):352-358.

20. Ursino S, D'Angelo E, Mazzola R, et al. A comparison of swallowing dysfunction after three-dimensional conformal and intensity-modulated radiotherapy : A systematic review by the Italian Head and Neck Radiotherapy Study Group. *Strahlentherapie und Onkologie : Organ der Deutschen Rontgengesellschaft [et al].* 2017;193(11):877-889.

21. Wu MC, Chang YC, Wang TG, Lin LC. Evaluating swallowing dysfunction using a 100-ml water swallowing test. *Dysphagia.* 2004;19(1):43-47.

22. Judy GD, Green R, Aumer SL, et al. Preservation of swallowing function with de-intensified chemoradiation therapy for HPV-associated oropharyngeal squamous cell carcinoma. *Advances in radiation oncology.* 2018;3(3):356-365.

23. Vermaire JA, Raaijmakers CPJ, Verdonck-de Leeuw IM, et al. Mastication, swallowing and salivary flow in patients with head and neck cancer; objective tests versus patient reported outcomes. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer.* 2021.

24. Monsalves MJ, Bangdiwala AS, Thabane A, Bangdiwala SI. LEVEL (Logical Explanations & Visualizations of Estimates in Linear mixed models): recommendations for reporting multilevel data and analyses. *BMC Med Res Methodol.* 2020;20(1):3.

25. Van der Elst W, Molenberghs G, Van Boxtel MP, Jolles J. Establishing normative data for repeated cognitive assessment: a comparison of different statistical methods. *Behav Res Methods.* 2013;45(4):1073-1086.

26. Carroll WR, Locher JL, Canon CL, Bohannon IA, McColloch NL, Magnuson JS. Pretreatment swallowing exercises improve swallow function after chemoradiation. *Laryngoscope.* 2008;118(1):39-43.

27. Logemann JA. Behavioural management for oropharyngeal dysphagia. *Folia Phoniatr Logop.* 1999;51:199–212.

28. Perry A, Lee SH, Cotton S, Kennedy C. Therapeutic exercises for affecting post-treatment swallowing in people treated for advanced-stage head and neck cancers. *Cochrane Db Syst Rev.* 2016(8).

29. Sugiyama T, Ohkubo M, Honda Y, et al. Effect of Swallowing Exercises in Independent Elderly. *Bull Tokyo Dent Coll.* 2013;54(2):109–115.

30. Robbins J, Gangnon RE, Theis SM, Kays SA, Hewitt AL, Hind JA. The effects of lingual exercise on swallowing in older adults. *J Am Geriatr Soc.* 2005;53(9):1483-1489.

31. Kristensen MB, Isenring E, Brown B. Nutrition and swallowing therapy strategies for patients with head and neck cancer. *Nutrition.* 2020;69:110548.

32. Brockbank S, Miller N, Owen S, Patterson JM. Pretreatment information on dysphagia: exploring the views of head and neck cancer patients. *Journal of pain and symptom management.* 2015;49(1):89-97.

7

Chapter 8

The course of swallowing problems in the first two years after diagnosis of head and neck cancer

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Abstract

Background

Head and neck cancer (HNC) and its treatment often negatively impact swallowing function. The aim was to investigate the course of patient reported swallowing problems from diagnosis to 3, 6, 12, and 24 months after treatment, in relation to demographic, clinical and lifestyle factors.

Methods

Data were used of the Netherlands Quality of Life and Biomedical Cohort Study in head and neck cancer research (NET-QUBIC). The primary outcome measures were the subscales of the Swallowing Quality of Life Questionnaire (SWAL-QOL). Linear mixed-effects models (LMM) were conducted to investigate changes over time and associations with patient-, clinical-, and lifestyle parameters as assessed at baseline.

Results

Data were available of 603 patients. There was a significant change over time on all subscales. Before treatment, 53% of patients reported swallowing problems, and 70%, 59%, 50% and 48% at 3, 6, 12, and 24 months after treatment, respectively. Swallowing problems (i.e. longer eating duration) were more pronounced in case of female, current smoking, weight loss prior to treatment, stage III or IV tumor, and were more prevalent at 3 to 6 months after treatment. Especially patients with an oropharynx and oral cavity tumor, and patients receiving (C)RT following surgery or CRT only showed a longer eating duration after treatment, which did not return to baseline levels.

Conclusion

Half of the patients with HNC report swallowing problems before treatment. Eating duration was associated with sex, smoking, weight loss, tumor site and stage, treatment modality, and was more pronounced 3 to 6 months after treatment.

Introduction

Head and neck cancer (HNC) is the seventh most common cancer worldwide, accounting for an estimated 650,000 new cases and 350,000 deaths every year.[1] HNC is most often caused by alcohol and/or tobacco use, or the human papilloma virus (HPV).[2] Curative treatment options for HNC include surgery, radiotherapy (RT) and chemo radiation (CRT). Treatment extent and intensity vary, and the choice of treatment modality depends on tumor site, tumor stage, comorbidities, and wishes and expectations of patients.[3,4] Surgery may compromise lingual mobility, strength, and muscle coordination in the head and neck region.[4-6] High-intensity radiation treatment regimens have resulted in improved survival and tumor control, but may also lead to acute effects such as pain, mucositis, and decrease in saliva production, and late effects such as trismus, masticatory deficits, dysphagia (swallowing dysfunction), and xerostomia.[4,7,8] Chemotherapy can add to these effects by increasing oral mucositis, nausea, vomiting, loss of appetite, and xerostomia.[9] These side effects occur in a considerable proportion of patients after HNC treatment despite efforts to spare structures related to oral food processing, salivary function, and swallowing.[7,10] During the food process, several muscles, nerves and connective tissue structures need to work together to break down food into smaller particles which bind to each other through saliva, and form a food bolus ready for swallowing and digestion.[11,12] The number of teeth and occlusal units are of great importance to grind and break down food. Tooth loss, the presence of cavities, inadequate restorations, malocclusion or periodontal disease can adversely affect chewing function and thereby also swallowing.[13,14] Side effects of treatment may have a negative influence on swallowing function and thereby on the ability to eat and drink, which in turn impact health related quality of life (QoL) of patients.[1,15,16]

To evaluate patient reported outcomes (PROs) regarding dysphagia, several tools are available such as the swallowing subscale of the European organization for research and treatment of cancer quality of life questionnaire (EORTC QLQ-H&N35), the M.D. Anderson Dysphagia Inventory (MDADI),[17,18] and the Swallowing quality of life questionnaire (SWAL-QOL).[16] An important study using the EORTC QLQ-H&N35 to assess swallowing (n=2458) provided a survey at baseline, and 4 and 12 months post-baseline.[19] This study included all possible patients with HNC (all curative treatment options and tumor sites). Swallowing was diminished especially 4 months after treatment. Factors associated with swallowing and social eating were: tumor site, age, treatment, smoking, socio-economic status, and sex.[19]

Unlike the EORTC QLQ-H&N35 questionnaire (which only has a swallowing and social eating subscale), the SWAL-QOL questionnaire includes multiple subscales to assess swallowing related quality of life. Multiple studies assessed swallowing as measured with the SWAL-QOL, either as prospective cohort study to investigate swallowing differences over time,[7,20-

[24] or as cross-sectional study to investigate swallowing at one point in time,[10,21,22,25,26] for example at baseline.[21] In these studies, different patients were assessed. Some studies only included patients that received RT or CRT,[7,10,20,22,23,25,26] other studies only patients that received surgery,[24] and others included patients with all curative treatment options.[21,27] In addition, tumor site differed from one tumor site (e.g. laryngeal [27]) to all tumors in the head and neck region. The number of patients included in the various studies assessing the SWAL-QOL, varied as well, from 22[20] to 1083 patients.[22] Most studies found that swallowing function was impaired across most domains for the majority of patients,[23,24,27] especially 6 to 12 months after treatment.[10]

To reduce the risk for persistent patient reported swallowing problems after treatment for HNC, it is important to identify factors associated with these swallowing problems. Information can be provided about possible problems that may occur after treatment and the possibility of rehabilitation during and after treatment can be discussed. This will lead to a better evaluation of possible treatment options and more patient centered care. As mentioned, previous research about the SWAL-QOL mainly focused on one type of treatment modality, or one type of tumor site.[28,29] In addition, most studies investigating swallowing problems in patients with HNC were too small to allow subgroup analyses.[30] One study included all patients with HNC and assessed a large cohort, but only assessed the subscales swallowing and eating duration of the EORTC QLQ-H7N35.[19] Factors that were found to be associated with poor patient reported swallowing problems included patient-related factors such as smoking, alcohol use, higher age, low socio-economic status, and being female, and tumor-related factors such as advanced tumor stage, multi-modality treatment, and tumor site.[10,19,31] However, to our knowledge, there are no studies that assessed the SWAL-QOL questionnaire and included the majority of these factors, included all treatment modalities and tumor sites, and assessed swallowing problems prospectively up to 2 years after treatment.

The primary aim of this study was to investigate the course over time in the first two years after HNC diagnosis of various aspects of patient reported swallowing problems as measured with the SWAL-QOL. The secondary aim was to identify demographic, clinical, and lifestyle factors associated with patient reported swallowing problems in patients with HNC.

Materials and methods

Data were used of 739 patients with HNC participating in the prospective NETherlands Quality of Life and Biomedical Cohort study in HNC cancer (NET-QUBIC), of which details were published previously.[32,33] Recruitment took place in 7 HNC centers throughout the

Netherlands between 2014 and 2018. Patients were included when they were 18 years or older, were diagnosed with oral, oropharyngeal, hypopharyngeal, or laryngeal HNC and were treated with curative intent (all treatment modalities). Patients with an unknown primary tumor, recurrent or residual disease, cognitive impairments, lymphoma, skin malignancies or thyroid cancer, and patients having trouble understanding or reading the Dutch language were excluded. All patients signed written informed consent before participation. The study protocol of this prospective observational cohort study was approved by the Medical Ethics Committee of the VUmc (NL45051.029.13) and all local participating centers.[32,33] In the present study, patients were included when they had completed the SWAL-QOL questionnaire at any given time point. The SWAL-QOL questionnaire was assessed before primary treatment (baseline, M0), 3 months (M3), 6 months (M6), 12 months (M12), and 24 months after treatment (M24). Demographic factors (age and sex), clinical factors (tumor stage,34 tumor site, HPV status (in oropharynx patients), treatment modality, comorbidity, and weight loss), and lifestyle factors (alcohol use and smoking) were assessed at baseline.

The primary outcome measure was the 47-item Swallowing Quality of life Questionnaire (SWAL-QOL).[16] This questionnaire comprises of 10 subscales on food selection (2 items), eating duration (2 items), eating desire (3 items), fear of eating (4 items), general burden (2 items), mental health (5 items), social functioning (5 items), communication (2 items), sleep (2 items), and fatigue (3 items). Furthermore, a symptom scale (14 items) is included. Based on the 23 items of the first seven mentioned scales, a total SWAL-QOL score can be calculated. All items refer to the last month. In NET-QUBIC, the subscales communication, sleep, and fatigue were removed, because of the considerable overlap with the Speech Handicap Index and the Multidimensional Fatigue Inventory. The 5-point items are transformed to scales ranging from 0 to 100, where a higher score indicates more swallowing problems. As found in previous research, a cut-off score on the total SWAL-QOL score of ≥14 points indicates a high level of swallowing problems in daily life.[26] The SWAL-QOL has been translated into Dutch and validated for use in patients with HNC.[16]

Baseline characteristics about age, sex, ACE-27 comorbidity score,[35] TNM7 classification (2010), and weight loss prior to treatment were collected from medical files. HPV status was collected for oropharynx tumors. A 13-item study-specific patient-reported questionnaire was used to assess smoking status and nicotine dependence. One item about passive smoking was included, 7 items about smoking behavior, and 5 items about nicotine dependence. For this study, patients were categorized as current smoker, nonsmoker (less than 100 units in their lifetime) or former smoker. A 21-item questionnaire was used to assess alcohol intake and dependence, consisting of questions about current alcohol intake

and history of alcohol intake (14 items), and alcohol dependence (7 items). The question 'do you drink regularly' was used to assess alcohol intake in the current study.

Statistical Analyses

Descriptive statistics were used to describe the study population. Differences between the total NET-QUBIC population and patients that filled in the SWAL-QOL were tested using ANOVA to assess differences in age, and chi-square tests were run to test for differences in sex, tumor site, tumor stage, primary treatment, alcohol consumption, smoking, comorbidity, and weight loss.

Linear mixed models (LMM) were used to assess if demographic, clinical, and lifestyle factors influenced changes over time of the total score and all subscales of the SWAL-QOL. Akaike's Information Criterion (AIC) was used to select the most appropriate covariance structure to fit the data.[36] To account for within-patient correlations, a random patient factor was added, and a random intercept was used to account for the different entry levels of patients. The fixed-effect factors timing of assessment, tumor site, treatment modality, tumor stage based on TNM classification,[34] sex, alcohol consumption, smoking, comorbidity, weight loss, HPV status, and age, as well as 2-way interactions of the factors treatment modality, tumor site, and tumor stage during the assessment period, were assessed. Timing of assessment consisted of 5 levels (M0, M3, M6, M12, M24), tumor site consisted of 3 levels (oropharynx, larynx or hypopharynx, oral cavity), treatment modality consisted of 4 levels (RT, CRT, surgery or CO_2 laser, surgery with post-operative (C)RT), tumor stage consisted of 4 levels (I:Tis or T1N0M0, II:T2N0M0, III:T3N0M0 or T2N1M0 or T3N1M0, IV:T4aN0M0 or TanyN2M0 or T4bN0M0 or TanyN3M0),[34] sex consisted of 2 levels (male, female), alcohol consumption consisted of 3 levels (drink regularly, seldom drink, drank in the past), smoking consisted of 3 levels (nonsmoker, former smoker, smoker), comorbidity consisted of 4 levels (none, mild, moderate, severe), weight loss consisted of 3 levels (no weight loss, 1-5 kg weight loss, >5 kg weight loss), HPV status consisted of 2 levels for oropharynx patients only (positive, negative), and age was defined as a continuous variable. The model included a stepwise backward selection of factors, in which factors that were not significant at a $p<0.10$ level were removed, beginning with the interactions. A hierarchical structure was maintained, meaning that if an interaction was included in the model, the main effects were also represented in the model. Risk factors were reported as estimated unstandardized regression coefficients with 95% confidence intervals (CI) and p-values.

The coefficients of the significant covariates, together with the value of the intercept of the mixed model analysis, were combined into a formula for the estimated SWAL-QOL subscale. The intercept is the value of the estimated SWAL-QOL subscale in which all coefficients

remain zero. Addition of the coefficients will lead to an increase or decrease of the estimated SWAL-QOL subscale. This formula can be used to estimate the QoL of patients during the follow-up period. For each time point, the formula was filled with average variable values for significant coefficients, as calculated by a restricted maximum likelihood approach. All analyses were performed using Statistical Package for the Social Sciences (SPSS) version 25 (Chicago, IL). A p-value <0.05 for the descriptive statistics and <0.10 for the linear mixed-effects model were considered statistically significant.

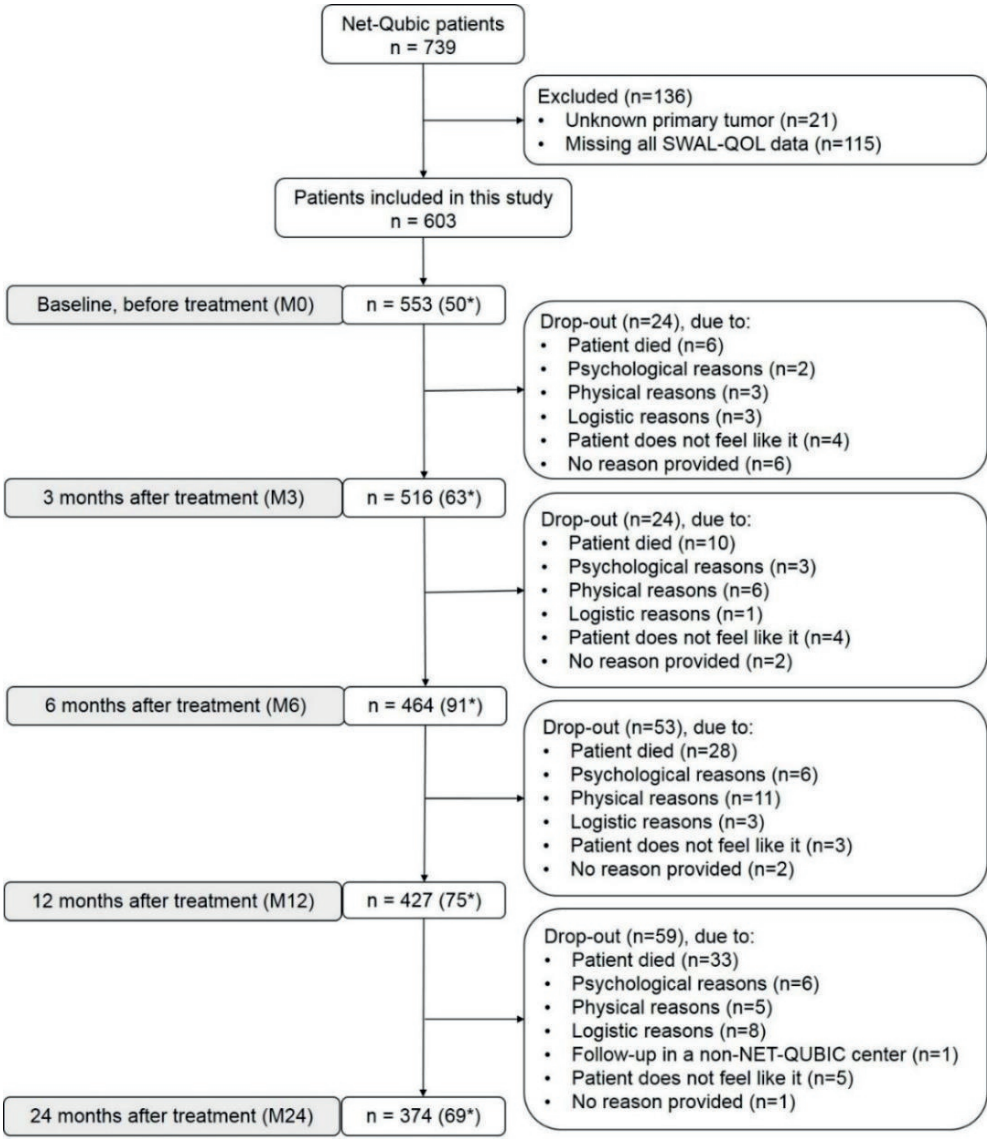
Results

Among the 739 patients participating in the NET-QUBIC research, 603 patients filled in the questionnaire at least once during the 2-year follow-up and were included in the LMM analyses. At baseline, 553 patients completed the SWAL-QOL questionnaire, 516 at 3 months, 464 at 6 months, 427 at 12 months, and 374 at 24 months (Figure 1). No significant differences were observed between patients that responded to the SWAL-QOL questionnaire and the total NET-QUBIC population (Table 1). Based on the SWAL-QOL cut-off score of ≥14, 53% of patients had problems before treatment, which increased to 70% at 3 months after treatment, and decreased to 59% at 6 months after treatment, 50% at 12 months after treatment, and 48% at 24 months after treatment.

Mean SWAL-QOL outcomes

The total score and subscales 'general burden', 'eating desire', and 'social functioning' showed higher mean scores for all patients 3 months after treatment (indicating more problems), after which these scores returned to baseline at 6 months after treatment and beyond (Figure 2). There was no change over time in 'fear of eating'. The subscales 'food selection' and 'symptoms' took longer to return to baseline levels, indicated by the significant differences at 6 months after treatment. 'Mental health' was higher 3 months after treatment, and lower at 24 months after treatment in comparison to baseline. 'Eating duration' increased from baseline to 3 months after treatment, remained significantly worse 6 months after treatment, and did not return to baseline 12 and 24 months after treatment. Because the total score and all subscales of the SWAL-QOL returned to baseline, except the subscale 'eating duration', the focus of the subsequent linear mixed model was on this subscale.

Figure 1. Flowchart depicting the number of patients at each time point



*: missing measurement

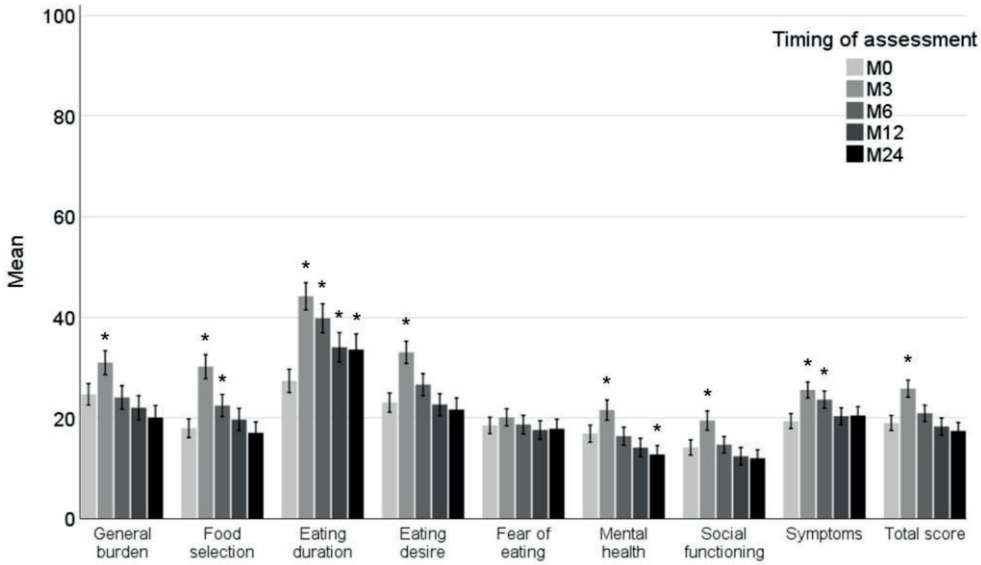
Table 1. Characteristics of patients that were included in the NET-QUBIC study, patients included in the linear mixed model analyses and patients that responded to the SWAL-QOL questionnaire (responders) at baseline (M0)

Variables	Total NET-QUBIC study	Patients included in LMM analyses	Responders M0	p-value	
	n = 739 n (%)	n = 603 n (%)	n = 553 n (%)	Total NET-QUBIC study versus patients included in LMM analyses	Total NET-QUBIC study versus responders M0
Age mean (SD)	63.3 (9.7)	63.5 (9.5)	63.5 (9.6)	0.602†	0.637†
Sex				0.943‡	0.860‡
Male	549 (74.3)	449 (74.5)	410 (74.1)		
Female	190 (25.7)	154 (25.5)	143 (25.9)		
Tumor site				0.927‡	0.837‡
Oropharynx	262 (35.5)	217 (36.0)	201 (36.3)		
HPV positive	130 (49.6)	114 (52.5)	106 (52.7)	0.425‡	0.679‡
HPV negative	99 (37.8)	74 (34.1)	68 (33.8)		
Missing	*33 (12.6)*	*29 (13.4)*	27 (13.4)		
Larynx or hypopharynx	257 (34.8)	210 (34.8)	191 (34.5)		
Oral cavity	199 (26.9)	176 (29.2)	161 (29.1)		
Unknown primary	*21 (2.8)*	*0*	*0*		
Tumor stage				0.562‡	0.715‡
1	163 (22.1)	150 (24.9)	139 (25.1)		
2	132 (17.9)	113 (18.7)	105 (19.0)		
3	127 (17.2)	98 (16.3)	88 (15.9)		
4	317 (42.9)	242 (40.1)	221 (40.0)		
Primary treatment				0.831‡	0.901‡
RT	241 (32.6)	199 (33.0)	189 (34.2)		
CRT	215 (29.1)	163 (27.0)	147 (26.6)		
Surgery or CO_2 laser	152 (20.6)	133 (22.1)	121 (21.9)		
Surgery with PO(C)RT	129(17.4)	107 (17.7)	96 (17.3)		
Other	*2 (0.3)*	*1 (0.2)*	*0*		
Alcohol consumption				0.999‡	0.991‡
Drink regularly	313 (42.4)	302 (50.1)	298 (53.9)		
Seldom drink	170 (23.0)	164 (27.2)	164 (29.7)		
Drank in past	88 (11.9)	85 (14.1)	85 (15.4)		
Missing	*168 (22.7)*	*52 (8.6)*	*6 (1.0)*		
Smoking				0.997‡	0.982‡
Nonsmoker	105 (14.2)	101 (16.7)	100 (18.1)		
Former smoker	321 (43.4)	311 (51.6)	309 (55.9)		
Smoker	146 (19.7)	140 (23.2)	139 (25.1)		
Missing	*168 (22.7)*	*51 (8.5)*	*5 (0.9)*		
Comorbidity				0.907‡	0.731‡
None	204 (27.6)	177 (29.4)	164 (29.7)		
Mild	264 (35.7)	218 (36.2)	203 (36.7)		
Moderate	155 (21.0)	119 (19.7)	108 (19.5)		
Severe	76 (10.3)	61 (10.1)	52 (9.4)		
Missing	*40 (5.4)*	*28 (4.6)*	*26 (4.7)*		
Weight loss				0.945‡	0.745‡
No weight loss	471 (63.7)	386 (64.0)	357 (64.6)		
1-5 kg	121 (16.4)	96 (15.9)	88 (15.9)		
>5 kg	71 (9.6)	55 (9.1)	48 (8.7)		
Missing	*76 (10.3)*	*66 (11.0)*	*60 (10.8)*		

*: p-value <0.05; †: ANOVA, ‡: Chi-square

CRT: Chemo radiation, LMM: Linear Mixed Model, PO: post-operative, RT: Radiotherapy, SD: Standard deviation, SWAL-QOL: Swallowing Quality of Life questionnaire

Figure 2. Mean scores of the SWAL-QOL total score and subscales with standard error from baseline (M0) up to 2 years (M24) after treatment in patients with head and neck cancer



*: p<0.05 in comparison to baseline
SWAL-QOL: Quality of Life in Swallowing Disorders questionnaire

Eating duration evaluated with Linear Mixed Model

The factors alcohol, comorbidity, HPV status, age, and the interaction between timing of assessment and tumor stage were not associated with eating duration, and were therefore removed from the model. The factors sex, smoking, weight loss, tumor site, treatment, tumor stage, and timing of assessment were associated with a worse eating duration (Table 2).

The eating duration was worse in females in comparison to males (+4.15). Furthermore, smoking (+11.23 in comparison to nonsmokers) and losing weight before treatment (+7.56 for >5 kg in comparison to no weight loss), and more advanced tumor stage (stage III-IV) (+11.01 for stage IV in comparison to stage I),[34] were associated with a worse eating duration. The eating duration increased from baseline to 3 months after treatment (+8.15), remained significantly worse 6 months after treatment (+6.67), and did not return to baseline 12 and 24 months after treatment (+1.33 and +6.11, respectively). In addition, significant interactions were found for timing of assessment with tumor site and treatment, indicating that the course over time differed between different tumor sites and different treatment modalities (Figure 3). Patients with a tumor located in the oropharynx or oral cavity showed a worsening in eating duration 3 and 6 months after treatment, after which the numbers did not return to baseline 12 and 24 months after treatment. Patients with a

tumor in the hypopharynx or larynx did not show a worsening in eating duration after treatment, instead, the scores remained constant over time. Patients receiving adjuvant (C)RT, and patients receiving definitive CRT only showed the worst decline in outcomes from baseline to 3 months after treatment. These numbers did not return to baseline but remained high from 6 months to 24 months after treatment. Patients receiving RT only showed a mild worsening from baseline up to 3 months after treatment, after which the numbers slowly returned to baseline. Patients receiving surgery only or CO_2 laser treatment (for early laryngeal cancers) showed no decline after treatment.

LMM total score and other subscales

The LMM analyses revealed that the total score and the subscales 'general burden', 'food selection', 'eating desire', 'fear of eating', 'mental health', 'social functioning', and 'symptoms' scored worse when the patient was a smoker at baseline, had more comorbidities at baseline, and received CRT or surgery followed by (C)RT. In addition, receiving CRT or surgery followed by (C)RT led to more deterioration shortly after treatment. Having a more advanced tumor stage (stage III and IV) also resulted in a worse outcome for the total score and subscales 'general burden', 'food selection', 'eating desire', 'fear of eating', 'mental health', and 'symptoms'. Having a tumor in the oral cavity led to worse outcomes on the total score and subscales 'general burden', 'food selection', 'eating desire', 'mental health', 'social functioning', and 'symptoms'. Losing weight before treatment resulted in a worse outcome on the total score and subscales 'general burden', 'social functioning', and 'symptoms'. Patients with a higher age showed a worse outcome on the subscales 'food selection' and 'eating desire'. Drinking alcohol regularly led to less problems on the subscales 'mental health' and 'social functioning'.

Table 2. Linear mixed model estimates for the subscale eating duration of the SWAL-QOL

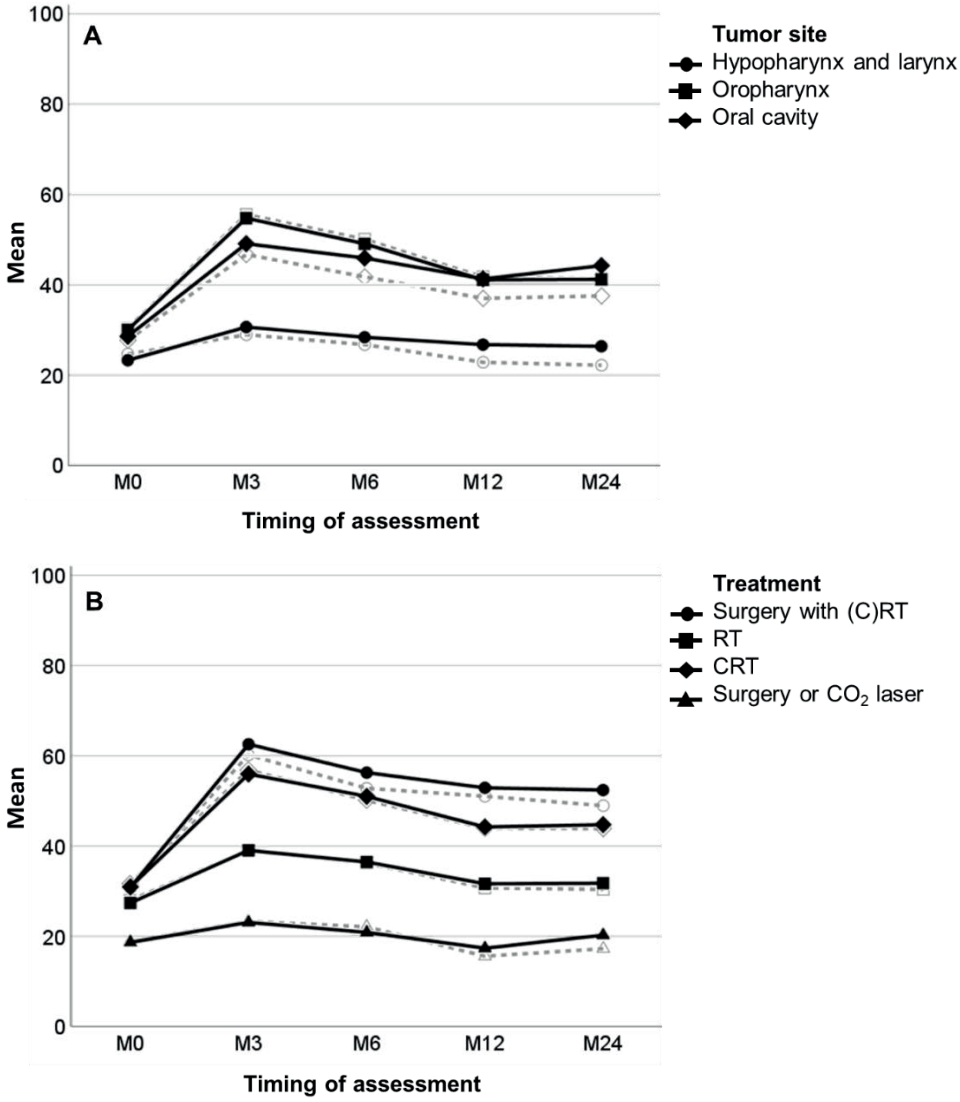
Characteristic		Estimate (95% CI)	p-value	Interactions with timing of assessment									
Intercept				*M0*	M3		M6		M12		M24		
		47.66 (36.56 to 58.75)		**Estimate (95% CI)**	**Estimate (95% CI)**	**p-value**	**Estimate (95% CI)**	**p-value**	**Estimate (95% CI)**	**p-value**	**Estimate (95% CI)**	**p-value**	
Sex	*Male*	-4.15 (-8.78 to 0.48)	0.079*										
	Female	*Reference*											
Weight loss	*No weight loss*	-7.56 (-14.57 to -0.55)	0.035*										
	1-5 kg	-0.10 (-8.25 to 8.04)	0.980										
	>5 kg	*Reference*											
Smoking	*Non smoker*	-11.23 (-17.53 to -4.93)	0.001*										
	Former smoker	-8.01 (-12.82 to -3.19)	0.001*										
	Smoker	*Reference*											
Tumor stage	*I*	-11.01 (-18.01 to -4.00)	0.002*										
	II	-7.72 (-14.38 to -1.06)	0.023*										
	III	2.39 (-3.90 to 8.68)	0.457										
	IV	*Reference*											
Timing of Assessment	*M0*	*Reference*											
	M3	8.15 (2.39 to 19.92)	0.006*										
	M6	6.67 (-0.20 to 13.53)	0.057*										
	M12	1.33 (-5.97 to 8.63)	0.721										
	M24	6.11 (-1.50 to 13.72)	0.116										

Table 2 (continued)				*M0*	M3		M6		M12		M24	
				Estimate (95% CI)	**Estimate (95% CI)**	**p-value**	**Estimate (95% CI)**	**p-value**	**Estimate (95% CI)**	**p-value**	**Estimate (95% CI)**	**p-value**
Tumor site	*Hypopharynx and larynx*	-8.56 (-17.24 to 0.12)	0.053*	*Reference*	-10.97 (-18.71 to -3.24)	0.005*	-12.84 (-21.99 to -3.69)	0.006*	-7.35 (-17.15 to 2.44)	0.141	-12.59 (-22.81 to -2.36)	0.016*
	Oropharynx	-5.35 (-14.31 to 3.61)	0.242	*Reference*	0.50 (-7.67 to 8.67)	0.904	-4.30 (-14.01 to 5.42)	0.386	-5.18 (-15.57 to 5.21)	0.328	-9.81 (-20.65 to 1.04)	0.076*
	Oral cavity	*Reference*		*Reference*								
Treatment	CO_2 laser or surgery	*Reference*		*Reference*								
	RT	6.82 (-2.30 to 15.95)	0.142	*Reference*	9.95 (2.08 to 17.82)	0.013*	11.78 (2.46 to 21.10)	0.013*	9.32 (-0.61 to 19.25)	0.066*	9.58 (-0.71 to 19.86)	0.068*
	CRT	2.93 (-7.56 to 13.42)	0.584	*Reference*	18.79 (10.15 to 27.43)	<0.001*	19.40 (9.24 to 29.56)	<0.001*	17.46 (6.67 to 28.25)	0.002*	17.85 (6.58 to 29.12)	0.002*
	Surgery with PO(C)RT	2.77 (-6.17 to 11.71)	0.543	*Reference*	24.28 (16.67 to 31.89)	<0.001*	20.64 (11.59 to 29.69)	<0.001*	22.39 (12.56 to 32.22)	<0.001*	18.48 (8.14 to 28.82)	<0.001*

*: p<0.10; CI: Confidence Interval, CRT: Chemo radiation, PO: Post-operative, RT: Radiotherapy, SWAL-QOL: Swallowing Quality of Life questionnaire

Estimated eating duration = 47.66 - 4.15male - 7.56no weight loss - 0.10(1-5kg weight loss) - 11.23non smoker – 8.01 former smoker – 11.01tumor stage1 - 7.72tumor stage2 + 2.39tumor stage3 + 8.15M3 + 6.67M6 + 1.33M12 + 6.11M24 - 8.56hypopharynx&larynx – 5.35oropharynx + 6.82RT + 2.93CRT + 2.77Surgery&(C)RT – 10.97hypopharynx&larynx*M3 – 12.84hypopharynx&larynx*M6 - 7.35hypopharynx&larynx*M12 - 12.59hypopharynx&larynx*M24 + 0.50oropharynx*M3 – 4.30oropharynx*M6 - 5.18oropharynx*M12 – 9.81oropharynx*M24 + 9.95RT*M3 + 11.78RT*M6 + 9.32 RT*M12 + 9.58RT*M24 + 18.79CRT*M3 + 19.40CRT*M6 + 17.46CRT*M12 + 17.85CRT*M24 + 24.28Surgery&(C)RT*M3 + 20.64Surgery&(C)RT*M6 + 22.39Surgery&(C)RT*M12 + 18.48Surgery&(C)RT*M2

Figure 3. The mean outcomes for eating duration based on tumor site (A) and treatment modality (B) to provide insight in the raw and modelled data



The solid lines represent the linear mixed model outcomes of the final model, the striped lines represent the raw data
CRT: Chemo radiation, RT: Radiotherapy

Discussion

This large 2-year prospective cohort study (n=603) identified factors associated with worse swallowing as measured with the SWAL-QOL in patients with HNC and all treatment modalities. In this study, it was shown that patient-reported problems with swallowing increased from baseline to 3 months after treatment, and slowly decreased from 6 months onwards with return to baseline levels at 2 years after treatment in patients with HNC. Based on the SWAL-QOL cut-off score of ≥14, which indicates swallowing problems in daily life, 53% of patients had problems before treatment, which increased to 70% at 3 months after treatment, and decreased to 59% at 6 months after treatment, 50% at 12 months after treatment, and 48% at 24 months after treatment. After treatment, the subscale eating duration showed the most problems and did not return to baseline. Therefore, this subscale was used in a LMM to identify factors associated with a worse eating duration, to indicate which patients could benefit from preventive strategies and rehabilitation during and after treatment. Eating duration was associated with sex, smoking, weight loss, tumor site, treatment, tumor stage, and timing of assessment. In addition, the interactions of timing of assessment with tumor site and treatment modality were significant, indicating that the course over time differed for different tumor sites and different treatment modalities.

Comparison with literature

Based on a cut-off score on the total SWAL-QOL score of ≥14 points,[26] a previous cross-sectional study of patients with HNC (n=52) found a deviant score in 79% of patients, which is higher than the 70% found in this research at 3 months after treatment. One explanation could be that almost 60% of the patients in that study were treated with 3D conformal RT, in which salivary glands were not spared. After 2005, IMRT was introduced, enabling a significant reduction of dose to the salivary glands.[26] Since then, IMRT has been further optimized, sparing, e.g., parotid glands, pharyngeal constrictor muscles, and the supraglottic larynx.[37] Another cross-sectional study with healthy controls (n=111, mean age=56 years, 44% male) showed that mean scores of all subscales were between 3.7 (social functioning) and 10.4 (fear of eating).[38] Although these healthy controls were slightly younger and a higher percentage of females responded to the questions, it strongly indicates that most of the patients with HNC already experience swallowing problems before treatment (Figure 2), and that these problems remain, even 2 years after treatment.

A prospective cohort study from 2021 investigated factors associated with swallowing and social eating (n=2458) as measured with the EORTC QLQ-H&N35, and found that multi-modality treatment, oropharynx tumors, age, sex, living alone, low socio-economic status

and smoking were outcome predictors,[19] which were also found in the current study. Another prospective cohort study from 2009 investigated factors associated with swallowing problems as measured with the SWAL-QOL after curative RT in HNC (n=529), showed in their multivariate analysis that T3-T4 HNC tumors, bilateral irradiation, weight loss, oropharynx tumors, accelerated RT, and concomitant CRT were related to a worse outcome.[7] Besides the factors bilateral irradiation and accelerated RT, which were not part of the current study, the factors are similar to those found in the current study with respect to eating duration. Another prospective cohort study (n=587) from 2016 found the following factors to be associated with less HNC symptoms: older age, higher education, private insurance, no current tobacco use, alcohol use, no comorbidities, early-stage cancer and no current feeding tube.[31] No other studies reported a positive effect of older age regarding HNC symptoms. A cross-sectional study (n=52) investigating tumor site and RT technique in a multivariable regression analysis found that only tumor site was significantly associated with total SWAL-QOL score.[26] Another cross-sectional study (n=110) in patients receiving RT or CRT found that advanced tumors, patients receiving CRT, use of a nasogastric tube, tracheotomy, and continuation of smoking and drinking alcohol decreased QOL.[10]

The effect of smoking on treatment outcome has been described in several studies, in which it is known that survival rates are lower and recurrence rates are higher in patients who continue to smoke in comparison to patients who stop smoking.[39,40] In addition, smokers are at higher risk for treatment failure, disease recurrence, and development of second primary tumors.[41] Smokers showed a poorer response to RT, and increased toxicity and side effects from RT.[42] After surgery, smokers showed significantly higher rates of wound complications and general morbidity, and had an increased risk of infection.[43] In the current study, patients who smoked at baseline reported more swallowing problems in comparison to nonsmokers. Smoking cessation may therefore not only be important for survival and disease recurrence, but may also reduce swallowing problems before and after treatment. Besides smoking, it is known that the frequency and severity of swallowing problems are more pronounced when patients lose weight pretreatment (possibly because of the tumor), and that swallowing problems increase when weight loss increases.[21] These effects were also found in the current study, where patients who had lost weight at time of diagnosis experienced more problems in comparison to patients who had no weight loss prior to treatment. It is important that patients receive a nutritional assessment or even undergo placement of a feeding tube during treatment to maintain a healthy weight, and to minimize patient-reported problems in the long term.[21,44]

Strengths and limitations

The strengths of this study were the prospective study design, the large number of patients, and the use of the LMM checklist with recommendations for reporting multilevel data and analyses.[45] Because only 35 patients received CO_2 laser treatment, and these results were comparable to the results of patients that received surgery, it was decided to combine these groups. In addition, patients with a larynx and hypopharynx tumor were combined as well (n=205 and n=52 in the total NET-QUBIC population, respectively). A limitation of this study was the fact that only 374 patients filled in the questionnaire 2 years after treatment.[32,33] The 739 patients that were included in the NET-QUBIC research are already a selection of the total HNC population, in which it is unknown whether the non-responders perform worse or better regarding swallowing problems. In addition, there was a relatively large group of patients with missing measurements at each time point (Figure 1). Another limitation of this study was that information about rehabilitation during or after treatment was not taken into account.

Conclusion

Patients with HNC reported an increase in swallowing problems from baseline to 3 months after treatment, and a slow decrease from 6 months onwards with return to baseline level. The subscale eating duration of the SWAL-QOL showed the most problems after treatment. A longer eating duration was associated with female sex, smoking and weight loss at time of diagnosis, having tumor stage III or IV, and being 3 to 6 months after treatment. Especially patients with an oropharynx and oral cavity tumor showed a persistent increase in eating duration. In addition, patients receiving (C)RT following surgery, and patients receiving CRT only showed the worst decline in outcomes, which did not return to baseline levels after treatment.

References

1. Platteaux, N., et al., *Dysphagia in head and neck cancer patients treated with chemoradiotherapy.* Dysphagia, 2010. 25(2): p. 139-52.
2. Rettig, E.M. and G. D'Souza, *Epidemiology of head and neck cancer.* Surg Oncol Clin N Am, 2015. 24(3): p. 379-96.
3. Kreeft, A.M., et al., *Speech and swallowing after surgical treatment of advanced oral and oropharyngeal carcinoma: a systematic review of the literature.* European Archives of Oto-Rhino-Laryngology, 2009. 266(11): p. 1687-1698.
4. Pace-Balzan, A., R.J. Shaw, and C. Butterworth, *Oral rehabilitation following treatment for oral cancer.* Periodontol 2000, 2011. 57(1): p. 102-17.
5. Russi, E.G., et al., *Swallowing dysfunction in head and neck cancer patients treated by radiotherapy: Review and recommendations of the supportive task group of the Italian Association of Radiation Oncology.* Cancer Treatment Reviews, 2012. 38(8): p. 1033-1049.
6. Riffat, F., D.A. Gunaratne, and C.E. Palme, *Swallowing assessment and management pre and post head and neck cancer treatment.* Curr Opin Otolaryngol Head Neck Surg, 2015. 23(6): p. 440-7.
7. Langendijk, J.A., et al., *A predictive model for swallowing dysfunction after curative radiotherapy in head and neck cancer.* Radiother Oncol, 2009. 90(2): p. 189-95.
8. Nemeth, D., et al., *Importance of chewing, saliva, and swallowing function in patients with advanced oral cancer undergoing preoperative chemoradiotherapy: a prospective study of quality of life.* Int J Oral Maxillofac Surg, 2017. 46(10): p. 1229-1236.
9. Caputo, J.B., et al., *Masticatory performance and taste perception in patients submitted to cancer treatment.* J Oral Rehabil, 2012. 39(12): p. 905-13.
10. Silveira, M.H., et al., *Quality of life in swallowing disorders after nonsurgical treatment for head and neck cancer.* Int Arch Otorhinolaryngol, 2015. 19(1): p. 46-54.
11. Teguh, D.N., et al., *Trismus in patients with oropharyngeal cancer: relationship with dose in structures of mastication apparatus.* Head Neck, 2008. 30(5): p. 622-30.
12. van der Bilt, A., et al., *Oral physiology and mastication.* Physiol Behav, 2006. 89(1): p. 22-7.
13. Pereira, L.J. and A. van der Bilt, *The influence of oral processing, food perception and social aspects on food consumption: a review.* J Oral Rehabil, 2016. 43(8): p. 630-48.
14. Pedroni-Pereira, A., et al., *Lack of agreement between objective and subjective measures in the evaluation of masticatory function: A preliminary study.* Physiol Behav, 2018. 184: p. 220-225.
15. McHorney, C.A., et al., *The SWAL-QOL outcomes tool for oropharyngeal dysphagia in adults: I. Conceptual foundation and item development.* Dysphagia, 2000. 15(3): p. 115-21.
16. Bogaardt, H.C., et al., *Cross-cultural adaptation and validation of the Dutch version of SWAL-QoL.* Dysphagia, 2009. 24(1): p. 66-70.
17. Goepfert, R.P., et al., *Predicting two-year longitudinal MD Anderson Dysphagia Inventory outcomes after intensity modulated radiotherapy for locoregionally advanced oropharyngeal carcinoma.* Laryngoscope, 2017. 127(4): p. 842-848.
18. Bashir, A., et al., *Quality of life of head and neck cancer patients before and after cancer-directed treatment - A longitudinal study.* J Cancer Res Ther, 2020. 16(3): p. 500-507.
19. Patterson, J.M., et al., *Trends in, and predictors of, swallowing and social eating outcomes in head and neck cancer survivors: A longitudinal analysis of head and neck 5000.* Oral Oncol, 2021. 118: p. 105344.
20. Kraaijenga, S.A., et al., *Prospective clinical study on long-term swallowing function and voice quality in advanced head and*

neck cancer patients treated with concurrent chemoradiotherapy and preventive swallowing exercises. Eur Arch Otorhinolaryngol, 2015. 272(11): p. 3521-31.

21. Lango, M.N., et al., *Baseline health perceptions, dysphagia, and survival in patients with head and neck cancer.* Cancer, 2014. 120(6): p. 840-7.
22. van der Laan, H.P., et al., *Impact of radiation-induced toxicities on quality of life of patients treated for head and neck cancer.* Radiother Oncol, 2021. 160: p. 47-53.
23. Kraaijenga, S.A.C., et al., *Evaluation of long term (10-years+) dysphagia and trismus in patients treated with concurrent chemo-radiotherapy for advanced head and neck cancer.* Oral Oncology, 2015. 51(8): p. 787-794.
24. Lahtinen, S., et al., *Quality of life in head and neck cancer patients at 5 years after free flap reconstruction: a significant decline during the follow-up.* Eur Arch Otorhinolaryngol, 2022.
25. de Campos, R.J., P.V. Palma, and I.C. Leite, *Quality of life in patients with dysphagia after radiation and chemotherapy treatment for head and neck tumors.* J Clin Exp Dent, 2013. 5(3): p. e122-7.
26. Rinkel, R.N., et al., *Prevalence of swallowing and speech problems in daily life after chemoradiation for head and neck cancer based on cut-off scores of the patient-reported outcome measures SWAL-QOL and SHI.* Eur Arch Otorhinolaryngol, 2016. 273(7): p. 1849-55.
27. Rinkel, R.N., et al., *Patient-reported symptom questionnaires in laryngeal cancer: voice, speech and swallowing.* Oral Oncol, 2014. 50(8): p. 759-64.
28. Christianen, M.E., et al., *Predictive modelling for swallowing dysfunction after primary (chemo)radiation: results of a prospective observational study.* Radiother Oncol, 2012. 105(1): p. 107-14.
29. Lahtinen, S., et al., *Swallowing-related quality of life after free flap surgery due to cancer of the head and neck.* Eur Arch Otorhinolaryngol, 2019. 276(3): p. 821-826.
30. Bjordal, K., et al., *A Prospective Study of Quality of Life in Head and Neck Cancer Patients. Part II: Longitudinal Data.* Laryngoscope, 2001. 111: p. 1440–1452.
31. Reeve, B.B., et al., *Factors that impact health-related quality of life over time for individuals with head and neck cancer.* Laryngoscope, 2016. 126(12): p. 2718-2725.
32. Jansen, F., et al., *Study retention and attrition in a longitudinal cohort study including patient-reported outcomes, fieldwork and biobank samples: results of the Netherlands quality of life and Biomedical cohort study (NET-QUBIC) among 739 head and neck cancer patients and 262 informal caregivers.* BMC Med Res Methodol, 2022. 22(1): p. 27.
33. Verdonck-de Leeuw, I.M., et al., *Advancing interdisciplinary research in head and neck cancer through a multicenter longitudinal prospective cohort study: the NETherlands QUality of life and BIomedical Cohort (NET-QUBIC) data warehouse and biobank.* BMC Cancer, 2019. 19(1): p. 765.
34. Paleri, V., H. Mehanna, and R.G. Wight, *TNM classification of malignant tumours 7th edition: what's new for head and neck?* Clin Otolaryngol, 2010. 35(4): p. 270-2.
35. Rogers, S.N., et al., *Feasibility study of the retrospective use of the Adult Comorbidity Evaluation index (ACE-27) in patients with cancer of the head and neck who had radiotherapy.* Br J Oral Maxillofac Surg, 2006. 44(4): p. 283-8.
36. Burnham, K.P. and D.R. Anderson, *Multimodel Inference.* Sociological Methods & Research, 2016. 33(2): p. 261-304.
37. Christianen, M.E., et al., *Delineation of organs at risk involved in swallowing for radiotherapy treatment planning.* Radiother Oncol, 2011. 101(3): p. 394-402.
38. Rinkel, R.N., et al., *The psychometric and clinical validity of the SWAL-QOL questionnaire in evaluating swallowing problems experienced by patients with oral and oropharyngeal cancer.* Oral Oncol, 2009. 45(8): p. e67-71.

39. van Imhoff, L.C., et al., *Prognostic value of continued smoking on survival and recurrence rates in patients with head and neck cancer: A systematic review.* Head Neck, 2016. 38 Suppl 1: p. E2214-20.

40. von Kroge, P.R., et al., *The Impact of Smoking Cessation and Continuation on Recurrence and Survival in Patients with Head and Neck Cancer: A Systematic Review of the Literature.* Oncol Res Treat, 2020. 43(10): p. 549-558.

41. Du, E., et al., *Long-term Survival in Head and Neck Cancer: Impact of Site, Stage, Smoking, and Human Papillomavirus Status.* Laryngoscope, 2019. 129(11): p. 2506-2513.

42. McCarter, K., et al., *Smoking, drinking, and depression: comorbidity in head and neck cancer patients undergoing radiotherapy.* Cancer Med, 2018. 7(6): p. 2382-2390.

43. Gronkjaer, M., et al., *Preoperative smoking status and postoperative complications: a systematic review and meta-analysis.* Ann Surg, 2014. 259(1): p. 52-71.

44. Ackerman, D., et al., *Nutrition Management for the Head and Neck Cancer Patient*, in *Multidisciplinary Care of the Head and Neck Cancer Patient*, E. Maghami and A.S. Ho, Editors. 2018, Springer International Publishing: Cham. p. 187-208.

45. Monsalves, M.J., et al., *LEVEL (Logical Explanations & Visualizations of Estimates in Linear mixed models): recommendations for reporting multilevel data and analyses.* BMC Med Res Methodol, 2020. 20(1): p. 3.

Chapter 9

Summary and Discussion

NET-QUBIC objectives

This PhD project was part of the NET-QUBIC research: the NETherlands QUality of life and BIomedical Cohort studies in Head and Neck Cancer. In this research, the VUmc, Radboudumc, UMCG, UMC Utrecht, Erasmus MC, Noordwest Ziekenhuisgroep Alkmaar and the Medisch Centrum Leeuwarden worked together to create a large database (n=739) and gained information about many quality of life (QoL) aspects in patients with head and neck cancer (HNC). In the UMC Utrecht, the primary objective was to build models to predict the burden of masticatory, swallowing and salivary dysfunction. The goal of these models was to identify patients at risk for developing masticatory, swallowing and salivary dysfunction. It was hypothesized that a prediction model using both objective function outcomes and patient-reported outcomes (PROs) will have a significantly better predictive accuracy in comparison to a model based on patient-reported outcomes alone. The secondary objectives were to establish the interaction between saliva, swallowing and masticatory function up to 2 years after treatment, and to investigate the course in time of saliva, swallowing and masticatory function and PROs during the first two years after treatment. The ultimate goal of the NET-QUBIC research was to build an optimal model for patients with HNC, to predict the longitudinal QoL effects on saliva, swallowing and masticatory function after treatment. When various treatment options have the same expected survival rates, this model will facilitate a balanced trade-off between the treatment options based on expected QoL. This will result in personalized care for each patient. In addition, it may be used to better inform patients about their options.

Overview

This thesis addresses main complications that may occur after treatment for head and neck cancer; xerostomia, dysphagia and masticatory deficits. As stated in the introduction of this thesis, there are many different steps and processes that need to work in a timely and often simultaneous or consecutive manner in order for food processing to be successful. Due to head and neck cancer or its treatment, many of these processes can deteriorate, which results in deficits in food processing.

In **chapter 2**, a review is reported that describes the current literature regarding masticatory ability as measured with the UW-QoL (University of Washington Quality of Life) questionnaire in patients with oral cancer. This review shows a large variety in methodology, tumor subsite in the oral cavity, treatment modality, and timing of assessment between the different reported studies, to such a degree that outcome scores are difficult to compare. These results highlight the necessity for more comparable outcome measures.

To address possible complications that may occur after treatment for head and neck cancer, the test-retest reliability of the objective tests used to measure masticatory performance and swallowing function was investigated. This reliability was tested in **chapter 3** for the masticatory performance as measured with the mixing ability test (MAT), and in **chapter 4** for the swallowing function as measured with the 100 mL water swallow test (WST). Intraclass correlation coefficients (ICC) of both MAT and WST showed a good and excellent reliability (ICC=0.886 and ICC=0.923, respectively). The smallest detectable changes (SDC) and standard errors of measurement (SEM) were calculated for use in the upcoming studies.

In **chapter 5**, the associations of the MAT, WST and a salivary flow test were tested against the patient-reported outcome measures (PROMs) of the European Organization for Research and Treatment of Cancer Quality of Life core Questionnaire, Head and Neck module (EORTC QLQ-H&N35), the Swallow Quality of Life questionnaire (SWAL-QOL), and the Groningen Radiation-Induced Xerostomia (GRIX) questionnaire. In this chapter, it was concluded that the objective tests and PROs measure different constructs and can therefore not be interchanged, but should be used separately to determine objective and patient-reported function.[1] To predict the burden of complications and their impact on quality of life, it is important to use both objective functioning tests and patient-reported outcomes, because objective information obtained from measurements may be different from a patient's perspective.

The next step and goal of this PhD project was to create models that assess the risk of developing complications regarding mastication, swallowing and salivary flow. Publications on risk models for complications after treatment for HNC most often discuss only one type of complication, after one specific type of treatment. In addition, the majority only uses patient-reported outcomes or objective measurements, but not both.[2-7] This led to the development of the associative models in **chapter 6 and 7**, in which factors are shown that have a negative impact on objective masticatory performance and swallowing function, respectively. Besides the models based on objective tests, it was also important to create models based on PROs. In this way, differences between the different factors found in these models can be investigated. Therefore, in **chapter 8**, the outcomes of the SWAL-QOL questionnaire are shown. Because different factors have an effect on objective tests and questionnaires, this highlights the additive value that these tests can have in combination with PROs in order to create the total picture of a patient, and to predict which patients are at risk to develop problems after treatment.

Future perspectives

The ultimate goal of the NET-QUBIC research was to create one prediction model, taking into account both objective and subjective measures, and exploring the interaction between mastication, salivary flow and swallowing. However, because of the low correlation between objective and subjective measures, as described in **chapter 5**, it was impossible to create a prediction model taking into account both objective and subjective measures. Because of the low correlation between objective and subjective measures, it was expected that different items than the items described in **chapter 6 and 7** will have an effect on the patient-reported outcomes, which are shown in **chapter 8** for the SWAL-QOL questionnaire. In addition, because of the high correlation between chewing, swallowing and salivary flow as described in the introduction, it would be preferred to combine all tests and create one outcome that includes the whole food process.

There is a huge amount of data in the NET-QUBIC research to elaborate on. For example, nowadays swallowing structures and salivary glands are delineated in patients that received radiotherapy and marked as organs at risk (OAR). Correlating the dose on the OARs to the measured complications will result in normal tissue complication models (NTCP), which can be used to further optimize radiotherapy treatment. However, masticatory muscles are not delineated yet. It is expected that marking the masticatory muscles as OAR and subsequently sparing these organs in the radiotherapy plan can reduce masticatory problems after treatment. In addition, because of the high correlation between mastication and swallowing, sparing the masticatory muscles can result in less swallowing problems as well.

The discrepancy between clinical measures and patients' own evaluations of their health has been described since the 1980s.[8,9] PROs are increasingly used in daily practice, because these measures are easy and fast to perform.[10] Their use reflects a growing appreciation of the importance of patient's feelings and satisfaction with treatment.[10] Objective measures are based on performance, irrespective of experience. They are thus an accurate and unbiased representation, recording only what is observed.[9,11] PROs depend on individual values and priorities, which may differ between persons and even within persons.[9] Internal standards, values, and the conceptualization of quality of life can change over the course of a disease trajectory.[8] A PRO is based on what people actually experience and how a person evaluates his or her functioning, rather than his or her performance as measured with objective tests.[12] Individuals differ in what they find important, and expectation about one's progress after treatment may change over time and in response to personal circumstances. Patients may develop a degree of adaptation over time, in which their PRO improves, but their objective measure stays the same or worsens, which is also known as

response shift.[13] Survivors may have adapted to their new health situation and experience a change in their frame of reference, which may affect QoL outcomes.[14] Besides, most cognitive function studies in patients with cancer find that self-reported outcome measures correlate more strongly with factors such as depression, fatigue and anxiety than with objective measures.[1] Patients could also be biased by the explanation of their doctor about a certain treatment. For example, when they are being told to undergo proton- instead of photon treatment because of the lower complication possibility, patients might be more likely to rate their symptoms to be lower. In addition, PROMs are often long and thus time consuming. These items describe the complexity of PROs.

Future research should discuss the preferred and most important outcome, which influences the type of measurement you should use. When recording a patient's experience, PROs should be measured. When recording whether a type of treatment resulted in an actual change in outcome, objective measures should be used. In order to create the overall picture of a patients' performance and develop strategies to reduce side-effects of oncological treatment, it is important to measure both the patient's evaluation of his or her oral functioning and the objective function of the various organs involved. In this way, objective tests are an addition to PROs, which will lead to creating the complete picture of a patient's functioning and wellbeing. As found in the associative models for the objective tests in **chapter 6 and 7**, and for the SWAL-QOL questionnaire in **chapter 8**, different factors are of importance for the outcome measure. Preferably, in the future, all objective tests and PROs can be combined into one overall score, to predict the patients at risk for developing food processing and swallowing problems after HNC treatment.

A possible improvement in future research could be to assess how PROs and objective measures co-vary across time.[1] Instead of looking at the correlation between PROs and objective measures at a given time point, an improvement could be to look at the changes in a PRO or objective measure between different time points and compare the fluctuation over time between PROs and objective measures. In addition, a more uniform way of reporting results should be used. **Chapter 2** describes a review measuring PROs regarding mastication in patients with oral cancer. There was a large variety in the way PROs were presented. In addition, different subgroups of patients were measured, as the tumor sub-site in the oral cavity, treatment, and timing of assessment differed in all studies. Multiple studies performed a cross-sectional study, making it impossible to investigate changes over time. Future research should therefore assess patients at multiple points in time to be able to compare PROs and tell something about the impact of, e.g., a certain treatment on QoL. In addition, a uniform way of reporting results should be used when presenting PROs, preferably with the help of guidelines and the use of validated PROs.[15]

An important aspect about the use of objective tests in clinic is that they should be fast and easy to perform. The salivary flow test described in this research often failed, either because the patient did not want to perform this test or because the Lashley cups used to collect the parotid flow did not stay in place. In addition, collecting saliva for 10 minutes often was too long for patients, leading to the termination of the measurement before these 10 minutes. Besides, these measurements are known to have large standard deviations, causing data to be easily over interpreted.[16] A recommendation would therefore be to use a simple and highly reproducible test to measure objective changes in patients. This can be difficult to accomplish in case of the salivary flow measurements, because it is important to collect data from both the parotid glands and the submandibular glands. Submandibular gland function is the most significant determinant for dry mouth complaints during the night, while parotid gland function is more important than submandibular gland function for severe complaints of dry mouth during the day.[17]

Rehabilitation

As seen in **chapter 8**, most subscales of the SWAL-QOL questionnaire returned to baseline levels at 2 years after treatment. However, baseline levels are already worse in comparison to healthy subjects, indicating that problems with food processing and swallowing remain, even 2 years after treatment. To improve the food process, different rehabilitation therapies are available. It is important to refer patients that may benefit from rehabilitation therapy both during and after cancer treatment in a timely manner to the corresponding therapist. Although rehabilitation needs in the HNC population are increasingly being recognized, HNC is still an underrepresented population in cancer rehabilitation research.[18] In addition, care is fragmented and referral is inconsistent and often late in recovery when problems have become chronic and are less amendable to intervention.[19] It is therefore important to increase awareness about possibilities for patients both during and after treatment.

Rehabilitation treatment focused on mastication often consists of physiotherapy in order to increase the maximal mouth opening, and/or increase the muscle force needed to break down food. **Chapter 6** describes the patients that will most likely experience problems with masticatory performance after treatment, and will thus most likely benefit from oral physiotherapy. These are elderly patients, patients with a large tumor (mainly disease stage III and IV), and patients with a tumor in the oral cavity who are 3 to 6 months after treatment. By training and exercising the masticatory muscles, oral motor and sensory functions used in mastication will improve.[20]

In **chapter 8**, especially the subscale 'eating duration' was explored, because this subscale did not return to baseline levels after treatment. Here it was found that patients with a

large tumor are at risk (disease stage III and IV). In addition, patients with a tumor in the oral cavity and oropharynx, and patients receiving chemoradiation or surgery followed by radiotherapy or chemoradiation experienced the most problems after treatment. This subscale is mainly influenced by masticatory processes in the mouth, that need to break down the food into small enough particles ready to be swallowed.[21] The mixing ability test explored in **chapter 4 and 6** is only one part of these processes, in which the food is transported and mixed between the teeth. Besides mixing, saliva is needed to break down the food and moisten it, and the swallowing process needs to start.

It was remarkable that only the subscale eating duration did not return to baseline levels after treatment, while all other subscales did (general burden, food selection, eating desire, fear of eating, mental health, social functioning, and symptoms). One possible explanation could be that this subscale is the most notable for patients, especially when comparing their eating duration to other people. For example, it can be confronting when patients dine out and find their companions finish their plate much faster than they do. HNC survivors may require specially prepared food and/or use compensatory strategies to facilitate safe swallowing, which may limit their ability and wish to dine out.[22] Other subscales might be less notable or are easier to adjust to, possibly because of coping strategies and/or response shift of patients after treatment.[8,23]

Swallowing exercises by a speech therapist can be provided during the course of (chemo) radiation treatment, where promising results were found.[24] These exercises are designed to improve swallowing safety, for example by reducing penetration or aspiration, and by increasing the efficiency of swallowing.[25] As found in **chapter 7**, especially older patients, and patients that received extensive surgery involving, e.g., the tongue, base of tongue or larynx may benefit from these swallowing exercises. These exercises can prevent dysphagia, or reduce its severity.[26] Older patients are at a higher risk of aspiration due to a decrease in mastication and swallowing function, in which swallowing exercises may help maintain or improve oral function.[27-29] These proactive exercises may also lead to superior swallowing related QoL, better tongue base and epiglottic movement, lower rates of percutaneous endoscopic gastrostomy (PEG) placement, and an improved diet after treatment.[30]

Besides rehabilitation focused on mastication and swallowing, patients may also benefit from physical therapy such as lymphatic drainage, massages, exercises, education, and compression therapy in order to improve tiredness, depression, anxiety, and overall wellbeing.[19] As also seen in **chapter 8**, patients that smoke and patients that lose weight before and during treatment, are at a higher risk to develop problems. Smoking cessation is not only important for improved survival and lower disease recurrence, but also for

reducing complaints before and after treatment. Referral to a dietician in order to receive a nutritional assessment or even undergo placement of a feeding tube during treatment to maintain a healthy weight, can minimize patient-reported problems.

Another possibility is to refer patients even before the start of treatment, and provide them with prehabilitation exercises that can target nutrition, mental health, and physical health. Before the start of treatment, exercises are recommended that include general stretching and range of motion exercises, mouth opening, and swallowing specific exercises.[31] These programs can prevent or limit impairment caused by HNC treatment. Besides, a baseline functional level can be established, and impairments that occur because of treatment can be targeted sooner.

In addition to providing (p)rehabilitation exercises, patients can be informed about expected difficulties they may experience after treatment. It is important to set realistic expectations about what to expect after treatment, so patients can cope with the effects of treatment on daily functioning.[32] Information about expected difficulties can reduce distress and anxiety during treatment, and can increase active patient participation and satisfaction with provided care.[32] The results found in **chapter 6, 7 and 8** of this thesis are a first step in detecting patients at risk for developing masticatory and/or swallowing problems. These results can be used to guide patients in their decision about different treatment options, by providing information about expected problems they may experience after treatment, and the duration of these problems.

Preferably, in the future, all patients with head and neck cancer with a referral to a head and neck surgeon or dental surgeon for treatment will be informed about possible problems during and after their treatment. In addition, they will be informed about possibilities to consult a physiotherapist, speech therapist or dietician whenever needed. By knowing possible difficulties that may occur, a better evaluation about treatment options can be made and more patient centered care can be provided.

References

1. O'Farrell E, Smith A, Collins B. Objective-subjective disparity in cancer-related cognitive impairment: does the use of change measures help reconcile the difference? *Psychooncology.* 2017;26(10):1667-1674.

2. Speksnijder C, Van Der Bilt A, Merkx MAW, Koole R. Mastication and tongue function in patients treated for malignancies in tongue and/or floor of mouth; a one year prospective study. *Physiotherapy (United Kingdom).* 2011;97:eS1164.

3. Roesink JM, Moerland MA, Battermann JJ, Hordijk GJ, Terhaard CH. Qualitative dose-volume response analysis of changes in parotid gland function after radiotherapy in the head-and-neck region. *Int J Radiation Oncology Biol Phys.* 2001;51(4):938–946.

4. Langendijk JA, Doornaert P, Rietveld DH, Verdonck-de Leeuw IM, Leemans CR, Slotman BJ. A predictive model for swallowing dysfunction after curative radiotherapy in head and neck cancer. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology.* 2009;90(2):189-195.

5. Christianen ME, Schilstra C, Beetz I, et al. Predictive modelling for swallowing dysfunction after primary (chemo)radiation: results of a prospective observational study. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology.* 2012;105(1):107-114.

6. Speksnijder CM, van der Glas HW, van der Bilt A, van Es RJ, van der Rijt E, Koole R. Oral function after oncological intervention in the oral cavity: a retrospective study. *Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons.* 2010;68(6):1231-1237.

7. Dijkema T, Raaijmakers CP, Ten Haken RK, et al. Parotid gland function after radiotherapy: the combined michigan and utrecht experience. *International journal of radiation oncology, biology, physics.* 2010;78(2):449-453.

8. Sprangers MAG, Schwartz CE. Integrating response shift into health-related quality of life research: a theoretical model. *Social science & medicine.* 1999;48:1507-1515.

9. Buitenweg DC, Bongers IL, van de Mheen D, van Oers HAM, van Nieuwenhuizen C. Subjectively different but objectively the same? Three profiles of QoL in people with severe mental health problems. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation.* 2018;27(11):2965-2974.

10. Carr AJ, Higginson IJ. Are quality of life measures patient centred? *BMJ.* 2001;322(7298):1357-1360.

11. Mascolo MF. Beyond Objectivity and Subjectivity: The Intersubjective Foundations of Psychological Science. *Integr Psychol Behav Sci.* 2016;50(4):543-554.

12. Lycke M, Lefebvre T, Pottel L, et al. Subjective, but not objective, cognitive complaints impact long-term quality of life in cancer patients. *J Psychosoc Oncol.* 2019;37(4):427-440.

13. Frowen J, Drosdowsky A, Perry A, Corry J. Long-term swallowing after chemoradiotherapy: Prospective study of functional and patient-reported changes over time. *Head & neck.* 2016;38 Suppl 1:E307-315.

14. Schwartz CE, Sprangers MA. Guidelines for improving the stringency of response shift research using the thentest. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation.* 2010;19:455–464.

15. Astrup GL, Rohde G, Rimehaug SA, et al. Comparing the use of patient-reported outcomes in clinical studies in Europe in 2008 and 2018: a literature review. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation.* 2021.

16. Houweling AC, Philippens ME, Dijkema T, et al. A comparison of dose-response models for the parotid gland in a large group of head-and-neck cancer patients. *International journal of radiation oncology, biology, physics.* 2010;76(4):1259-1265.

17. Dijkema T, Raaijmakers CP, Braam PM, Roesink JM, Monninkhof EM, Terhaard CH. Xerostomia: a day and night difference. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology.* 2012;104(2):219-223.

18. Parke SC, Oza S, Shahpar S, et al. Identifying Gaps in Research on Rehabilitation for Patients With Head and Neck Cancer: A Scoping Review. *Archives of Physical Medicine and Rehabilitation.* 2019;100(12):2381-2388.

19. Rodriguez AM, Komar A, Ringash J, et al. A scoping review of rehabilitation interventions for survivors of head and neck cancer. *Disabil Rehabil.* 2019;41(17):2093-2107.

20. Lin CS, Wu CY, Wu SY, Lin HH, Cheng DH, Lo WL. Age-Related Difference in Functional Brain Connectivity of Mastication. *Frontiers in aging neuroscience.* 2017;9:82.

21. van der Bilt A, Engelen L, Pereira LJ, van der Glas HW, Abbink JH. Oral physiology and mastication. *Physiology & behavior.* 2006;89(1):22-27.

22. Chan KMK, Chan HKW, Siu JYL, Pu D, Nund RL, Ward EC. Impact of Head and Neck Cancer Treatment on Survivors' Mealtime Experience. *Laryngoscope.* 2019;129(7):1572-1578.

23. Hanna E, Sherman AC. Quality-of-Life Issues in Head and Neck Cancer. *Current Oncology Reports.* 1999;1:124–128.

24. Carroll WR, Locher JL, Canon CL, Bohannon IA, McColloch NL, Magnuson JS. Pretreatment swallowing exercises improve swallow function after chemoradiation. *Laryngoscope.* 2008;118(1):39-43.

25. Logemann JA. Behavioural management for oropharyngeal dysphagia. *Folia Phoniatr Logop.* 1999;51:199–212.

26. Perry A, Lee SH, Cotton S, Kennedy C. Therapeutic exercises for affecting post-treatment swallowing in people treated for advanced-stage head and neck cancers. *Cochrane Db Syst Rev.* 2016(8).

27. Sugiyama T, Ohkubo M, Honda Y, et al. Effect of Swallowing Exercises in Independent Elderly. *Bull Tokyo Dent Coll.* 2013;54(2):109–115.

28. Robbins J, Gangnon RE, Theis SM, Kays SA, Hewitt AL, Hind JA. The effects of lingual exercise on swallowing in older adults. *J Am Geriatr Soc.* 2005;53(9):1483-1489.

29. Kristensen MB, Isenring E, Brown B. Nutrition and swallowing therapy strategies for patients with head and neck cancer. *Nutrition.* 2020;69:110548.

30. Hutcheson KA, Bhayani MK, Beadle BM, et al. Use it or lose it: eat and exercise during radiotherapy or chemoradiotherapy for pharyngeal cancers. *JAMA otolaryngology--head & neck surgery.* 2013;139(11):1127–1134.

31. Loewen I, Jeffery CC, Rieger J, Constantinescu G. Prehabilitation in head and neck cancer patients: a literature review. *J Otolaryngol Head Neck Surg.* 2021;50(1):2.

32. Brockbank S, Miller N, Owen S, Patterson JM. Pretreatment information on dysphagia: exploring the views of head and neck cancer patients. *Journal of pain and symptom management.* 2015;49(1):89-97.

Nederlandse samenvatting

Dit proefschrift bespreekt verschillende complicaties die kunnen optreden na de behandeling van hoofd-halskanker, waarbij met name gekeken wordt naar het kauwen, de speekselproductie en het slikken. Om het voedselproces goed te laten verlopen, zijn verschillende processen betrokken die tijdig en vaak ook gelijktijdig op moeten treden. Door de hoofd-halskanker zelf en/of de behandeling kunnen één of meerdere van deze processen worden aangedaan, waardoor problemen optreden bij het voedselproces.

Het doel van kauwen is om voedsel af te breken in kleinere delen en deze aan elkaar te binden met behulp van speeksel. Op deze manier wordt het voedsel een bolus die makkelijk kan worden doorgeslikt. In de mond ondergaat voedsel daarvoor verschillende stappen: (1) Het voedsel wordt van de voorste tanden naar de kiezen getransporteerd. Hierbij werken lippen, tong, gebit, kaken en wangen samen met het aangemaakte speeksel om het aangeboden voedsel te vermalen. Tijdens het kauwen wordt het voedsel geanalyseerd door middel van smaak, reukzin in de neus en orale receptoren van het zogenaamde 'somatosensorische systeem'. Dit systeem is onderdeel van het sensorische zenuwstelsel dat reageert op veranderingen in het lichaam. Wanneer deze sensorische cellen worden geactiveerd, zetten zij een proces in werking waardoor bijvoorbeeld smaak wordt waargenomen. (2) Het voedsel wordt omgezet in een voedselbolus door middel van speeksel en de kiezen die worden aangestuurd door verschillende spieren, waardoor het voedsel de gewenste consistentie krijgt om door te kunnen slikken. (3) Het gekauwde voedsel wordt naar het orofaryngeale, achterste gedeelte, van de tong getransporteerd. (4) De neus en luchtpijp worden afgesloten en de bovenste slokdarmsfincter wordt geopend, waardoor de slikactie veilig plaats kan vinden.

Tijdens het kauwen en slikken zijn meerdere zenuwen en spieren betrokken die op een gecoördineerde manier samen moeten werken om de bewegingen effectief uit te voeren. Er zijn daardoor veel factoren die het kauwproces kunnen beïnvloeden, zoals het aantal occlusale eenheden (de tanden in de onder- en bovenkaak die op elkaar passen ('occlusie') om zo voedsel te vermalen), de bijtkracht, de maximale mondopening, de hoeveelheid en dikte van het speeksel en het gebruik van de spieren in de mond inclusief de tong. De maximale bijtkracht bepaalt de kracht die gebruikt kan worden om voedsel te vermalen en snijden. Wanneer de maximale mondopening vermindert, wordt de maximale bijtkracht lager en kan voedsel minder makkelijk worden ingenomen. De tong zorgt voor de beweging van voedsel tussen de tanden en vermengt het voedsel met speeksel om zo een voedselbolus te vormen. Speeksel is hierbij essentieel omdat dit het voedsel bevochtigt, een eerste aanzet geeft om vet en zetmeel af te breken, meehelpt in de smaaksensatie en helpt bij het creëren van een voedselbolus zodat deze gemakkelijk kan worden doorgeslikt.

Het omzetten van voedsel en het naar achteren transporteren gebeurt vrijwel gelijktijdig, waarbij voedsel naar voren over het tongoppervlak wordt bewogen en de kauwbeweging plaatsvindt. Nadat het voedsel gekauwd is, wordt het doorgeslikt. Het slikken is een natuurlijk (fysiologisch) proces dat wordt gevormd door orale-, faryngeale- (structuren in de keelholte) en slokdarmfasen. Het in gang zetten van het slikproces gebeurt vrijwillig en hangt af van een drempelwaarde van de grootte van de voedseldeeltjes en de bevochtiging van de voedselbolus door middel van speeksel. De tong drukt de voedselbolus tegen het harde gehemelte en initieert zo de beweging naar het achterste deel van de tong. In dit stadium is het samentrekken van de lippen en wangen cruciaal om te voorkomen dat vast voedsel en vloeistof uit de mondholte kunnen ontsnappen. De faryngeale fase wordt beschouwd als een reflexreactie en gebeurt daarom automatisch. De slokdarmfase treedt op door zowel bewuste waarneming en aansturing van spieren als onbewuste bewegingen. De slokdarmfase bestaat uit een golf van spiercontracties, die het voedsel voortbewegen naar de maag. Concluderend, het kauw-, speekselproductie- en slikproces is een complex systeem waarbij meerdere structuren betrokken zijn die (bewust en onbewust) nauw met elkaar samenwerken.

In patiënten met hoofd-halskanker kan dit kauw-, speekselproductie- en/of slikproces zijn aangedaan. Dit kan komen door de tumor zelf, die in bepaalde structuren groeit en deze aantast, of door de behandeling die nodig is om de tumor te verwijderen. De behandeling voor hoofd-halskanker kan bestaan uit een operatie (chirurgie), bestraling (radiotherapie), chemotherapie, of een combinatie van bovenstaande. Wanneer patiënten chirurgisch behandeld worden, wordt de tumor met een deel van het omliggende weefsel weggesneden. Soms is een reconstructie van het weggesneden weefsel nodig en/of worden lymfeklieren in de hals verwijderd. Radiotherapie maakt gebruik van ioniserende straling om weefsel te doden. Door radiotherapie toe te dienen in een kleine dosering verspreid over gewoonlijk 7 weken, sterft het tumorweefsel af, terwijl het gezonde omliggende weefsel tijd heeft om te herstellen. Dit gebeurt doordat tumorweefsel gemuteerd is en zichzelf hierdoor minder goed kan herstellen dan gezond weefsel. Chemotherapie wordt meestal gegeven door middel van het toedienen van cisplatine. Dit middel remt de celdeling doordat het aan DNA bindt. In combinatie met radiotherapie geeft het een versterkend effect, door het herstellende vermogen van cellen te remmen.

Naast het type behandeling zijn er andere factoren van belang die invloed hebben op het voedselproces, zoals de grootte en locatie van de tumor. Ook factoren zoals leeftijd hebben invloed op de snelheid en effectiviteit van spieren die betrokken zijn bij het voedselproces.

Om te meten in welke mate het voedselproces is aangedaan na de behandeling voor hoofd-halskanker, zijn verschillende testen beschikbaar. In dit proefschrift wordt het kauwen

gemeten door middel van de 'Mixing Ability Test' (MAT). Deze test meet de mate van voedselvermenging. Het slikken wordt gemeten door middel van de 'Water Swallowing Test' (WST), waarbij 100 mL water zo snel mogelijk moet worden opgedronken. Hierbij wordt gekeken hoe lang iemand erover doet om deze 100 mL op te drinken en hoeveel slikken hij/zij hiervoor nodig heeft. De speekselproductie wordt gemeten door 10 minuten lang het speeksel op te vangen dat geproduceerd wordt door de beide parotisklieren en door de submandibularisklieren. Hierbij wordt gebruik gemaakt van citroenzuur om de klieren te stimuleren. De parotisklieren liggen net onder de huid bij het oor en de submandibularis klieren bevinden zich in de mondbodem.

Naast deze objectieve testen zijn er ook vragenlijsten beschikbaar. Vragenlijsten meten hoe de patiënt zich voelt op het moment van invullen. De meest gebruikte vragenlijst voor patiënten met hoofd-halskanker is de vragenlijst van de 'European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire' (EORTC), waarvan een module voor patiënten met hoofd-halskanker beschikbaar is. Deze vragenlijst meet hoofd-hals specifieke problemen en bekijkt verschillende aspecten van het voedselproces. Daarnaast wordt in dit proefschrift ook de Nederlandse versie van de 'Swallowing Quality of Life Questionnnaire' (SWAL-QOL) gebruikt, welke kijkt naar problemen gerelateerd aan het voedselproces en met name het slikken. Als laatste wordt de 'Groningen Radiation-Induced Xerostomia' (GRIX) vragenlijst gebruikt om xerostomie (een droge mond) en plakkerig speeksel gedurende de dag en nacht te bepalen.

In dit proefschrift worden de objectieve testen en vragenlijsten gebruikt om mogelijke complicaties te meten in patiënten met hoofd-halskanker. Dit gebeurt op verschillende tijdstippen: vóór hun behandeling, en 3, 6, 12, en 24 maanden na behandeling. De data zijn afkomstig uit het NET-QUBIC onderzoek (in het Nederlands: het Kubus onderzoek), een nationale studie waarbij 739 patiënten en hun naasten zijn geïncludeerd. In het Kubus onderzoek werd hun kwaliteit van leven gemeten, inclusief het kauw-, speekselproductie-, en slikproces.

Hoofdstuk 2 beschrijft een review waarin het kauwen centraal staat. In deze review wordt een overzicht gegeven van de kauw uitkomst van de 'University of Washington Quality of Life' (UW-QoL) vragenlijst in patiënten met orale kanker (mondkanker). De UW-QoL vragenlijst wordt vaak gebruikt in patiënten met mondkanker, waarbij patiënten voor deze kauw-vraag moeten aangeven of ze normaal kunnen kauwen, alleen zacht voedsel kunnen kauwen, of geen voedsel kunnen kauwen (zowel hard als zacht). In dit hoofdstuk wordt gezien dat de uitkomst van de UW-QoL, zelfs bij deze subgroep van patiënten met hoofd-halskanker, nog zeer veel van elkaar kan verschillen. De uitkomsten worden niet altijd op een constante en eenduidige manier gerapporteerd en studies verschillen zeer in de

tijdstippen van het uitvragen van de vragenlijst en welke sub-locatie van mondkanker zij meenemen. Veel studies vragen eenmalig hoe het met patiënten gaat, waardoor geen vergelijking kan worden gemaakt vóór en na de behandeling. Hierdoor is het onduidelijk of er een verbetering of verslechtering optreedt en wat de behandeling dus voor invloed heeft gehad op de kwaliteit van leven.

Omdat de objectieve testen nog niet gevalideerd zijn in de groep patiënten met hoofd-halskanker die in dit proefschrift wordt beschreven, wordt in **hoofdstuk 3 en 4** de test-hertest betrouwbaarheid van de kauwtest (MAT) en de water slik test (WST) bepaald. In deze hoofdstukken wordt de ICC (Intraclass Correlation Coefficient), SDC (Smallest Detectable Change) en SEM (Standard Error of Measurement) berekend. De betrouwbaarheid van de MAT was goed (ICC=0.886) en die van de WST uitstekend (ICC=0.923). De SEM laat zien wat voor meetfout er optreedt bij iedere meting en hoe betrouwbaar de testen zijn in deze hoofd-hals patiëntenpopulatie. Deze variabele wordt samen met de SDC gebruikt in de hierop volgende hoofdstukken om te kunnen spreken van een echt verschil tussen de metingen en niet van een meetfout van de test.

In **hoofdstuk 5** wordt de correlatie tussen de objectieve testen en de vragenlijsten gemeten. Hieruit blijkt dat objectieve testen niet hetzelfde meten als vragenlijsten en dat deze daarom niet zomaar uitgewisseld kunnen worden. Wanneer men complicaties en de impact hiervan op de kwaliteit van leven wil voorspellen, is het belangrijk om daarvoor zowel objectieve functioneringstesten als vragenlijsten te gebruiken. Objectieve uitkomsten zijn gebaseerd op observaties, ongeacht de ervaring van de patiënt. Hierdoor zijn deze uitkomsten accuraat en onbevooroordeeld. De uitkomsten van vragenlijsten hangen af van individuele waardes en prioriteiten, welke verschillend kunnen zijn tussen personen en zelfs binnen personen. Deze uitkomst is gebaseerd op wat mensen ervaren en hoe zij hun eigen functioneren beoordelen en daarom in mindere mate op de daadwerkelijke prestaties. Personen kunnen verschillen in wat zij belangrijk vinden en de verwachtingen in vooruitgang na behandeling kunnen veranderen met de tijd, afhankelijk van persoonlijke omstandigheden. Personen kunnen in de loop van de tijd een mate van aanpassing ontwikkelen, waarbij hun ervaring of gevoel verbetert, maar hun objectieve functioneren hetzelfde blijft of zelfs kan verslechteren. Daarom is de belangrijkste boodschap van dit hoofdstuk om zowel objectieve testen als vragenlijsten mee te nemen wanneer je een compleet beeld van de kwaliteit van leven en het functioneren van de patiënt wilt krijgen.

Het uiteindelijke doel van dit project was het creëren van predictiemodellen (voorspellingsmodellen) die het risico op complicaties vóór en na behandeling van hoofd-halskanker beschrijven. In de meeste publicaties wordt enkel één type complicatie beschreven, na één specifieke behandeling. Daarnaast worden enkel óf vragenlijsten, óf

objectieve testen gebruikt, maar niet beide. Echter, omdat in **hoofdstuk 5** een lage correlatie werd gevonden tussen objectieve testen en vragenlijsten, was het niet mogelijk een predictiemodel te creëren dat zowel objectieve testen als vragenlijsten meeneemt. Om deze reden is ervoor gekozen om aparte modellen te ontwikkelen voor de objectieve testen en de vragenlijsten. In **hoofdstuk 6** staan daarom factoren beschreven die een negatieve impact hebben op het objectieve kauwen en in **hoofdstuk 7** staan factoren beschreven die een negatieve impact hebben op het objectieve slikken. In **hoofdstuk 8** staan de factoren beschreven die een negatieve impact hebben op de uitkomsten van de SWAL-QOL vragenlijst.

In toekomstig onderzoek is het belangrijk om allereerst de belangrijkste uitkomst vast te stellen. Wanneer de ervaringen van de patiënt het meest van belang zijn, moeten vragenlijsten uitgegeven worden. Wanneer men wil meten of bijvoorbeeld het type behandeling zorgt voor een andere kauw- of slikuitkomst, moeten objectieve testen worden meegenomen. Wanneer het totale beeld van de patiënt belangrijk is, om bijvoorbeeld een strategie te bedenken om bijwerkingen te verminderen, wordt geadviseerd om zowel objectieve testen als vragenlijsten mee te nemen.

Om het voedselproces te verbeteren, zijn er verschillende revalidatie behandelingen beschikbaar. Het is hierbij belangrijk dat patiënten op tijd een verwijzing krijgen, zodat zij snel geholpen kunnen worden en de minste bijwerkingen van hun behandeling krijgen. Wanneer patiënten kauwproblemen ondervinden, kan een orale fysiotherapeut door middel van oefeningen de maximale mondopening vergroten en de spieren die nodig zijn voor het kauwen opnieuw trainen. Zoals aangegeven in **hoofdstuk 6**, hebben met name oudere patiënten, patiënten met een grotere tumor (stadium III of IV) en patiënten met een tumor in de mond problemen met het vermalen van voedsel. Het is daarom belangrijk dat met name deze groep er weet van heeft dat deze revalidatiebehandelingen beschikbaar zijn. Problemen treden met name 3 en 6 maanden na behandeling op, waardoor het aan te raden is om tijdig met revalidatie oefeningen te beginnen.

Wanneer patiënten slikklachten (dysfagie) krijgen, zijn er verschillende slikoefeningen beschikbaar welke al gelijktijdig met radiotherapie of chemoradiatie gegeven kunnen worden, of na een chirurgische behandeling. Deze oefeningen zijn erop gericht om de veiligheid van het slikken te verbeteren en zo bijvoorbeeld aspiratie (verslikken waardoor er voedsel of vloeistof in de luchtwegen komt) te verminderen en de efficiëntie van het slikken te verhogen. Zoals gevonden is in **hoofdstuk 7**, kunnen met name oudere patiënten en patiënten die (uitgebreide) chirurgie als primaire behandeling hebben gekregen hier profijt van hebben, omdat zij de meeste klachten ontwikkelen na hun behandeling. Op deze manier kan dysfagie voorkomen worden, of de ernst van dysfagie worden verminderd. Ook

lopen oudere patiënten een verhoogd risico op aspiratie, doordat zij een verminderde eet- en slikfunctie hebben. Daarom zijn ook voor deze patiënten slikoefeningen belangrijk om een goede orale functie te behouden. Daarnaast is het erg belangrijk dat patiënten tijdens hun behandeling op gewicht blijven en de juiste voedingsstoffen binnen krijgen om de behandeling zo goed mogelijk te doorstaan. Een diëtiste kan hier tijdens de behandeling adviezen over geven, of patiënten een sonde aanbieden wanneer zij zelf niet meer genoeg voedsel tot zich kunnen nemen.

In **hoofdstuk 8** werd gezien dat de meeste factoren uit de SWAL-QOL vragenlijst, zoals de voedselkeuze, etensduur, het trek hebben in eten, de mentale gezondheid en het aantal symptomen gerelateerd aan slikken, verslechteren na de behandeling. Deze waardes komen na 6 tot 12 maanden weer terug op de waardes van vóór de behandeling. Wat echter ook werd gezien is dat de etensduur ook 2 jaar na behandeling significant langer was dan vóór de behandeling. Deze factor is daarom uitgebreider uitgewerkt in een model, waarbij gezien werd dat vrouwen, mensen die gewicht verliezen vóór hun behandeling en mensen die roken tijdens de behandeling, meer problemen met betrekking tot de etensduur aangeven. Daarnaast werd gezien dat een grotere en uitgebreidere tumor (stadium III of IV), een tumor in de mond of orofarynx en een behandeling met chemoradiatie, of chirurgie gecombineerd met (chemo)radiotherapie, zorgen voor meer problemen. Een belangrijk aspect waar patiënten zelf iets aan kunnen veranderen is dat zij stoppen met roken. In eerder onderzoek is al aangetoond dat roken een negatief effect heeft op de overleving en het al dan niet krijgen van een 2^{e} tumor of een recidief van de eerdere tumor. Wat uit **hoofdstuk 8** blijkt is dat roken er ook voor zorgt dat patiënten na hun behandeling meer klachten ervaren.

Het is belangrijk dat patiënten die de grootste kans lopen om klachten te ontwikkelen vóór hun behandeling geïnformeerd worden over de mogelijke problemen die zij na de behandeling kunnen krijgen. Daarnaast is het belangrijk dat zij geïnformeerd worden over de mogelijke revalidatietechnieken tijdens én na hun behandeling. Het is belangrijk om realistische verwachtingen te scheppen over wat zij na hun behandeling kunnen verwachten, zodat patiënten beter kunnen omgaan met de effecten en bijbehorende klachten van de behandeling op het dagelijks functioneren. Informatie over de te verwachte problemen kan stress en angst tijdens de behandeling verminderen en kan zorgen voor een actievere deelname van de patiënt aan de behandeling en daarnaast een hogere tevredenheid over de geleverde zorg.

List of Acronyms

AIC: Akaike's Information Criterion

CI: Confidence Interval

COSMIN: Consensus-based Standards for the selection of health Measurement Instruments

CRT: Chemo Radiation Therapy

EORTC QLQ-C30: European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire

EORTC QLQ-H&N35: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Head and Neck module

FEES: Fibreoptic Endoscopic Evaluation of Swallowing

GRIX: Groningen Radiotherapy-Induced Xerostomia scale

HNC: Head and Neck Cancer

HPV: Human Papilloma Virus

ICC: Intraclass Correlation Coefficient

IQR: Inter Quartile Range

LMM: Linear Mixed Model

LoA: Limits of Agreement

MAI: Mixing Ability Index

MAT: Mixing Ability Test

MDADI: M.D. Anderson Dysphagia Inventory

NET-QUBIC: NETherlands QUality of life and BIomedical Cohort studies in head and neck cancer

N/A: Not Applicable

OAR: Organs at Risk

PORT: Post-Operative Radiation Therapy

PRO: Patient Reported Outcome

QoL: Quality of Life

REML: Restricted Maximum Likelihood approach

ROC: Receiver Operating Curve

RT: Radiation Therapy

SD: Standard Deviation

SDC: Smallest Detectable Change

SE: Standard Error

SEM: Standard Error of Measurement

SPSS: Statistical Package for the Social Sciences

SWAL-QoL: Swallowing Quality of Life Questionnaire

TNM: Tumor Node Metastasis (classification system)

UMCU: University Medical Center Utrecht

UW-QoL: University of Washington Quality of Life questionnaire

WST: Water Swallowing Test

List of Publications

Journal articles

Jorine A. Vermaire, Cornelis P. J. Raaijmakers, Evelyn M. Monninkhof, C. René Leemans, Robert J. Baatenburg de Jong, Robert P. Takes, Irma M. Verdonck-de Leeuw, Femke Jansen, Johannes A. Langendijk, Chris H. J. Terhaard, Caroline M. Speksnijder. The course of swallowing problems in the first 2 years after diagnosis of head and neck cancer. *Support Care in Cancer*. 2022. DOI: 10.1007/s00520-022-07322-w

Jorine A. Vermaire, Cornelis P.J. Raaijmakers, Evelyn M. Monninkhof, Irma M. Verdonck-de Leeuw, Chris H.J. Terhaard, Caroline M. Speksnijder. Factors associated with swallowing dysfunction in patients with head and neck cancer. *Oral diseases*. 2022.
DOI: 10.1111/odi.14192

Jorine A. Vermaire, Cornelis P.J. Raaijmakers, Evelyn M. Monninkhof, Irma M. Verdonck-de Leeuw, Chris H.J. Terhaard, Caroline M. Speksnijder. Factors associated with masticatory function as measured with the Mixing Ability Test in patients with head and neck cancer before and after treatment: a prospective cohort study. *Support care Cancer*. 2022;30(5):4429-4436. DOI: 10.1007/s00520-022-06867-0.

Jorine A. Vermaire, Cornelis P.J. Raaijmakers, Irma M. Verdonck-de Leeuw, Femke Jansen, C. René Leemans, Chris H.J. Terhaard, Caroline M. Speksnijder. Mastication, swallowing, and salivary flow in patients with head and neck cancer: objective tests versus patient-reported outcomes. *Support Care Cancer*. 2021;29(12):7793-7803.
DOI: 10.1007/s00520-021-06368-6

Jorine A. Vermaire, Chris H.J. Terhaard, Irma M. Verdonck-de Leeuw, Cornelis P.J. Raaijmakers, Caroline M. Speksnijder. Reliability of the 100 mL water swallow test in patients with head and neck cancer and healthy subjects. *Head Neck*. 2021;43(8):2468-2476. DOI: 10.1002/hed.26723

Jorine A. Vermaire, Florine M. Weinberg, Cornelis P. J. Raaijmakers, Irma M. Verdonck-de Leeuw, Chris H. J. Terhaard, Caroline M. Speksnijder. Reliability of the mixing ability test testing masticatory performance in patients with head and neck cancer and healthy controls. *J Oral Rehabil*. 2020;47(8):961-966. DOI: 10.1111/joor.13029

Joeri A.J. Douma, Maaike B. de Beaufort, Caroline S. Kampshoff, Saskia Persoon, **Jorine A. Vermaire**, Mai J. Chinapaw, Willem van Mechelen, Frans Nollet, Marie José Kersten, Jan H. Smit, Irma M. Verdonck-de Leeuw, Teatske M. Altenburg, Laurien M. Buffart. Physical

activity in patients with cancer: self-report versus accelerometer assessments. *Support Care Cancer*. 2020;28(8):3701-3709. DOI: 10.1007/s00520-019-05203-3

Florine M. Weinberg, **Jorine A. Vermaire**, Tymour Forouzanfar, Antoine J.W.P. Rosenberg, Caroline M. Speksnijder. Reproducibility and construct validity of the Utrecht Mixing Ability Test to obtain masticatory performance outcome in patients with condylar mandibular fractures. *J Oral Rehabil*. 2020;47(4):460-466. DOI: 10.1111/joor.12917

Jorine A. Vermaire, Caroline M. Speksnijder. 2019, April. *Fysiopraxis.* De fysiologie van het kauwen.

Lianne Remijn, **Jorine A. Vermaire**, Maria W.G. Nijhuis-van de Sanden, Brenda E. Groen, Caroline M. Speksnijder. Validity and reliability of the mixing ability test as masticatory performance outcome in children with spastic cerebral palsy and children with typical development: A pilot study. *J Oral Rehabil*. 2018;45(10):790-797.
DOI: 10.1111/joor.12690

Lianne Remijn, Brenda E. Groen, Richard Speyer, Jacques van Limbeek, **Jorine A. Vermaire**, Lenie van den Engel-Hoek, Maria W.G. Nijhuis-van der Sanden. Can mastication in children with cerebral palsy be analyzed by clinical observation, dynamic ultrasound and 3D kinematics? *J Electromyogr Kinesiol*. 2017;32:22-29.
DOI: 10.1016/j.jelekin.2016.11.005

Abstracts and conference proceedings

Jorine A. Vermaire, Cornelis P.J. Raaijmakers, Irma M. Verdonck-de Leeuw, Femke Jansen, C. René Leemans, Chris H.J. Terhaard, Caroline M. Speksnijder. 2021. *Poster at ESTRO*. Mastication, swallowing, and salivary flow in patients with head and neck cancer: objective tests versus patient-reported outcomes.

Jorine A. Vermaire, Florine M. Weinberg, Cornelis P. J. Raaijmakers, Irma M. Verdonck-de Leeuw, Chris H. J. Terhaard, Caroline M. Speksnijder. 2020. *Poster at ESTRO*. Reliability of the Mixing Ability Test testing masticatory performance in patients with head and neck cancer and healthy controls.

Chris H.J. Terhaard, **Jorine A. Vermaire**, Tim Dijkema, Mariëlle E.P. Philippens, Petra M. Braam, Judith M. Roesink, Cornelis P.J. Raaijmakers. 2018. *Abstract. Multidisciplinary head and neck cancers symposium*. Model Based Radiotherapy: Submandibular Dose-Response NTCP-Curve Based on Objective Measurements.

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Curriculum vitae

Jorine Vermaire was born in Goes, the Netherlands, on the 6th of August 1992. She grew up in the village Kattendijke, together with her parents, identical twin sister and younger sister. After primary school in Kattendijke, she attended secondary school in Goes at the Buys Ballot College, which she finished in 2010. Thereafter she started the bachelor program Biomedical Sciences at the Raboud University Nijmegen, followed by the master program Clinical Human Movement Sciences. During her studies, she completed various internships; her bachelor internship was at the cognitive neuroscience and biophysics department of the Donders institute in Nijmegen, and was about feedback-induced perceptual learning. During her master program she completed the global health minor, in which she performed an internship at the WHO regional office for Europe in Copenhagen, Denmark. She studied the main components of national influenza surveillance systems in countries of the WHO European region and made a comparison with surveillance guidelines between these countries. The second internship during her masters was at the Sint Maartenskliniek in Nijmegen, where she studied differences in chewing between healthy children and children with cerebral palsy. Her final internship was at the Radboud university medical center at the department IQ healthcare, where she performed a qualitative study about perceptions and expectations of patients with facial paralysis, and how healthy body feedback could help with rehabilitation.

After graduation in 2015, she applied for the position of research assistant in the UMC Utrecht to assist with the NET-QUBIC project (NETherlands Quality of life and Biomedical cohort studies In Cancer). During the two following years, she included patients with head and neck cancer, and performed the measurements corresponding to this research. In December 2017, she started her PhD position on the data collected in the NET-QUBIC project, at the department of radiation oncology under supervision of Chris Terhaard as promotor, and Caroline Speksnijder and Niels Raaijmakers as copromotors.

After her PhD, Jorine started a position as research coordinator at the Verbeeten institute in Tilburg.