TRISMUS

Incidence, Effects on Health-Related Quality of Life and Development of the Gothenburg Trismus Questionnaire

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UNIVERSITY OF GOTHENBURG

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ABSTRACT

The word trismus is modern latin, derived from the greek word ”trismos” meaning ”grinding” or ”rasping”. Trismus is defined as a limitation in the mouth/jaw-opening ability due to a reduced mandible mobility. A Maximal Interincisal Opening, (MIO) ≤ 35mm is often used as the cut-off point for trismus. It can occur as a result of tumor growth, and more importantly, as a side-effect to head and neck (H&N) oncology treatment. Trismus can also result from benign jaw related conditions, often referred to as temporomandibular disorders (TMD). The aim of this thesis was to investigate how trismus affects the quality of life and mental health in patients with H&N cancer and TMD, examine the incidence of trismus and ultimately to improve the management and care of patients with trismus.

Methods & Aims:
Study I; A retrospective study including 69 patients aiming to investigate trismus incidence in relation to different H&N cancer diagnoses and treatment regimens.
In *Study II* the incidence of trismus after oncology treatment was prospectively examined in 75 patients as well as the impact of trismus on Health Related Quality of Life (HRQL). We used Patient reported outcome (PRO) instruments, including the European Organization for Research and Treatment of Cancer Quality of Life Questionnaires, (EORTC QLQ), the Gothenburg Trismus Questionnaire (GTQ) and repeated measurements of MIO.

In *Study III* we developed and validated a trismus specific instrument, the Gothenburg Trismus Questionnaire. Patients with H&N cancer and TMD participated in the study. We used empirical evidence, a pilot study and a ”gold standard” validation procedure. The aim of *Study IV* was to measure the impact of trismus on HRQL and mental health in patients with H&N cancer and TMD. We used the PRO instruments Short-Form 36 Health Survey (SF-36), the Hospital Anxiety and Depression scales (HADS) and the GTQ.

Results:
The results showed that trismus is a common sequela after H&N cancer treatment. In the retrospective study 42% of the patients had post-treatment trismus and in the prospective material 38% had trismus 6 months following treatment. The latter study also highlighted that trismus severely impacts HRQL. The GTQ showed good psychometric properties and was well accepted by the patients and the results in study IV demonstrated that trismus significantly affects HRQL and mental health and that the GTQ has a clear clinical relevance.

Conclusions:
Our main findings demonstrate that trismus has a significantly negative impact on HRQL and mental health in both H&N cancer and TMD patients and that it is a common and sometimes excruciating sequela after H&N cancer treatment.
We suggest that the GTQ is used in clinical practice and in research, employed as a screening tool as well as an endpoint in intervention and rehabilitation studies.
Other implications are that patients with trismus should now be approached in a holistic way with respect for the underlying cause, treating not only the physical aspects of trismus but also addressing the patients' mental health. Further research is needed, especially addressing trismus rehabilitation, prevention and training.

Key words: Trismus, Cancer, Head and Neck, Radiation therapy, TMD, Oncology, PRO, HRQL, Questionnaire, Instrument.
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Figure 1; A classic picture of a man with tetanus and opisthotonus, a condition often historically associated with trismus.
By Sir Charles Bell, 1809

To my family

LIST OF PUBLICATIONS

This thesis is based on the following studies, wich will be referred to in the text by their roman numerals:

I. Johnson J, van As-Brooks CJ, Fagerberg-Mohlin B, Finizia C.
Trismus in head and neck cancer patients in Sweden: Incidence and risk factors.
Medical Science Monitor 2010;16:CR278-282.

II. Pauli N, Johnson J, Finizia C, Andréll P.
The incidence of trismus and long-term impact on health related quality of life in patients with head and neck cancer. Acta Oncol. 2013 Aug; 52(6):1137-1145.

III. Johnson J, Carlsson S, Johansson M, Pauli N, Ryden A, Fagerberg-Mohlin B, Finizia C.
Development and validation of the Gothenburg Trismus Questionnaire (GTQ).
Oral Oncology 2012 Aug; 48(8):730-736.

IV. Johnson J, Johansson M, Ryden A, Houltz E, Finizia C.
The impact of trismus on Health-Related Quality of life and mental health.
In manuscript

CONTENTS

ABBREVIATIONS AND EXPLANATIONS

ACE-27; Adult Comorbidity Evaluation 27

EBRT; External Beam Radiotherapy

ENT; Ear, Nose and Throat

EORTC QLQ-C30; The European organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core30

EORTC QLQ-H&N35; The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Head and Neck 35

Global QL; Global Quality of Life

GTQ; Gothenburg Trismus Questionnaire

Gy; Gray

HADS; the Hospital Anxiety and Depression Scale

H&N; Head and Neck

HRQL; Health Related Quality of Life

IMRT; Intensity modulated radiotherapy

IRT; Interstitial Radiotherapy or brachytherapy

KPSI; Karnofsky Performance Status Scale Index

MIO; Maximum Interincisal Opening

NIH; National Insitute of Health

PRO; Patient, or person, reported outcome

QoL; Quality of Life

RT; Radiation therapy

SF 36; Short-Form 36 Health Survey

SU; Sahlgrenska University Hospital

TMD; Temporomandibular disorders

TMJ; Temporomandibular joint

VGR; Region of West Sweden

WHO; World Health Organization

THESIS AT A GLANCE

	Aim and focus	Study design & size	Methods	Main results
Study I	To investigate trismus incidence in relation to different H&N cancer diagnoses and treatment regimens	Retrospective 69 patients included out of 246	Maximal Interincisal Opening (MIO) pre- and post oncological treatment	Trismus incidence was 42% post treatment. Poor physical function and high EBRT dosages (>50Gy) were related to more trismus
Study II	To measure trismus incidence after oncology treatment and the impact of trismus on HRQL	Prospective 75 patients included out of 127	Longitudinal study with PRO instruments and repeated MIO measurements	Highest trismus incidence was 38%, 6 months post treatment. Trismus severely affects HRQL
Study III	To develop and validate a trismus specific PRO instrument, the GTQ	Crossectional n=129	Empirical evidence, pilot study and a ”gold standard” psychometric procedure	The GTQ showed good psychometric properties and was well accepted by the patients
Study IV	To measure the impact of trismus on HRQL and mental health in patients with H&N cancer and TMD	Crossectional n=129	PRO instruments (GTQ, SF-36 and HADS) and MIO measurements	Trismus significantly affects HRQL and mental health. The GTQ has a clear clinical relevance

1 INTRODUCTION

Reduced mobility of the mandible, trismus, is a phenomenon frequently seen in head and neck (H&N) cancer patients and in patients with temporomandibular disorders (TMD) (1-3). Despite trismus being a common problem in H&N oncology, that can severely impact on important aspects of daily life including chewing, diet and social interaction, it has been given comparatively little attention in the literature.

This thesis addresses trismus with the overall aim of increasing the knowledge about trismus and improving the care for patients suffering from trismus by investigating trismus incidence and risk factors for trismus as well as by developing a trismus specific Patient Reported Outcome (PRO) instrument and measuring effects of trismus on Health Related Quality of Life (HRQL) and mental health. This thesis is divided into two main parts, adressing different aspects of trismus. In paper I and II the focus lies on trismus incidence, which to date is a surprisingly uncharted research area. Papers III and IV focus on the development and validation of a trismus specific PRO instrument, the Gothenburg Trismus Questionnaire (GTQ), and trismus related symtoms in relation to HRQL and mental health. Despite new and improved treatment techniques, no major improvement in survival among H&N cancer patients have been observed during the recent decades (4, 5). This emphasises the need for clinical trials that focus not only on survival but also on the patients experience and HRQL. As stated above, trismus can have a significant negative impact on many aspects of daily life, and subsequently, affect HRQL in a negative manner. However, to our knowledge, no trismus specific PRO instrument previously existed, although several instruments have isolated questions concerning trismus. Therefore, to further improve the treatment and care of patients with trismus, our research group developed and validated a comprehensive and self-administered, trismus specific instrument for trismus patients, the GTQ.

Our main objective was to create an instrument with clinical relevance that could be utilised in clinical settings in order to evaluate treatment and intervention effects, but also to act as a screening tool and as an aid in jaw rehabilitation studies.

2 BACKGROUND

The word trismus is modern latin, derived from the greek word ”trismos” meaning ”grinding” or ”rasping”. Trismus is defined as a limitation of the mouth/jaw-opening ability due to reduced mobility of the mandible. The normal range of mouth opening varies between different groups, age and genders (6-8). In a studie by Gallagher et al. the average maximum mouth opening was 43mm for males and 41mm for females (8). Trismus can occur as a result of local or metastatic tumor growth in Head and Neck (H&N) tumors, but more importantly as a side-effect to H&N oncology treatment, particularly radiotherapy and surgical intervention (9). Historically, trismus was often associated with tetanus. Trismus is present at the time of cancer diagnosis in approximately 2-9% of H&N cancer patients (1, 9). Multiple structures in the H&N area can be damaged by radiotherapy (RT), including the masseter and pterygoid muscles, nerves, supportive tissue and the temporomandibular joint (TMJ). Common aetiology for oncology related trismus includes radiation induced fibrosis and post-operative scaring. Risk factors for developing trismus are large tumor size, increasing radiotherapy dosage as well as tumor locations close to the muscles of mastication and the TMJ (2, 10). Furthermore, poor physical function prior to start of cancer treatment also appear to be a risk factor for developing trismus (2). The reported prevalence of trismus in H&N cancer patients varies widely, Table 1. The prevalence range is most likely explained by the various treatment regimens employed, point of measurement, different tumor sites involved but also due to the different criterias used to define trismus (11). A studie by our research group showed that the highest trismus incidence occurs 6 months efter radiation therapy, but generally trismus often develops within 1 to 9 months after completion of the RT (1, 12, 13). Nevertheless, trismus can also result from benign jaw related conditions, often referred to as Temporomandibular disorders (TMD). It can also occur more acutely in, for instance pericoronitis, tetanus, peridontal abscesses and trauma with mandibular fractures. Maximal Interincisal Opening (MIO) is a term used to describe the greatest distance between the incisal edge of the maxillary central incisors and the incisal edge of the mandibular central incisors in the midline when the mouth is open maximally, as shown in Figure 7.

Author	*Patients*	*Trismus Criteria*	*Trismus Prevalence*	*Trismus Incidence*
Ichimura & Tanaka, 1993 (9)	H&N cancer	≤ 35mm	2% at time of diagnosis	
Nguyen, 1988 (14)	H&N cancer Stage III-IV	< 40mm	30% at long time follow up	
Steelman & Sokol, 1986 (15)	Oral cavity or naspoharynx cancer	≤ 35mm	Ca 44% after RT	
Lee, 2011 (16)	H&N cancer	≤ 35mm		Pre surgery 41% Post surgery 71%

Table 1; ***Different studies showing the diversity of trismus incidence and prevalence***

Agerberg suggests the ability to put three fingers vertically between the frontal incisors as the normal mouth opening capacity for the single individual, Figure 2 (7). As mentioned, trismus affects many important aspects of daily life such as chewing, diet, eating difficulties, speech and social interaction (16). It can also interfere with the ability to practice effective oral hygiene, which is particularly important for patients undergoing radiation treatment (9).

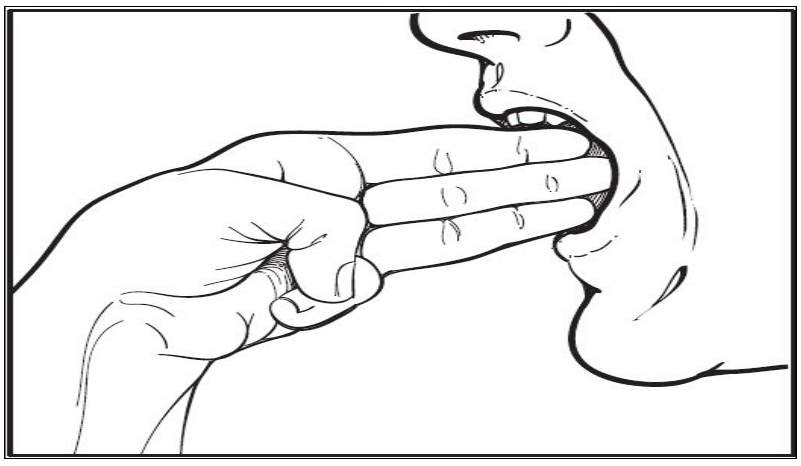


Figure 2; ***Illustrating normal mouth opening capacity according to Agerberg. Source www.myhealth.gov.my. Used with permission.***

2.1 Trismus definition

Historically, the reported trismus prevalence has varied greatly. One of the reasons for this variation was the lack of uniform criterias for the trismus definition. Trismus has previously been described as a mouth opening capability ranging from less than 20 mm up to less than 40 mm (11, 16). In 2005, Djikstra et al. published a study aiming to determine a functional cut off point for trismus. The Mandibular Function Impairment Questionnaire (MFIQ) was used and a total of 89 H&N cancer patients were asked if they experienced a limited mouth opening, after which mouth opening was measured.
The proportion of correct predictions was highest for cut-off point ≤ 35mm, with a sensitivity of 0,71 and a specificity of 0,98. Consequently, Dijkstra et al. concluded that a mouth opening of ≤ 35 mm should be the cut-off point for trismus in H&N cancer patients (11). Today, the measurement of 35 mm is a widely used definition based on functional criteria (12, 16, 17). A study by Scott et al. in 2007 further supported the 35 mm cut-off for trismus (17).

Figure 3; ***Impaired mouth opening, trismus.***
Photo by Jan Persson

2.2 Head and Neck cancer

Key points

- The majority of H&N cancers originate from squamous cells that line the mucus membranes inside the mouth and H&N area.
- Consumption of tobacco and alcohol as well as human papillomavirus infection are important risk factors for H&N cancers.
- Typical symptoms of H&N malignancies include a swelling or ulcer that does not heal, a persistent sore throat, dysphagia or a change in the voice.
- Radiation, chemotherapy and surgical intervention are important treatment modalities for H&N cancer.

H&N cancers represent an important group of malignancies owing to their potentially severe adverse effects on many important basic human functions (18). Approximately 1200 people in Sweden is diagnosed with cancer in the H&N region each year (19). Worldwide, the incidence of tumors of the lip and oral cavity alone were estimated at 263 900 new cases during 2008. This incidence, however, varies greatly in different parts of the world (20). Squamous cell carcinomas in the H&N area account for more than 90% of all upper aerodigestive tract malignancies. It is more common in males, two thirds of the cases affecting males, and in the Swedish region of Västra Götaland (VGR) the average age at the time of diagnosis is 67 years and during the last two decades, disease specific survival has been approximately 60% (4). Symptoms of H&N cancer varies depending on several factors, but can include a swelling, ulcers that do not heal, a persistent sore throat, difficulties swallowing and dysphonia (4, 21). Risk factors for developing H&N cancer include alcohol and tobacco consumption but also human papilloma virus infection and betel nut chewing (22-24). In the H&N region, intricate anatomical structures contribute to and are responsible for essential functions such as breathing, speech, olfaction, gustation and swallowing. Hence, tumor growth in this region as well as the consequences of treatment for H&N tumors can impair these functions.

Classification of H&N tumors

H&N cancer is a collective term for malignant tumors usually described as originating from the following anatomical regions; lips, oral cavity, pharynx, nose, sinuses, larynx and in the salivary glands, Figure 4, (4, 5). “Tumor Colli”, meaning lymph node metastasis in the neck with an unknown primary tumor, also qualifies as H&N cancer. In each of the above mentioned anatomical regions, several different tumors can arise, each with its own different origin, prognosis, treatment and risk of metastasis. Therefore, a more practical and disease specific method of arranging the tumors in the H&N area, is often used (4):

- Lip cancer
- Cancer of the oral cavity
  - Including cancer in the tounge, gingiva, floor of the mouth, buccae and the hard palate.
- Oropharyngeal cancer
  - Including cancer in the base of the tounge, tonsils, pharynx and the soft palate
- Nasopharyngeal cancer
- Hypopharyngeal cancer
- Cancer in the larynx
- Cancer in the salivary glands
- Cancer in the nose
- Cancer in the sinuses
- Tumor Colli

In the VGR the most frequent tumor in H&N cancer is that of the oral cavity and therewithin, cancer of the tounge is the most prevalent (4). Other tumors with a high frequency in the H&N area are oropharyngeal tumors.

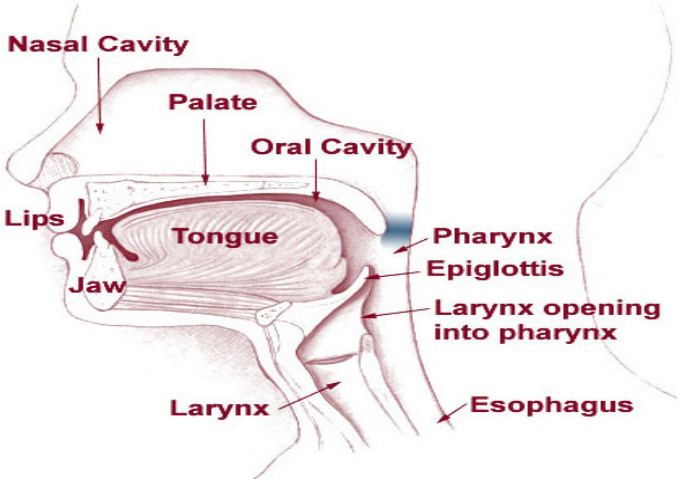


Figure 4; ***Anatomical overview of the H&N region***

Diagnosing H&N cancer

Several different methods of diagnosing and identifying H&N cancers exist in clinical use, where the clinical examination, sometimes performed in anesthesia, should be emphasised as the most important aspect.

Other methods employed are;

- Cytology and histopathological examination
- Radiology; Computer Tomography (CT), Positron Emission Tomography (PET-CT) and plain x-ray.
- Magnetic Resonance Imaging (MRI)
- Ultrasound

TNM classification

The TNM Classification of Malignant Tumors (TNM) is a system that classifies the progression of solid, malignant tumors (25).

- **T (0-4)** Describes the size of the primary tumor and whether it has invaded nearby tissue
- **N (0-3)** Describes if regional lymph nodes are involved and if so, to what extent
- **M (0-1)** Describes if there is distant metastasis present

The TNM staging system for solid tumors was devised by Prof. Pierre Denoix, using the size and extension of the primary tumor, its lymphatic involvement and the presence of metastases to classify the progression of cancer. Different cancer diagnoses, including H&N malignancies, have their own unique TNM staging criteria, based on the original TNM classification system. The Overall Stage Grouping, also known as the Roman Numeral Staging System, is a non-specific staging system used in cancer research and in the literature. This system uses numerals I, II, III, and IV (plus the 0) to describe the progression of cancer, see below for a simplified example.

- **Stage 0** Carcinoma in situ
- **Stage I** Tumors are localized to one part of the body.
- **Stage II** Tumors are locally advanced, often with regional lymph node metastasis.
- **Stage III** Tumors are also locally advanced, whether a cancer is designated as Stage II or Stage III depends on the specific type of cancer
- **Stage IV** Cancers have metastasized

At the time of diagnosis, nearly 60% of patients with H&N cancer have advanced stage cancer (Stages III or IV) and the prognosis varies greatly depending on several different factors, including cancer type and stage (4, 26).

Treatment of Head and Neck cancer

The main treatment modalities for H&N cancer include radiation therapy (RT), chemotherapy and surgical intervention, either as a single therapy or as a combination thereof (27, 28). The choice between RT, surgery or a combined approach is based on different variables such as tumor type and stage, location, patient preferences and the patient's overall health status. Some H&N cancers are treated mainly with RT and/or chemotherapy, such as oropharyngeal tumors, whilst others primarily undergo surgery with or without RT/chemotherapy (4). The frequent use of RT in H&N cancer treatment highlights the need for research that adresses the relationship between trismus and radiation techniques as well as radiation doses.

Radiation Therapy

Radiation is composed of energy, including photons, protons and electrons that induce tissue damage via the creation of hydroxyl radicals and can be administered as External Beam Radiotherapy (EBRT) or as Interstitial Radiotherapy (IRT or brachytherapy). The latter uses catheters that are implanted around the tumor to deliver the radiation in close proximity to the tumor and thereby sparing surrounding tissues. IRT can be used alone or in combination with external beam radiotherapy and/or surgery, and the dose per fraction and total dose varies depending on the type of IRT used (29). Different types of external beam therapies exist today alongside different schemes for radiation delivery, including hyperfractionation, Intensity Modulated Radio Therapy (IMRT) and Simultan Integrated Boost (SIB) (30, 31). The radiation is often administered using photons from a linear accelerator, Figure 5. A study by Bensadoun et al. implied that IMRT, compared to traditional EBRT, can reduce the incidence of trismus and other studies reports a decrease in xerostomia and dysphagia in patients who have received IMRT instead of conventional RT (10). However, a study by Kent et al. demonstrated no difference in trismus incidence when using IMRT compared to conventional EBRT (12). Conventional full dose EBRT usually ranges from 64 to 70 Gray (Gy), often with the target 68-70 Gy and with a fractionation of 2 Gy/day, 5 days/week for 7 weeks (4, 26). A frequently used full dose EBRT regimen is the protocol from the Danish Head and Neck Cancer Group, with 1-2 Gy/day, 6 days a week, with the target 68 Gy (32).
A study by Teguh et al. shows that the risk of developing trismus following RT increases by 24% for every 10 Gy of additional radiation delivered to the pterygoid muscle (33). RT kan be administered before or after surgery. Palliative radiotherapy treatment in VGR often employs a total dose of 54 Gy distributed over 3 Gy/day, 5 days/week for 4 weeks (4).

Figure 5; ***Linear accelerator. Visit Wikimedia Commons for intellectual property rights and terms***

Surgery

Surgery is another important treatment modality in H&N cancer and can be used alone or togheter with RT. Surgery alone is for example often used on more ventral and/or superficial tumors or on smaller tumors, for example in the oral cavity (4). Many factors are evaluated and taken into account prior to a surgical procedure in the H&N area. For instance, is it possible to remove the tumor radically and is the patient's general health and comorbidity status sufficient enough to survive the treatment (34)? When removing the primary tumor, a macroscopic margine in excess of 5-10mm is often preferred, but a review article by Hinni et al. concludes that adequate margins differ between cancers in the H&N area and that more studies with the goal to standardize margin assessment are needed (35). Primary radical lymphnode extirpation is often incorporated into the treatment when preoperative examination has shown regional metastases. The operation involves different areas in the neck region and can, for example, include manipulation of the Sternocleidomastoid muscle, the Internal jugular vein and the Accessory nerve (4). Salvage surgery is often reserved for when the primary chemoradiotherapy has failed to completely remove the tumor.

Chemotherapy and monoclonal antibodies

The role of chemotherapy in H&N cancer treatment has expanded from palliative care to a central component of curative programmes for locally advanced cancers (26). Chemotherapy is not utilised as a single modality in curative H&N cancer treatment, but can be used alone in palliative care. Today chemotherapy, often cisplatin in VGR, is frequently used in combination with radiation treatment (4, 26, 36, 37). The effect of most chemotherapeutic drugs is based on the interaction of molecules that are required for maintaining cellular integrity and proliferation (38). In H&N cancer, the most widely used are cisplatin, carboplatin, 5-fluorouracil, methotrexate and the taxanes and they are administered alone or as a combination (4, 38). When the chemotherapy is administered before RT its called *neoadjuvant* treatment, when administered at the same time as the RT is called *concomitant* treatment and when its administerad after the RT its called *adjuvant* treatment (37). The relationship between chemotherapy treatment and trismus is unclear and the litterature within this field is scarce. A study by Kent et al. demonstrated no difference in trismus incidence between patients who received RT and patients who received RT and chemotherapy as a combined approach

(12). In recent years a new therapy has been added to the treatment arsenal against H&N cancer, monoclonal antibodies, such as Cetuximab (Erbitux®) which act against the epidermal growth factor receptor, EGFR (38, 39).

Radiation treatment and the radiation fibrosis syndrome

Typical side effects of RT to the H&N area include xerostomia, mucositis, dysphagia, reduced skin elasticity, osteoradionecrosis and trismus (14, 40). Mucositis is an example of a sideffect that often occur early, based on the cellular turnover time, whereas trismus and osteoradionecrosis are often classified as late side effects (40). The term radiation fibrosis syndrome (RFS) describes the different clinical manifestations of fibrotic tissue that result from radiation treatment, while the term radiation fibrosis (RF) describes the pathological fibrotic tissue that often forms after radiation treatment (41). RF can affect many different tissue types, including nerve, muscle and vascular tissue. It causes several complications after RT, including trismus. MRI, following radiotherapy to the H&N area can demonstrate tissue abnormalities in multiple structures involved in the chewing apparatus (42). The side effects of radiation can be acute (during RT), early delayed (from the end of RT up to 3 months after treatment) or late (more than 3 months after the end of RT) (41). RF is usually a late complication, where three different histopathological stages can be described; a prefibrotic phase characterised by inflammation, an organised fibrotic phase and a late fibrotic phase characterised by fibrosis and parenchymal degeneration, which might severely limit the ability to open the mouth (41). There is evidence suggesting that trismus develops most rapidly within the first 9 months after treatment (1, 12, 13). The mechanisms of post radiation fibrosis is multifactorial. One important factor is radiation induced damage to microvascular structures resulting in chronic vascular and endothelial dysfunction, in addition to a thrombomoduline deficiency and subsequently an impaired ability to scavenge thrombin (41). This causes unregulated inflammatory, mitogenic and profibroblastic activity and results in a procoagulant state, generating progressive tissue fibrosis and sclerosis. Different factors affect the patients' risk of developing RFS and its varying degrees of severity, such as age, comorbidities and general health status. However, one of the major determinants seems to be attributed to the characteristics of the radiation treatment. The size of the radiation field, the tissues irradiated, type of radiation and radiation dose are all important factors in the development of RFS.

Furthermore, it is well established that two individuals with the same prerequisits and treatments can develop very different complications in response to RT, implying that there are elements, currently unknown to us, that play an important role in RFS (41). Surgery, post operative fibrosis and the surgical trauma inflicted on adjacent muscles also constribute to H&N cancer related trismus. Lee et al. found that patients with current or previous heavy alcohol intake had a smaller risk of developing trismus or presenting with trismus prior to treatment (16). This may be explained by alcohol intoxication reducing the pain during jaw movement, leading to a wider mouth opening. An alternate theory describes that alcohol also acts as a muscle relaxant and therefore, counteracts the collagen formation (16). A recent study by Lyons et al. suggests that polymorphism in the Transforming Growth Factor beta 1 (TGF-β1) gene is linked to the development of post radiation therapy trismus, and that TGF-β1 can be used as a predictor of the degree of post radiotherapy trismus (43).

2.3 MIO measurement techniques

A vital aspect of trismus research is the ability to accurately and in a reproducible manner measure a patient's MIO. In our studies, MIO was measured in millimetres using a ruler with the patient in an upright position. In dentate patients MIO was measured between the opposing incisal edges of the maxillary and mandibular incisors. In those dentate in only one jaw, the measurement was taken from the incisal edge of the anterior incisor to the opposing alveolar ridge.

Figure 7*; Measuring MIO.*

2.4 Treating trismus

As described previously, trismus can severly affect basic functions such as speech, food intake and social interaction. The jaw muscles are involved in mastication, biting and speech. During all of these tasks, it is imperative to be able to control the movement, force and position of the mandible. These tasks are complex and diverse and so is the architechture of the jaw muscles and the composition of the muscle fibers (44). The different muscle fibers and their distribution indicate that the jaw closing muscles are adapted to perform slow, tonic movements and to produce a smooth, gradable force, as the proportion of slow fibers are higher in the muscles involved in closing the jaw compared to muscles that open the jaw (44). These basic anatomical and physiological facts consistute important background information when constructing rehabilitation programmes and tailored jaw exercise systems, for example in trismus training and rehabilitation. Muscle training can be aimed at improving strength, stretching, speed and/or endurance (45). Different treatment regims for trismus has been developed during the years, some based on manual techniques, others on mechanical and electromechanical approaches. Examples include a wooden clothspin or manual stretching. Physiotherapy includes active range of motion exercises, hold relax techniques, manual stretching and joint distractions (46). Although many studies have been conducted regarding trismus and physiotherapy, few studies to date demonstrate the efficacy of using different physiotherapy techniques in patients with radiation induced trismus and fibrosis (47-49).

Figure 7; ***Training with the TheraBite© (left) and the Engström Mouth Stretcher (right). Photo by Jan Persson***

Hyberbaric oxygen and Pentoxifyllin have also been explored but shown no, or modest effects (50, 51). One of the trismus training devices available is the TheraBite®, a mechanical device with two mouthpieces that are inserted between the teeth of the upper and lower jaws, Figure 7. By sqeezing the handle, the TheraBite® assists mouth opening by applying a stretching force that follows the mandible's natural motion pathway (52). The TheraBite® has several potentially positive aspects and recently the TheraBite® has been modified with a elastic rubber band and can be used to train both actively and passively. Other medical devices designed for trismus physiotherapy is the Engströms Mouth Stretcher, with the resemblance of a large clothespin and with the ability to train both passively and actively, Figure 7, and the Jaw Dynasplint System©.

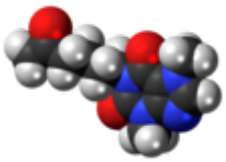
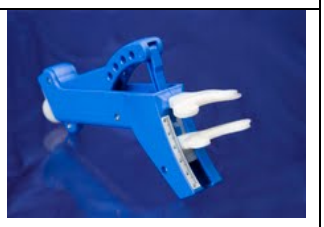
Treatment method	*Reference*	*Results*	*Picture*
Physiotherapy	Grandi et al. (48) Dijkstra et al. (46) Buchbinder et al. (47)	Useful in some cases	
Pentoxifylline	Chua et al. (50)	Modest effect	
Jaw Dynasplint System©	Shulman et al. Stubblefield et al. (53) (54)	Effective	
TheraBite©	Melchers et al. Kamstra el al. Buchbinder et al. (55) (52) (47)	Effective	
Botulinium toxin	Hartl et al. (56)	No improvement	
Hyperbaric oxygen	King et al. (51) Teguh et al. (57)	No improvement on trismus, but on other RT side effects	

Table 2; ***Different treatment techniques. The picture of the TheraBite is © Atos Medical AB, Sweden and the picture of the Jaw Dynasplint System is © Dynasplint Systems Inc.***
Other pictures; visit Wikimedia Commons for intellectual property rights and terms

2.5 Temporomandibular disorders

Temporomandibular disorders, TMD, is a term used to describe disturbances of the masticatory system. It presents with pain and dysfunction in the temporomandibular joint (TMJ), jaw muscles and associated structures. According to a National Institute of Health consensus panel, TMD refers to "a collection of medical and dental conditions affecting the TMJ and/or the muscles of mastication, as well as contiguous tissue components" (58). To the best of our knowledge, the incidence of TMD in Sweden is unknown, yet an increase in the prevalence of TMD symptoms has been observed during the last two decades, despite improvements in oral health (59). TMD is occasionally classified as a subgroup to musculoskeletal disorders and can be divided in two main groups, TMD of arthrogenous or myogenous origin (60). Although several TMD classification schemes have been developed, the two most common schemes in use today are the American Academy of Orofacial Pain (AAOP) classification and the Research Diagnostic Criterias for Temporomandibular Disorders (RDC/TMD) (3).

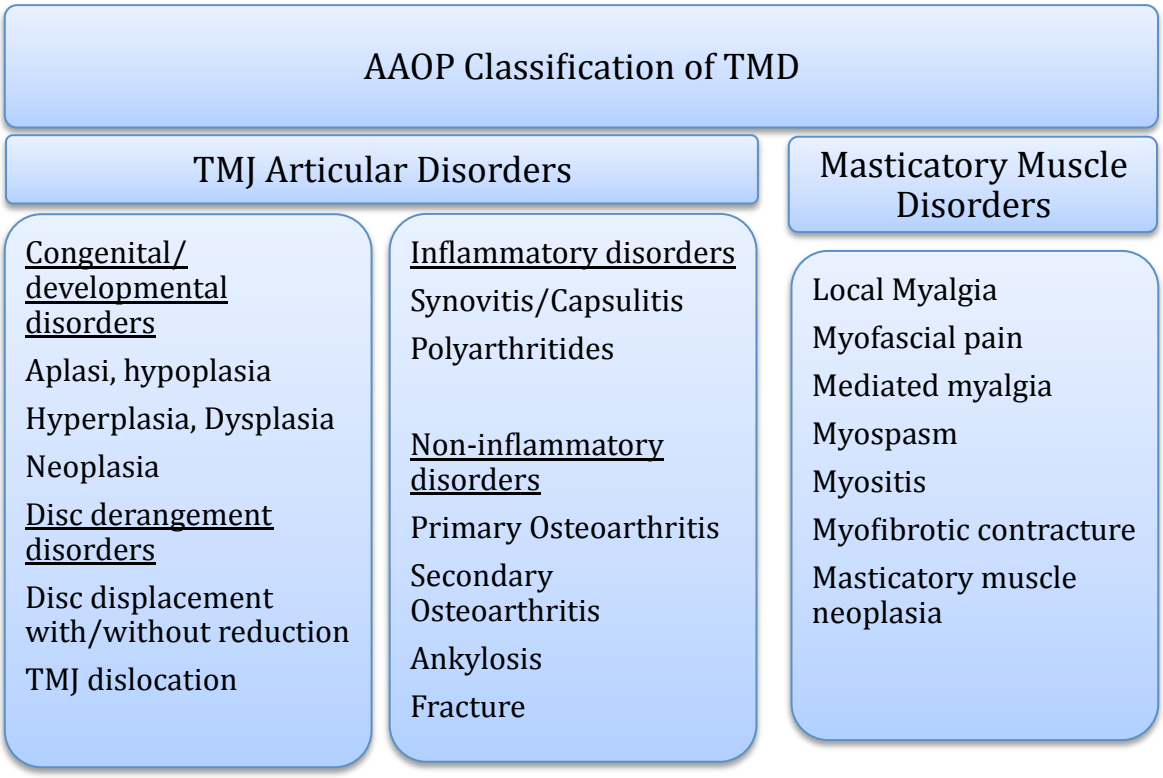


Figure 6; ***AAOP classification of TMD***

Characteristic symptoms of TMD encompass facial pain, clicking noises in the TMJ, limited jaw opening as well as deviations in the TMJ and the masticatory muscles movement pattern (3). Orofacial pain is a common symptom of TMD and among the orofacial pain disorders, TMD constitutes a substantial part (61). This pain is often chronic in nature with variations over time (3, 61). Often, TMD symptoms are more commonly reported by younger and middle-aged individuals, whereas some studies also indicate that TMD is more frequent among women (59). Additionally, TMD and other chronic pain disorders have features in common, such as aetiology, psychological and psychiatric factors (62). The etiology, for instance, is often multifactorial, involving trauma, inflammation, occlusal factors, psychological conditions and bruxism. Psychological factors and psychiatric disorders, mainly depression and anxiety disorders, have been suggested as an initiating factor as well as cause of prolongation of TMD (63-65). This relationship is suggested to be more pronounced in TMD of muscular origin (66). The prevalence of trismus in TMD patients is difficult to investigate due to the heterogenus nature of symptoms, clinical signs and classifications in the TMD group . Several studies suggest that TMD prevalence in the general population is high, with one study reporting a lifetime prevalence as high as 93% (61, 67). Treatment is based on the underlying disease and is often regarded in a multidisciplinary manner (68), often led by a dentist. Occlusive therapy and functional exercises is often a part of the treament, but also pharmacological treatment, including antidepressant medication, surgery and psychological treatment are treatment modalities used for TMD depending on its underlying cause (3).

3 PATIENT REPORTED OUTCOMES AND HRQL

Patient reported outcomes (PRO), sometimes called ”person reported outcomes”, is a collective term that covers a range of measurements with the common criterion that the information is reported by the patients themselves (69). The use of PRO instruments is increasing and in 2006, the Food and Drug Administration (FDA) presented a set of guidelines for the development and evaluation of PRO instruments.
PRO data may be collected via self-administered instruments or by interviews. However, the latter only qualifies as a PRO if the interviewer is investigating the patient's views, not where he or she makes a professional clinical assessment of the patient's condition. PROs are therefore a mean of gathering patient outcomes rather than clinical outcomes. Several different types of PRO instruments exists today;

- **Disease-specific PROs-** e.g. Asthma Quality of Life Questionnaire
- **Population-specific PROs**- e.g. Child Health and illness Profile
- **Dimension-specific PROs**- e.g. Becks Depression Inventory
- **Generic PROs-** e.g. Short Form-36 Health Survey

In clinical trials, a PRO instrument can be used to measure the impact of an intervention on one or more aspects of patients’ health status. PROs can also be used to measure more complex concepts such as HRQL, which is a broad and loosely defined term that can embrace several different aspects and dimensions of health. It is subjective and multidimensional, embracing physical and occupational functions, psychological and social factors and also somatic sensations. It can also include socioeconomic aspects of health, all with the central characteristic that the dimensions and aspects of HRQL can only be assesed by subjective measures (69). Hence, the term quality of life, QOL, refers more to the general well-being of individuals and includes not only health related aspects but also economical, social, environmental and other factors.

WHO defines QOL as (70); *” The individuals’ perceptions of their position in life, in the context of the cultural and value systems in which they live and in relation to their goals, expectations, standards and concerns ”.*

In recent years, HRQL measurements have become a valuable endpoint in many studies. This may be explained by the fact that many diseases today are incureable and are more

chronic in nature. Consequently, it is increasingly important to weight new therapies and treatment regimes against potential losses in HRQL, which is particularly emphasised in palliative care. Today, many patients, patient support-groups, etichal committees and founding bodies are interested in the way a new treatment, scientific project or medication will affect the patient's HRQL. Examples of instruments used in H&N cancer care and research are displayed in Table 3.

Instrument	Reference
EORTC QLQ Head and Neck35	Bjordal et al. (71)
Functional Assesment of Cancer Therapy Head and Neck Scale	List et al. (72)
Head and Neck Cancer Inventory	Funk et al. (73)
H&N Cancer Quality of Life Questionnaire	Terrell et al. (74)

Table 3; ***Examples of instruments often used in H&N cancer care and research***

3.1 Psychometrics

A commonly used method of measuring and assessing QOL is by using questionnaires, or *instruments*, designed to assess either a specific part of QOL, *specific* instruments, or to have a more general approach to QOL, *generic* instruments (69, 75).
Some scales and instruments are designed primarily to differentiate between people's QOL; *discriminative scales,* whereas others are designed to measure change in QOL; *evaluative scales.* In general, the discriminative scales need to have a good ability to produce stable and consistent measurements when the patients status is unaltered, i.e. have a high test-restest reliability. The evaluative scales often needs to be sensitive to change, i.e. have a good responsiveness. The instruments in current use vary greatly in design and scope, ranging from instruments containing one question to instruments using multiple questions and domains. When creating an instrument today, psychometric techniques are often employed, meaning that different methods, often based on mathematical approaches, are used to evaluate and find underlying, latent, dimensions (69, 76).

Other methods of developing an instrument include the clinimetric approach, which in contrast to the pshycometric approach, tries to measure mulitiple attributes with a single index and tries to find the most important attributes to be included in the index (76-78). It is important to highlight that the psychometric testing during the creation of a new instrument is to be considered an aid in the development and that all of the results must be interpreted in light of the underlying hypothesis and, when applied, the clinical setting. When constructing and validating an instrument or questionnaire today, using psychometric methods, the following areas is often adressed to further enhance the quality of the instrument (69, 79):

1. Content validity
2. Construct validity
3. Reliability
4. Sensitivity and responsiveness
5. Item reduction and missing items, floor/ceiling effects and scaling errors

1. Content validity

Is often considered a non psychometric phase and focuses on identifying and understanding the area that we want to examine so that all the relevant aspects are included and covered in the instrument. It also ensures that the irrelevant aspects are excluded. It is conceived through literature reviews, inputs from an expert panel and feedback from patients, including interviews, focus groups and pilot studies. How the questions are perceived by the patients is also evaluated.

2. Construct validity

In this part of the validation process, the theoretical constructs behind the items is tested, i.e. does the hypothesized domain appear to be an adequate model and does it measure the underlying factors. *Exploratory factor analysis* is an example of a common method that can be used to identify and confirm the domain structure and identifying items that reflect the same underlying factor. Exploratory factor analysis is based on correlations and correlation matrixes, and does not make use of any prior knowledge about the structures that we want to examine.

If you have an anticipated factor structure that you want to test, *confirmatory factor analysis* can be used. Eigenvalues and screeplots, both strongly associated with the factor analysis, are also often used when assesing and describing the construct validity. Testing the construct validity can involve several other steps and procedures.

2.1 Internal consistency examines to what extent the different items within a domain are correlated to each other and the unidimensional latent construct. It is often measured with Cronbachs alpha, a commonly used statistical method in medical research. A Cronbachs alpha coefficient > 0,7 is often regarded as sufficient, and the alpha coefficient will increase when the correlations between the items increase. Assesing the internal consistency is also often regarded as a part of the reliability evaluation.

2.2 Convergent validity can be analysed using Spearmans non-parametric correlation. By comparing a domain or rating to other domains or ratings that we assume are associated, we can assess the convergent validity. For example, we expect a correlation between domains measuring pain and depression and by showing that correlation we show that a postulated dimension correlates with another dimension that, in theory, should be interrelated to the tested domain.

2.3 Discriminant validty tests if, and how well, the items within a domain correlate to items within a different, not related, domain. Under normal circumstances, two different scales, assuming they are not interrelated, should not correlate strongly with each other. i.e displaying low correlations.

3. Reliability

Reliability tests if the instrument is reliable and stable, if the scales yields reproducible and consistent results, provided that the prerequisites is unaltered, and can be assesed with Cronbachs alpha. One aspect of reliability is the *repeatability,* that tests if the instrument is able to produce similar and reproducible results in repeated measurements. Test-retest, intraclass correlation coefficient and inter-rater reliabilty are other methods used to test reliability and repeatability.

4. Sensitivity and Responsiveness

Sensitivity is the instruments ability to detect differences between groups, for example between two treatment groups in a clinical trial. When assessing sensitivity, standardised response mean (SRM) can be used. The more sensitive an instrument, the smaller the number of patients is needed to detect a difference. *Responsiveness,* closely related to sensitivity, is the ability of scale to detect changes within patients, and can be measured using effect size (EF). It ensures that the instrument is sensitive enough to detect a significant change in the measured variables, within patients and over time.

5. Item reduction

Is not considered a ”stand alone” step or phase but is rather done based on validity, reliability and sensitivity assessments. Items with pronounced floor or ceiling effects, over 40%, or items with over 5% missing data, are eligible for elimination. Items with poor subscale internal consistency reliability (scaling errors) are also eligible for elimination.

The different stages in the validation process described here in a simplified way, are examples of a common method utilised to adress the validation procedure but other approaches to validation also exists. Other important steps to consider when designing and constructing instruments is which type of respons alternative to use, e.g. the Likert scale or the Visual Analog scale (VAS) and also deciding the appropriate recall period, which is often dependent on the characteristics of the phenomenon of interest.

4 AIMS OF THE THESIS

4.1 The overall aim

The overall aim of this thesis is to improve the knowledge about trismus, and improving the care of patients with trismus by investigating trismus incidence, developing and validating a trismus specific PRO instrument as well as measuring the impact of trismus on HRQL and mental health.

4.2 Specific aims

Study I

The aim was to retrospectively study the relationship over time between maximum interincisal opening (MIO) and radiation dose in specified H&N cancer diagnoses. We also studied the TNM classification, tumor size, tumor stage, and Karnofsky Performance Status Scale Index (KPSI) in different H&N cancer diagnoses in relation to MIO.

Study II

The aim of the study was to assess the incidence of trismus prospectively and to analyse the impact on HRQL in patients undergoing treatment for H&N cancer. By conducting this study, we aimed to increase the knowledge in an area of trismus research that is previously comparatively uncharted. Furthermore the study investigated the instrument the Gothenburg Trismus Questionnaire, according to its responsiveness to change over time in H&N cancer patients.

Study III

Due to the paucity of PRO questionnaires specifically addressing trismus, this study was initiated with the aim to develop and validate a comprehensive, trismus specific self-administered questionnaire, the Gothenburg Trismus Questionnaire.

Study IV

Studies that investigate the relationship between trismus, HRQL, and mental health are scarse. Therefore this study aimed to measure the impact of trismus on HRQL and mental health in patients with H&N cancer and TMD.

5 MATERIAL, PATIENTS AND METHODS

H&N malignancies in the VGR are referred to the Otorhinolaryngology clinic at Sahlgrenska University Hospital and to the weekly tumor board for assessment. The tumor board consists of representatives from several diciplines involved in the patients care, for example H&N surgeons, oncologists and pathologists. The main goal of the tumor board is to, in an efficient, qualitative and timesaving way, create an individual plan for each patient. The H&N cancer patients from VGR that participated in our studies, with the exception of the retrospective study, were asked to participate during the tumor boards. Patients with TMD were seen by a stomatognatic physiologist and included at the Department of Orofacial Pain, Gothenburg, Sweden. In study III and IV, patients were also recruited with the help and collaboration of the Department of Otorhinolaryngology, Karolinska University Hospital, Stockholm, Sweden and the Department of Oral and Maxillofacial Surgery, Faculty of Odontology, Gothenburg University. The age and gender matched controlgroup were recruited at the ENT clinic at Sahlgenska Univeristy Hospital/Mölndal.

Study	Patients n	Age mean years	Gender % Female/Male	Control group n	Methods and instruments
I	69	55	41/59		KPSI MIO
II	75	62	40/60		EORTC QLQ C30 EORTC QLQ H&N35 GTQ HADS MIO
III/IV Total TMD H&N	 129 51 78	 - 42 59	 - 78/22 47/53	 129	Psychometric procedure Validity & reliability EORTC GTQ HADS SF36 MIO

Table 4; ***Material and methods overview***

The individuals from the research group conducting the MIO measurements were trained and coordinated in using the same technique to minimize measurement errors. Following discussions with oral surgeons and stomatognatic physiologists we decided to exclude edentulous patients. This decision was based on difficulties obtaining reproducable measurements, but also on the fact that the lips interfered with the measurement procedure in the edentulous patient cohort. In table 4 the essential parts of the material and methods in the different studies are summarized.

5.1 Study I

During a five year period 69 out of 246 patients with primary or recurrent oral, oropharyngeal, nasopharyngeal, submandibular or parotid gland tumors were included. The included patients all had available records of MIO measurements before and after oncological treatment, whereas patients were excluded if there was no, or insufficient, data regarding MIO. All the measurements were conducted by the same researcher. Patients were analysed according to age, gender, radiation dose, uni- or bilateral radiation, tumor site and stage as well as with KPSI. A total of 98,8% had invasive squamous cell carcinomas and the most frequently occuring tumor was tonsillar cancer. MIO was measured over time (range: 3–48 months), with a cut-off criterion for trismus of 35 mm.

5.2 Study II

During 2007, all patients with primary H&N cancer referred to the department of Otorhinolaryngology at Sahlgrenska University Hospital, and presented at a weekly tumor board were invited to participate in the study. Patients with a tumor diagnosis not expected to develop trismus were excluded, i.e. cancer of the esophagus, skin, larynx and hypopharynx. During the study year, PRO questionnaires were filled out before start of oncological treatment and then at 3, 6 and 12 months following completion of the oncological treatment. The patients answered the HRQL questionnaires EORTC QLQ-C30, EORTC QLQ H&N35 and GTQ. The Hospital Anxiety and Depression Scale (HADS) was utilised in order to assess depression and anxiety. Prior to start of treatment, instruments were distributed to the patients. MIO was measured before and after oncological treatment at 3, 6 and 12 months and the criterion for trismus employed was MIO ≤35 mm.

5.3 Study III & IV

A total of 138 patients with TMD or H&N cancer with trismus (MIO ≤ 35 mm) were asked to participate in the study. Nine patients failed to return the instruments (response rate 93%), resulting in a final 129 participants. Of these, 51 patients had TMD and 78 patients had H&N cancer diagnosis. The TMD patients were younger (42 years) than the H&N cancer patients (59 years). The TMD cohort also had a larger proportion of females as well as a longer duration of trismus compared to the H&N cancer patients. Patients with poor language comprehension and cognition were considered non-eligible. Patients with H&N cancer and trismus were included at the Department of Oral and Maxillofacial Surgery, Faculty of Odontology, Gothenburg University and the Departments of Otorhinolaryngology at Sahlgrenska University Hospital, Gothenburg and Karolinska University Hospital, Stockholm, Sweden. Patients were identified and considered eligible for the study at oncology multidisciplinary meetings or at follow-up visits after oncological treatment when clinical signs of trismus (MIO ≤ 35 mm) were evident. Instruments were distributed to patients at the clinic and mailed back. The study also encompassed an age- (5-year interval) and gender-matched trismus free control group (n=129) from the department of Otorhinolaryngology at Sahlgrenska University Hospital, Mölndal, Sweden. The patients in the control group answered the instruments in clinic and demonstrated no subjective or objective evidence of trismus. The GTQ was developed in two stages. Firstly, GTQ items were developed by input from an expert panel, literature reviews and patient interviews. Secondly, the psychometric properties of the GTQ were evaluated, including validity and reliability (80). The references for validation used were SF-36, EORTC QLQ-C30 and EORTC QLQ-H&N35. The draft version was tested in a pilot study (n=18), where participants were asked, for instance, how items were perceived and whether certain relevant questions were lacking or difficult to understand (80). In study IV the participants responded to the following PRO instruments; GTQ, SF-36 and HADS.

5.4 Patient Reported Outcomes and other instruments

Short-Form 36 Health Survey (SF-36)

The SF-36 is a widely used generic instrument for measuring HRQL and the Swedish version has well-documented reliability and validity (81). The instrument contains 36 items in eight domains: Physical Functioning (PF, 10 items), Role limitations due to Physical problems (RP, four items), Bodily Pain (BP, two items), General Health (GH, five items), Vitality (VT, four items), Social Functioning (SF, two items), Role limitations due to Emotional problems (RE, three items), Mental Health (MH, five items) with a recall period of four weeks and one question concerning perceived health during the last year. A score for each domain ranging from 0 (worst HRQL) to 100 (best HRQL) is calculated using a standardised scoring system (69, 81).

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire QLQ-C30 and QLQ-H&N35

The EORTC QLQ-C30 is a cancer-specific questionnaire that evaluates HRQL in cancer patients (82). The questionnaire consists of five functional scales, a global quality of life scale, three symptom scales and six single items, totalling 30 questions that describes the patients' symptoms and functional level during the prior week. The EORTC QLQ-C30 can be used with different "add-on" modules, addressing a specific cancer type. In order to assess patients with H&N cancer, a complementary 35-item module, the EORTC QLQ-H&N35, may be used (71). Calculated scale scores range from 0 to 100. On the functional scales and global quality of life scales, a score of 100 represents maximum functioning, whereas on the symptom scales and single items, a score of 100 indicates the highest possible symptom burden. A change in score over time of >10 points could be interpreted as clinically significant (83).

Hospital Anxiety and Depression Scale (HADS)

The HADS is an instrument frequently used as a screening tool to detect mood disorders in physically ill patients (84, 85). The HAD scale consists of 14 items on a four-point response scale ranging from 0 to 3. Seven items for depression and 7 items for anxiety with a score range from 0 to 21. For each factor (anxiety or depression), the results are interpreted as follows: < 8 points indicates within normal range, 8-10 points indicates possible anxiety or depression and >10 points indicates probable anxiety or depression.

Gothenburg Trismus Questionnaire (GTQ)

The Gothenburg Trismus Questionnaire is a newly developed symptom-specific trismus questionnaire, designed to serve as a screening tool and endpoint in intervention and jaw physiotherapy/rehabilitation studies in trismus patients (80). The GTQ was well accepted by the patients, with satisfactory compliance and low rates of missing items. It has demonstrated good psychometric properties (validity and reliability) after item reduction (80). The GTQ contains 21 items of which 13 items are divided into the three domains; Jaw related problems (6 items), Eating limitation (4 items) and Muscular tension (3 items). The remaining 8 items are retained as single items. The domains and single items range from 0-100, where 100 indicates maximum symptom burden and 0 equates to no symptoms. The questionnaire has a one-week recall period for the three domains.

Adult Comorbidity Evaluation 27 (ACE 27)

The Adult Comorbidity Evaluation 27 is a validated 27 item, chart derived, scale originating from the Kaplan-Feinsteins Comorbidity Index that evaluates the patients comorbidities. The ACE-27 was developed by Piccirillo and colleagues at the Barnes-Jewish hospital in Washington. The ACE-27 grades comorbid conditions into one of three levels of severity according to the individual organ decompensation and prognostic impact (34). The prognostic value of comorbidity measured by the ACE-27 has been shown in previous studies (86, 87).

Karnofsky Performance Status Scale Index (KPSI)

The Karnofsky Performance Status Scale Index measure the patient's functional status and ability to carry out activities of daily living. The score ranges from 100 to 0, where 100 is "perfect" health and 0 is death. The assessment is made by a healthcare professional. The KPSI was one of the first instruments that broadend the assessment of the patient beyond the clinical examination. The system is named after Dr David Karnofsky and the original purpose was to allow physicians to evaluate a patient's ability to survive chemotherapy for cancer (88).

6 STATISTICS

In all studies, comparison between groups for sociodemographic and clinical characteristics used the following tests; Fisher's Exact test for dichotomous variables; the Mantel–Haenszel Chi Square Exact test for ordered categorical variables and the Mann–Whitney U-test for continuous variables. All tests were two-tailed and the significance level was set to 5% throughout.

In study I Wilcoxon's signed rank test was used to test changes in MIO within groups.

In study II, prediction of change in MIO, normally transformed, was also done by using a stepwise regression analysis. All significant variables in the first analyses were included as possible predictors in the stepwise regression analysis.

In study III we used confirmatory and exploratory factor analysis. The scoring of the GTQ was carried out by calculating a mean for each domain, which is then transformed to a scale ranging between 0 and 100, where a higher score indicates greater perceived dysfunction due to trismus. Regarding missing items in a domain, the non-missing items within that given domain were rescaled to generate a value comparable to subjects responding to all items. If more than 50% of the items within the domain were missing, the domain score was set as missing. Tests for comparing GTQ scores for patients and controls were performed using the Mann–Whitney U-test.

In study IV descriptive statistics with mean values and 95% confidence interval (CI) were calculated according to standard procedures. Differences between-group analyses were carried out using the Mann-Whitney U test.

7 ETICS

All studies were approved by the Regional Ethical Review Board at Gothenburg University and performed in accordance with the Declaration of Helsinki.

The research group took great efforts to include the patients in the most etihcal and lenient way possible, always bearing in mind the exposed situation the patients were in.

8 MAIN RESULTS

8.1 Study I

A total of 42% of patients had post-treatment trismus (MIO ≤35 mm), with the highest incidence in patients with parotid gland tumors. The patients with trismus also had significantly larger tumors, higher total radiation dose and poorer physical function before the start of the treatment according to the KPSI. The mean MIO values at baseline were significantly different between patients with trismus (mean: 43mm) and patients without trismus (mean: 51mm). No statistically significant differences were found between the included and exluded patients.

8.2 Study II

The incidence of trismus was 9% pre-treatment and 28% at the one year follow-up post-treatment. The highest incidence, 38%, was found 6 months post-treatment. Patients with tumors of the tonsils were most prone to develop trismus. The radiation therapy offered was EBRT, IRT or a combination of both. Sixty-six patients (88%) received radiation therapy in combination with chemotherapy or surgery. Out of these, 71% received a total dosage of > 50 Gy and 29% received < 50 Gy. The radiation dosage ranged from 40.8-72 Gy. Forty-one per cent (41%) of the patients had IRT in addition to ERT with a dosage ranging from 2-25 Gy. Patients with trismus reported greater HRQL impairments with regard to the GTQ domains; Mouth Opening ($p < 0.001$), Jaw Related Problems ($p < 0.05$), Eating Limitations ($p < 0.05$) and Muscular Tension ($p < 0.001$) 6 months post-treatment. According to the EORTC QLQ H&N35 scores the patients with trismus reported significantly more problems with dry mouth, swallowing and pain. Statistically significant differences were found where the non-eligible patients had a higher co-morbidity, lower Karnfosky index and were more often living alone in comparison with the study group. The GTQ has previously shown good psychometric qualities and the present study documented its responsiveness over time.

8.3 Study III

The pilot study confirmed the relevance of the trismus specific symtom items of the GTQ and no patients found the items in the pilot version upsetting or difficult to understand. No items were omitted due to ceiling effects or missing data, but 18 items were exluded due to floor effects. The convergent validity was good, with all items demonstrating a correlation of ≥ 0,4 with their relevant domain. After item reduction, three domains with an eigenvalue > 1 were identified, scree plot analysis also supported three domains. Two items were omitted since they did not load clearly enough in one domain. All three domains showed good internal concistency, with good test-retest reliability and Chronbahs alpha value > 0,70. All items in the 21-item version GTQ showed good variability. Convergent and discriminant validity was assessed by comparing the GTQ domains with the EORTC and SF-36. The known-group validity showed that the GTQ could significantly discriminate between trismus and non-trismus patients, i.e. cancer/TMD patients and patients from the control group.

8.4 Study IV

Trismus patients reported significantly higher dysfunction in all GTQ domains and more facial pain compared to the control group. Trismus patients also reported a significant impact on all items due to limitations in opening the mouth. The greatest dysfunction was found for TMD patients regarding Jaw Related Problems. When comparing the trismus subgroups, the TMD patients reported significantly more Jaw Related Problems and Muscular Tension than the cancer group. They also experienced more facial pain in all aspects, i.e. *right now*, *worst* and *average pain*. TMD patients also reported more mouth opening limitations, whilst there were no significant differences between TMD *vs.* H&N cancer patients regarding the impact on social, leisure, family activities or work. The trismus groups also scored significantly lower, thereby indicating a lower HRQL, on all SF-36 domains except General Health, compared to the control group. According to the HADS, a greater proportion of trismus patients displayed decreased mental health compared to the control group. The greatest differences were seen regarding depression, where a greater number of both TMD and H&N cancer patients were classified as having a possible mood disorder. The TMD patients also had a larger proportion of anxiety disorders, whereas the H&N cancer patients did not differ from the control group in this aspect.

9 DISCUSSION

This thesis adresses trismus, its incidence, effects on HRQL and mental health as well as the development and validation of a trismus specific PRO instrument, the GTQ.
Despite the fact that trismus can affect many important areas such as food intake, social interaction, chewing, speech, impaired oral hygiene and also HRQL and mental health it has previously been given relatively little attention in the literature. This thesis, and the studies its based on, has tried to fill some of the knowledge gaps in the field of trismus, previously not fully addressed or researched, with the end goal to help patients with trismus and to aid caretakers who work with trismuspatients to gain a more holistic view of these patients and to deliver a more trismusoriented care. The developement of the GTQ is a part of this aim, supplying the caretakers and researchers with a tool to follow rehabilitation and interventions. While the risk of developing trismus might not be the first thing a patient with a newly diagnosed, and possibly life threatening, H&N cancer worries about, it might affect the patient in a radical way a long time after he or she has been declared free from cancer. Therefore, it is important that we adress the potential trismus issue early and allocate the adequate resources and knowledge to, if possible, prevent the development of trismus. If that is not possible, it is of importance that we manage and treat trismus as soon as it is discovered, bearing in mind that trismus affects not only important basic physiologic functions but also affects HRQL and mental health. Now we also know more about what factors predispone for trismus and can incorporate that knowledge in our clinical work to anticipate the patients individual need for rehabilitation and support. To manage this in an effective and professional way, we need to make the issue of trismus a natural part of the management of H&N cancer patients and integrate trismus in our present structures in a natural way. One example could be to institute a registered nurse and a specialized reception focused on trismus and other sideeffects caused by the oncological treatment. Its main tasks should be prevention, screening, managing care diaries (89), rehabilitation/physiotherapy, follow ups, regular tracking of MIO and also psychological care and support. All this in close collaboration with other involved specialists like physicians, dietitians and pshycologists.
The results from the different studies in this thesis show that trismus is a common complication after treatment of H&N cancer and that it affects HRQL and mental health in a negative way.

9.1 Discussion areas of specific interest

IMRT - the importance of delivering the radiation to the right place

One interesting advance in the field of radiation therapy is the Intensity Modulated Radio Therapy, IMRT. IMRT is an high-precision radiotherapy technique that use linear accelerators to deliver the radiation dose to a tumor or to a specific area within the tumor (90). IMRT allows for the radiation dose to conform more precisely to the three-dimensional (3-D) shape of the tumor by modulating the intensity of the radiation beam in multiple small volumes (91). IMRT also allows higher radiation doses to be focused to regions within the tumor while minimizing the dose to adjacent structures. IMRT is planned by using 3-D computed tomography (CT) or magnetic resonance images (MRI) of the patient. IMRT can also have a positive effect on other radiation induced sequelae such as dysphagia and xerostomia (92). Several studies have found a relationship between the developement of trismus and the radiation dose delivered to the patient, and the use of IMRT could possibly be a way to decrease the risk of trismus by reducing the radiation dose delivered to sensitive tissues surrounding the tumor (10, 93-95). Investigating the different structures involved and their individual roles in the development of trismus is also an important and interesting reserach field. A study by Goldstein et al. suggested that the pterogyiod muscle is of extra importance in the developement of trismus after radiation therapy (13). Another study by van der Molen stated that the two significant predictors of the occurrence of trismus 10 weeks post-treatment were the radiation doses to the masseter and pterygoid muscles (95). It is important that the field of trismus and radiation therapy is explored further and more knowledege is gained, maybe focusing on some of the areas mentioned above.

MIO and the trismus definition– a valuable concept in need of refinement and evolvement

Historically the lack of a uniform criteria for trismus has been a disadvantage when researching trismus. Now many researchers use the criteria suggested by Djikstra et al. (11) and by doing so facilitating trismus research. However, potential drawbacks with a fixed and uniformed trismus definition for all patients must be adressed and evaluated. For example, is it possible to strenghten the MIO/trismus concept by correlating it to body size, total length, mandible length or perhaps gender (96)?

Edentulous patients – a challenging group

In our studies we have choosen not to include edentulous patients, but we recognise that this might be a controversial decision. We have based our decision on the view that edentulous patients are percived as more difficult to get accurate and reproducable MIO measurements on, and retrieving accurate MIO measurements is one of the fundamental cornerstones in our studies. This decision was made after extensive discussions with members of our research team, all senior clinical experts in the area.
Nevertheless, other researchers have included edentulous patients in their work, with different approaches, and a potential benefit from this could be that they do not exclude any patients and by doing so the actual clinical situation might be reflected in a more accurate way. We ackowledge that there is no ”right or wrong” but rather advantages and disadvantages that have to be weighted against each other for the optimal result in each specific situation and for each specific purpose.

9.2 Study specific discussions

Study I; Trismus in head and neck cancer patients in Sweden: Incidence and risk factors

The results showed that trismus is a common sequelae efter H&N cancer treatment. In 62% of the patients (18/29), trismus was identified early, i.e. 3–9 months after treatment and was a long-term problem in many of the patients. The patient group that received higher external beam radiation dosages (i.e. >50 Gy) presented with a significantly higher incidence of trismus. This finding is in accordance with previous studies that also have used 50 Gray as a cut off and in which doses of >50 Gy to the TMJ and pterygoid muscles have been suggested to induce trismus, although controversy exists regarding a dose-dependent effect on trismus as the amount of radiation increases (15, 33, 97, 98). One study by Teugh et al. found a 24% increased risk for developing trismus for every 10 Gray of radiation delivered (33). The developement of trismus may also have been affected by other factors. For example, we found significantly poorer physical function prior to treatment according to the KPSI in the trismus patients treated with high EBRT dosages. This was an interesting finding indicating that intervention and rehabilitation optimizing the patients’ physical function, co-morbidity,

and nutritional support before, during, and after treatment might reduce trismus incidence in H&N cancer patients. The retrospective nature of this study, the small sample and the fact that MIO was not measured at the same time points in all patients are limiting factors in the interpretation of the results. The small sample, however, is strengthened because it included baseline data and also because we were able to obtain the exact radiation dose each patient received in the data collected.

Study II; The incidence of trismus and long-term impact on health-related quality of life in patients with head and neck cancer

Studies that adress trismus incidence are, to the best of our knowledge, scarce, and that despite the fact that a deeper knowledge about trismus incidence is an important part of information when trying to forecast trismus in the clinical setting. The highest incidence (38%) of trismus in this prospective study was detected at six-month post-treatment. At the 12-month follow-up there was a decrease in the incidence (28%) that can partially be explained by the fact that some patients improved but also because several patients died during the first year of follow-up. The patients with cancer of the tonsils were most prone to develop trismus in this study and this group also constituted the largest diagnosis in our material. In larger materials there is a possibility that other tumor locations also are at high risk of developing trismus. Other studies have suggested that parotid gland tumors as a group are prone to develop restricted mouth opening (2). The GTQ showed that the trismus patients reported more problems with pain than those without trismus. Pain is often associated with depression, anxiety and insomnia (99). The pain itself, as well as the associated symptoms, affects the patient ’s daily life activities and result in impaired social and physical function which negatively affects QOL. In the present study the patients with H&N cancer reported problems with pain both pre-and post-treatment, especially at the three-month follow-up occasion. The pain, as well as the cancer diagnosis, might affect the prevalence of anxiety and depression in the study population. The three-month follow-up occasion, where a symptom peak for all patients was found, corresponded in time to about six months after being diagnosed with cancer. We chose to evaluate the patients in accordance to when they finished their oncological treatment in order to get consistency in the results and a possibility to compare with different treatment schedules. The study also showed that about one-

third of the patients suffered from probable or possible anxiety and one-fifth of the patients from probable or possible depression at the time of diagnosis. At the three month follow-up there were still one-fifth of the patients that filled the criteria for probable or possible depression or anxiety. These figures correspond well to earlier research on H&N cancer and mental distress using the HADS (100). The patients in this study suffered from impaired HRQL both before and after receiving their oncological treatment. The observed HRQL and trismus specific impairments with regard to mouth opening and jaw-related problems, problems with dry mouth and swallowing, eating limitations, muscular tension and pain post-treatment are in accordance with the incidence of trismus, and congruent with results from other studies (101, 102). According to the GTQ, trismus not only affects eating and dental hygiene, because of the mechanical restricted mouth opening, but also social and family life, which is important knowledge when treating patients with trismus. The study also showed that the GTQ is responsive to change over time, a central part of the validity of an instrument.
A possible study limitation is the fact that in order to analyse the risk factors for developing trismus, a larger sample size is needed. Answering the questionnaires requires effort from patients and, as such, there is a risk that patients, with high comorbidity as well as morbidity due to the tumor, do not have the strength to respond and therefore creating a bias.

Study III; Development and validation of the Gothenburg Trismus Questionnaire (GTQ)

As mentioned earlier, there are few prospective studies regarding the incidence of trismus and the patients experience of trismus in daily life activities, but PRO instruments specifically adressing trismus are, to our knowledge, even rarer. Due to this paucity the present study was initiated with the aim to develop and validate a comprehensive trismus specific self-administered questionnaire, the GTQ. The present study describes the development and validation of such an instrument. The items of the GTQ instrument were developed based on a literature review of published trismus studies, non-validated trismus-related questions and the experiences of an expert panel. This inital step in the developement procedure is very important, beeing the ”foundation” on which the other validation steps are based on. None of the 18 patients in the pilot

study said that they were missing any questions when specifically asked, indicating that the content validity phase succeeded in isolating the essential issues. The principal component analysis then identified three domains, Jaw Related Problems, Eating Limitations, and Muscular Tension. These domains represent aspects that are known to be of great difficulty to trismus patients and are of high clinical relevance in TMD patients as well as in H&N cancer patients. Evaluation of construct validity demonstrated low to moderate correlations with most of the domains in the EORTC and SF-36. This was as expected as in some cases including trismus, disease-specific instruments are needed to assess clinically important changes in health status that are too specific to be detected using generic health status instruments. Compared to TMD patients, the H&N cancer patients reported significantly less problems in the domains Jaw Related Problems and Muscular Tension. These results may be related to the fact that the entire mastication apparatus can be involved in TMD patients, i.e. both the mastication muscles and the TMJ (3). The condition also involves inflammation and increased muscular tension and pain. H&N cancer patients, on the other hand, primarily suffer from a radiation-induced muscular fibrosis and a mechanical effect of the jaw opening capacity. Other possible explanations to these results may involve that the TMD patients have experienced symptoms of longer duration, were somewhat younger and included a larger proportion of females. In parallel with the increased importance of PROs, the methodology for developing PROs has evolved. To cover everything that is relevant and to ensure that items are comprehensive the patient input is today more emphasized, and strongly recommended already in the exploratory phase when generating items. In this initial validation, 18 items were omitted due to substantial floor effects. This might be explained by the fact that item generation was based on clinical experience and empirical evidence only, i.e. no patient interviews were carried out prior to the exploratory item generation. Furthermore, some items may have produced unacceptable floor effects due to how they were phrased. For example, a patient may have a cramping feeling concentrated to the jaw only and could therefore have underreported on ‘‘cramping feelings in the face or jaw’’. This item was omitted due to a pronounced floor effect, but may still be clinically relevant if presented as two separate items. This is also relevant for two other items, ‘‘fatigue/stiffness in your jaw’’ and ‘‘problems opening your mouth wide or taking a big bite’’. A key issue when developing PROs is to select the optimal recall period. The most appropriate recall period is

dependent on the characteristics of the phenomenon of interest. Recall always asks patients to rely on their memory to aggregate and summarize their experience, which may introduce a variety of inaccuracies and biases that can affect the data, and studies have shown that shorter recall periods are more optimal when symptoms are fluctuating. Therefore, in forthcoming versions of the GTQ, the recall period for severity items as well as for the pain and MIO related questions, will be referred to the last week (or now), instead of the last month as were the case for some questions in the first GTQ version. A limitation of the study is the cross-sectional design, preventing us from investigating the GTQ's ability to detect responsiveness to change over time, but this is adressed in Study II. Another limitation is the above-mentioned lack of patient input in the exploratory phase of the item generation phase. While many validation studies completely lack patient input, we performed patient interviews during the confirmatory phase.

The GTQ – a continous work

Most research groups and individuals that work with the developement of instruments recognize that a "final edition" of their instrument seldom exists, but rather continuously work to improve their instruments. The GTQ is no exception and future improvements and refinements of the GTQ might include the following steps and methods:

- Focusgroups, with the aim to see if the content validity of the instrument could be further improved
- Structured interviews, also with the aim to further improve the content validity
- Shorter recall periods in some items, for example in pain related items
- Improving the formulation on some of the questions further, and by doing so decreasing the risk of misinterpretation

Another interesting approach would be to see if clinimetric methods could be utilised to further improve the GTQ, but combining clinimetrical and psychometrical methods is still not uncomplicated (76-78).

Study IV; The impact of trismus on Health-Related Quality of Life and mental health

We know that the incidence of trismus is high after H&N oncology treatment and to the best of our knowledge the incidence of TMD in Sweden is unknown. However, in the last two decades an increase in the prevalence of TMD symptoms has been observed. Despite this, the effect of trismus symptomatology on HRQL and mental health is largely unexplored. As could be expected, trismus patients in the study reported higher levels on all symptom domains and decreased HRQL and mental health compared to the control group. Several components of the trismus symptomatology can explain these findings, but manifestations of the underlying disease itself (TMD/H&N cancer) can also contribute to the results. The trismus group scored lower on all SF-36 domains, except for the General Health (GH) domain, compared to the control group, thereby indicating a lower HRQL. This may be explained by the general characteristics of the questions in the GH domain, making it too blunt to distinguish between these patient groups. The HADS scores indicate that the trismus patients experience more problems with anxiety and depression than the control group. The TMD group had the largest proportion of patients with anxiety and depression. Several studies have previously suggested that mood disorders can play a role in the TMD symptomatology and that TMD is often co-existent with depression and anxiety (3, 63, 65, 99). The relationship between cancer, pain and mood disorder is complex. Mood disorders may be a response to pain, but pain itself can also constitute a significant physical and psychological stressor that may induce or aggravate psychological distress (65, 99). When comparing the trismus subgroups, the TMD patients reported more severe trismus symptoms compared to the cancer patients, including jaw related problems, muscular tension and pain. One explanation for this could be due to the TMD group being more heterogeneous including patients with arthritis, disc problems, muscular problems, trauma and luxation, conditions often involving pain and inflammation (3). The longer duration of trismus in the TMD group might also affect the results and the fact that TMD patients experienced more pain than trismus cancer patients was also demonstrated by the SF-36 Bodily Pain scores. The only other difference between the trismus groups regarding HRQL was found for the Role limitations due to Physical problems domain, where the H&N cancer patients reported significantly more problems than the TMD group. Effects of the cancer disease itself, as well as long lasting side effects of treatment regimens, such as

nutritional aspects and speech impairment, may affect the patient in a more radical and generalised way than TMD. A limitation of this study is the cross-sectional design. Another possible limitation includes the clinical heterogeneity between the H&N cancer and TMD patients within the trismus group, and also the clinical heterogeneity within the TMD group itself.

Patients with TMD - a heterogenous group

One of the potential difficulties when researching patients with TMD is the heterogenous nature of the TMD group. The following citation is taken from Daniele Manfredinis book "Current Concepts on Temporomandibular Disorders" (2010) and summarizes some of the challenges researchers faces within this field:

-*" This book will probably be one of the last in which the term "temporomandibular disorders" is used, since terminological specifications will hopefully be introduced in the near future, as soon there is an improvement in knowledge about the pathophysiology of these disorders. Indeed, the absence of a validated pathophysiological model for many TMD symtoms has led to the adaption of this generic term to group together signs and symptoms with different etiopathogenesis and more importantly, to adopt a symptomatic and common approach towards the management of diseases of the temporomandibular joint and muscles."*

Historically the field of TMD has been characterized by a paradigmatic contrast between guidelines provided by the scientific community and the clinical practitioners. We have tried to bear the above in mind when conducting and constructing our studies but recognises the potential difficulties this might cause.

10 CONCLUSION AND IMPLEMENTATION

Trismus is a common complication after H&N cancer therapy and affects HRQL and mental health in a negative way.
The GTQ is a trismus specific and validated PRO instrument that offers clinicians as well as researchers an effective tool when caring for trismus patients and when researching trismus.
More research is needed to further address trismus prevention, rehabilitation and training.

Our main findings demonstrate that trismus is a common sequela after H&N cancer treatment and has a significantly negative impact on HRQL and mental health in both H&N cancer and TMD patients. The implications are that patients with trismus should be approached in a holistic way with respect for the underlying cause, treating not only the physical aspects of trismus but also addressing the patients' mental health. The fact that trismus is a common and potentially grave sequela also puts an extra responsibility on the health care staff and organizations working with H&N cancer patients to incorporate a framework that facilitates and improves the quality of the trimsus care. As stated earlier, trismus can be the result of several different etiologies, with their own unique features, making future trismus research not only challenging but also imperative if we want to be able to provide the patients with targeted and personalized trismus therapy.

10.1 Future perspectives

Our research has hopefully been able to make the field of trismus a little bit more illuminated, however much work remains, especially in the important areas of trismus treatment, rehabilitation and prevention. Complementary and larger studies are also needed in order to predict which patients are predisposed to develop trismus. Historically, function is often already reduced before starting the rehabilitation, but can we prevent the developement of trismus by intervening even before, and during, the oncology treatment (103)? This research field is very interesting and needed, but also challenging, demanding reflection and afterthought when designing studies and instruments for evaluation (103).

Can we, guided by genetic screening and with structured training and nutritional programs, together with methods such as IMRT, pentoxifylline treatment and perhaps even HBO treatment, prevent the developement of trismus in other, possibly additive, ways? As previously mentioned, some evidence for this exists, but more research is needed. Trismus can in some cases be a truly shattering condition and scientific advances in this important area can be of great significance to patients, relatives and also to caregivers involved. Therefore it is important to continue the trismus research with no loss of momentum and with the allocation of adequate resources.

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13 SUMMARY IN SWEDISH – SVENSK SAMMANFATTNING

Trismus, svårigheter att öppna munnen, är en vanlig och besvärande biverkan till cancer i huvud-hals (H&N) regionen, antingen som en direkt effekt av tumörens påverkan på exempelvis muskler och nerver eller som en biverkan av tumörbehandling, framför allt strålbehandling. H&N cancer är ett samlingsnamn som inkluderar flera olika tumörtyper i H&N regionen, exempelvis tumörer i halsmandlarna, tungan, spottkörtlarna samt tumörer i svalget. Cancer i H&N området utgör ca 3% av all cancer i Sverige men är en viktig grupp, inte minst på grund av de allvarliga biverkningar som behandlingen kan ge upphov till. Trismus kan även uppkomma vid andra sjukdomar i käkregionen, såsom vid temporomandibulär dysfunktion (TMD), ett tillstånd som karaktäriseras av smärta och nedsatt funktion i ansikte och käkar. Det har tidigare saknats en tydlig och allmängiltlig definition för trismus och historiskt har flera olika mått på gapförmåga använts. Sedan 2005 är trismus ofta definierat som en gapförmåga ≤ 35mm, ett mått som nu blivit allt mer accepterat. Trismus kan påverka flera viktiga och grundläggande mänskliga funktioner såsom tal, födointag, munhygien och social interaktion. Riskfaktorer för att utveckla trismus vid behandling av H&N cancer är framför allt relaterade till olika karakteristika hos strålbehandlingen såsom stråldos och strålfält, men även andra faktorer som tumörtyp och tumörstorlek samt patientens allmänna hälsotillstånd har betydelse. Trots att trismus är en potentiellt allvarlig biverkan vid H&N cancer, och i stor utsträckning kan påverka patienternas hälsorelaterade livskvalitet (HRQL) negativt, finns det förhållandevis lite skrivet i litteraturen om trismus och dess påverkan på HRQL. Det övergripande syftet med detta arbete har varit att undersöka hur trismus påverkar livskvaliteten, kartlägga förekomsten av trismus bland patienter som behandlats för H&N cancer samt förbättra omhändertagandet av patienter med trismus. Som ett led i detta arbete har forskningsgruppen även utvecklat och validerat ett trismusspecifikt frågeformulär, the Gothenburg Trismus Questionnaire (GTQ), som kan användas både i vården av patienter med trismus och inom trismusforskningen.

Metod och Resultat:

Avhandlingen första studie är en retrospektiv undersökning av patienter som genomgått behandling mot H&N cancer. Studien visar att trismus är en vanlig komplikation vid strålbehandling där så många som 42% av patienterna hade trismus efter avslutad

cancerbehandling. Resultaten visar även att patienter som fått strålbehandling med höga stråldoser eller som hade nedsatt allmäntillstånd före behandlingsstart hade ökad risk att utveckla trismus.
I nästa studie mättes gapförmåga, patienternas trismussymtom samt livskvalitet före och upp till ett år efter avslutad cancerbehandling. Resultaten visar att trismus är vanligast 6 månader efter behandling, då 38% av patienterna uppvisade en gapförmåga på mindre än 36 mm. Riskfaktorer för att utveckla trismus var bl.a. en stor tumör och hög stråldos till tumören. Patienter med trismus rapporterade även ökade smärtproblem, sämre livskvalitet och en negativ påverkan på det sociala livet och familjelivet jämfört med patienter utan trismus. Biverkningar av strålbehandling såsom sväljsvårigheter, torr mun och smärta var vanligare hos trismuspatienterna jämfört med H&N cancerpatienter utan trismus.
I studie III och IV har ett trismus specifikt frågeformulär, GTQ, utvecklats och trismus påverkan på HRQL undersökts. Formuläret är framtaget för att användas i vård och rehabilitering av trismuspatienter, men också inom trismus och cancerforskning. Studierna visar att GTQ är lättanvänt samt har goda psykometriska egenskaper.
I Studie IV undersöktes hur trismus påverkar HRQL och den mentala hälsan hos patienter med H&N cancer och TMD. Totalt deltog 129 trismuspatienter, samt en ålders och könsmatchad kontrollgrupp utan trismus. Resultaten indikerar att trismus påverkar HRQL och den mentala hälsan negativt. Studien stödjer även tidigare resultat att GTQ har en klar klinisk relevans och med fördel kan användas i rehabiliterings- och interventionsforskning.

Sammanfattningsvis visar avhandlingen att trismus är en vanlig och besvärande biverkan vid H&N cancer behandling med en negativ påverkan på mental hälsa och HRQL. Detta understryker behovet av att patienter med trismus tas om hand med ett holistiskt synsätt där fokus läggs inte bara på patientens fysiska hälsa utan även på psykologiska aspekter av patientens hälsotillstånd. GTQ kan med fördel användas i vården av trismuspatienter och i trismusforskning.

14 APPENDIX

GTQ item 1-21

Gothenburg Trismus Questionnaire (GTQ)
Please read each question carefully and answer by marking the alternative that best applies to you. Answer all questions and mark only one alternative for each question.

During the **last week,** have you had:

		Not at all	Mild	Moderate	Severe	Very severe
1.	Fatigue/ stiffness in your jaw	☐1	☐2	☐3	☐4	☐5
2.	Aches or pain in your face and jaw	☐1	☐2	☐3	☐4	☐5
3.	Pain moving your jaw (opening mouth/ chewing)	☐1	☐2	☐3	☐4	☐5
4.	Problems when opening your mouth wide or taking a big bite	☐1	☐2	☐3	☐4	☐5
5.	Pain or soreness in your jaw muscles	☐1	☐2	☐3	☐4	☐5
6.	Problem yawning	☐1	☐2	☐3	☐4	☐5
7.	Noises from your jaw	☐1	☐2	☐3	☐4	☐5

Due to your jaw problems, to what extend are you limited or incapable to:

(If you do not have any jaw problems, please go to question 12)

		Not at all	Mild	Moderate	Severe	Very severe
8.	Eat solid food	☐1	☐2	☐3	☐4	☐5
9.	Put food in mouth	☐1	☐2	☐3	☐4	☐5
10.	Eat soft food	☐1	☐2	☐3	☐4	☐5
11.	Bite off	☐1	☐2	☐3	☐4	☐5

Do you usually:

		Not at all	Seldom	Sometimes	Often	Very often
12.	Clench your teeth	☐1	☐2	☐3	☐4	☐5
13.	Press with your tongue	☐1	☐2	☐3	☐4	☐5

14. How much facial pain do you have **right now**?

None	Very mild	Mild	Moderate	Severe	Very severe	Unbearable
☐1	☐2	☐3	☐4	☐5	☐6	☐7

15. How strong was the worst pain you have had during the **last month**?

None	Very mild	Mild	Moderate	Severe	Very severe	Unbearable
☐1	☐2	☐3	☐4	☐5	☐6	☐7

16. On average, how strong has your pain been during the **last month**?

None	Very mild	Mild	Moderate	Severe	Very severe	Unbearable
☐1	☐2	☐3	☐4	☐5	☐6	☐7

17. How much has your facial pain interfered with your social, leisure and family activities during the **last month**?

Not at all	A little	Moderately	Quite a bit	Very much	Have not had any facial pain
☐1	☐2	☐3	☐4	☐5	☐0

18. How much has your facial pain affected your ability to work (including both gainful employment and household duties) during the **last month**?

Not at all	A little	Moderately	Quite a bit	Very much	Have not had any facial pain
☐1	☐2	☐3	☐4	☐5	☐0

19. How limited are you in your ability to open your mouth **right now**?

Not at all	**A little**	**Moderately**	**Quite a bit**	**Very**
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

20. How much has your limitation to open your mouth interfered with your social, leisure and family activities during the **last month**?

Not at all	**A little**	**Moderately**	**Quite a bit**	**Very much**	**Have not been limited to open mouth**
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 0

21. How much has your limitation to open your mouth changed your ability to work (including both gainful employment and household duties) during the **last month**?

Not at all	**A little**	**Moderately**	**Quite a bit**	**Very much**	**Have not been limited to open mouth**
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 0

15 ORIGINAL PAPERS I-IV