

Treating radiation-induced trismus in head and neck cancer

Exercise intervention and risk structures

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Cover illustration: The masseter muscle.
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Abstract

The overall aim of this thesis was to investigate the incidence of trismus in head and neck cancer (HNC) and to evaluate the efficacy of a structured exercise program with jaw mobilising devices in patients with radiation-induced trismus. Another objective was to investigate anatomic risk structures related to the development of radiation-induced trismus. Patients in this thesis were treated with radiotherapy alone or in combination with surgery or chemotherapy at the Sahlgrenska University Hospital, Gothenburg, Sweden.

Paper I was a prospective study addressing trismus incidence, trismus-related symptoms, and health related quality of life (HRQL). Seventy-five HNC patients were followed before and at 3, 6, and 12 months after oncological treatment. Paper II was a prospective study with 100 HNC patients who developed trismus and who were included in an intervention study assessing the effect of a structured exercise program with jaw mobilising devices. The intervention group was compared to a matched HNC control group. In Paper III, 50 patients of the intervention group in Paper II were included in a randomized prospective study where the effect and compliance to exercise with two different jaw mobilising devices were assessed. Paper IV aimed to investigate relationships between doses to various structures of mastication and the occurrence of trismus within the first year after radiotherapy. Prospectively collected clinical data for 216 HNC patients was associated with dose information from retrospectively delineated risk structures in the clinical treatment plans.

In Paper I, the incidence of trismus was 9% at baseline and 28% one-year post treatment. The highest incidence, 38%, was found six months post treatment. HNC patients with trismus reported greater problems with general and social eating, dry mouth, swallowing, appetite loss, and pain, as well as more jaw-related problems compared to HNC patients without trismus. In Paper II, the structured exercise program with jaw mobilising devices improved mouth opening. On average, the patients increased their mouth opening with 6 mm (95 % confidence interval: 5-8 mm). They also reported improvements in HRQL and less trismus-related symptoms compared to individuals of the control group. In Paper III, the largest increase in mouth opening was seen during the first four weeks of exercise. After the exercise period, 84 % in the TheraBite® group (n=21)

and 60 % in the Engström group (n=15) no longer fulfilled the trismus criteria. There was no statistical significant difference with respect to efficacy between the two jaw mobilising devices. On average, patients exercised two to three times daily as opposed to the suggested five times per day. In Paper IV, the mean dose of the masseter muscle and the temporomandibular joint were significant predictors for trismus.

In conclusion, regular assessments of trismus are important in HNC and both objective and subjective endpoints should be addressed in clinical studies. Structured jaw exercise programs using jaw exercise devices should be recommended for the treatment of patients with trismus in HNC. In future radiotherapy, the masseter muscle may be a possible candidate for trismus-sparing techniques in cases where the masseter muscle dose can be safely lowered without jeopardizing tumour control.

Keywords: Trismus, Head and Neck Cancer, Radiotherapy, Jaw Exercise Therapy, Mastication Structures

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List of papers

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

- I. **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):1137-45.
- II. **Pauli N**, Fagerberg-Mohlin B, Andréll P, Finizia C.
Exercise intervention for the treatment of trismus in head and neck cancer.
Acta Oncol.2014 Apr;53(4):502-9
- III. **Pauli N**, Andréll P, Johansson M, Fagerberg-Mohlin B, Finizia C.
Treating trismus - a prospective study on effect and compliance to jaw exercise therapy in head and neck cancer.
Head and Neck 2014. E-pub ahead of print.
- IV. **Pauli N**, Olsson C, Pettersson N, Johansson M, Haugen H, Steineck G, Finizia C.
Risk structures for radiation-induced trismus in head and neck cancer
Submitted

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Abbreviations

3D CRT	3D Conformal Radiation Therapy	HPV	Human Papilloma Virus
ACE-27	Adult Comorbidity Evaluation 27	HRQL	Health-Related Quality of Life
CT	Computed Tomography	IMRT	Intensity Modulated Radiation Therapy
CNS	Central Nervous System	MIO	Maximal Interincisal Opening
EBRT	External Beam Radiotherapy	MRI	Magnetic Resonance Imaging
EORTC	European Organization for Research and Treatment of Cancer	OAR	Organs At Risk
EORTC QLQ-C30	EORTC Quality of Life Questionnaire Core 30	PRO	Patient Reported Outcome
EORTC QLQ-HN35	EORTC Quality of Life Questionnaire Head and Neck Module	RT	Radiotherapy
GTQ	Gothenburg Trismus Questionnaire	TMD	TemporoMandibular Disorder
Gy	Gray, the unit for absorbed radiation dose, Gy= joule per kilogram	TMJ	TemporoMandibular Joint
HADS	Hospital Anxiety and Depression Scale	TNM	Classification system for malignant tumours T=primary Tumour N=regional lymph Nodes M=distant Metastasis
HNC	Head and Neck Cancer	UICC	Union for International Cancer Control

“...trismus can be explained as an inability to open the mouth, regardless of etiological factor”

Introduction

1.1 Trismus definition

Trismus or more informally lockjaw, has historically been associated with tetanus, and was regarded as one of the characteristic symptoms of this often lethal bacterial disease. Trismus in tetanus was caused by a generalized muscular spasm resulting from the effect of the neurotoxin produced by the bacteria *Clostridium Tetani*. Trismus was associated with tetanus and even regarded as a synonym for “tetanus limited to the neck and lower jaw“ in the late 1800:s¹. Approximately one hundred years later, in 1988, the definition of trismus was “a motor disturbance of the trigeminal nerve, especially spasm of the masticatory muscles, with difficulty opening the mouth”; a wording still associated with neurotoxicity and tetanus even though tetanus by then and nowadays is not the most common cause of trismus^{2, 3}. However, during the last decades the definition of trismus has expanded and trismus can be explained as an inability to open the mouth, regardless of etiological factor.

1.2 The temporomandibular joint and the muscles of mastication

The temporomandibular joint (TMJ) is the only joint in the body serving as both a hinge joint and a sliding joint. The joint consists of the mandibular condyles, the articular surface of the temporal bone, the capsule, the articular disc, the lateral pterygoid muscle and the ligaments. The TMJ has a complex three-dimensional movement pattern. The mandible can elevate (close the jaw), retract, protrude and rotate horizontally but also shift laterally. The movements of the TMJ are coordinated by the muscles of mastication but also depend on the dentition. The muscles of mastication are innervated by the trigeminal nerve⁴. The muscles of mastication consist of four pairs of muscles; the masseter muscles (*Figure 1*), the lateral and medial pterygoids and the temporal muscles. The masseter, the medial pterygoid and the temporal muscle elevate the mandible and thus close the jaw. These muscles exert a

power that is ten times greater than the muscles that open the jaw. The jaw opening is carried out by the lateral pterygoid muscles, the suprahyoid muscles and gravity⁵. The dominating force from the muscles responsible in closing the jaw explains why trismus is seen in conditions with general muscle spasms.

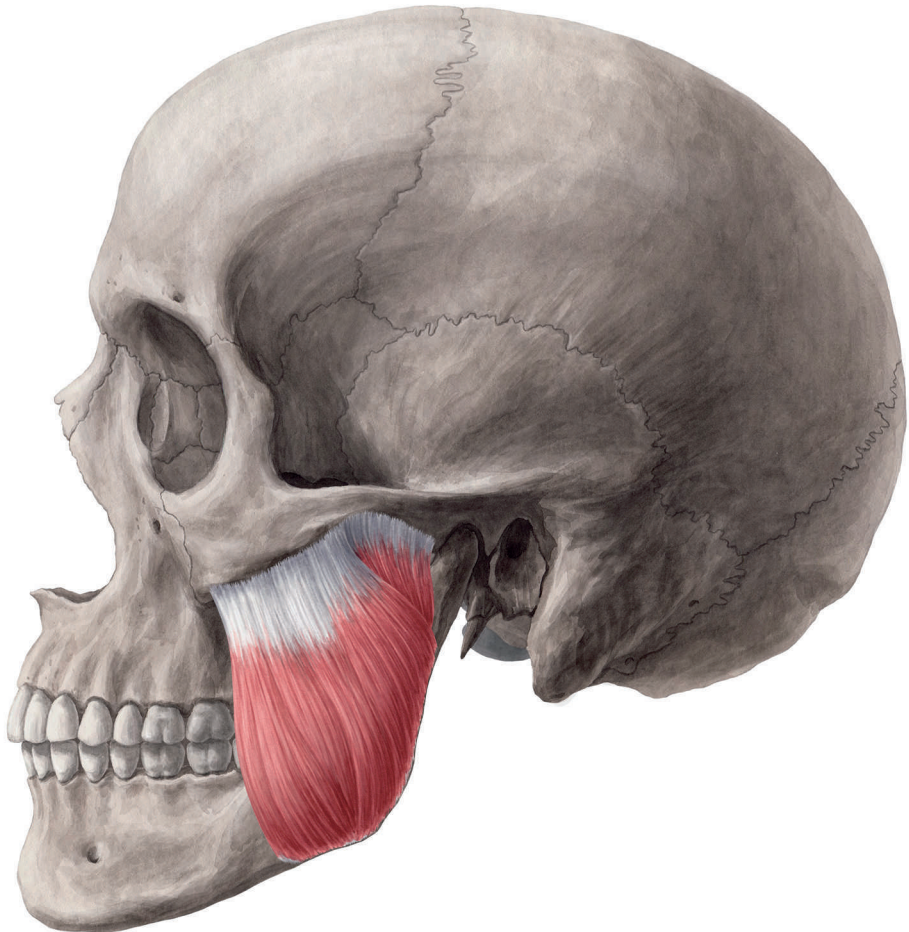


Figure 1. The Temporomandibular joint and the masseter muscle.
(with permission from Kenhub.com).

1.2.1 Normal mouth opening

Normal mouth opening has been reported to be approximately 40-60 mm when measured as the distance between the edges of the incisors of the mandible and the maxilla. There is a tendency towards a smaller mouth opening in women compared to men and a decrease in width in elderly compared to younger individuals⁶⁻¹⁰. The mouth opening ability is related to the length of the mandible and also related to the height of a person^{11, 12}. A practical rule of thumb is that an individual who can open the mouth as wide as the width of three fingers can be considered to have a normal mouth opening, *Figure 2*¹³.



Figure 2. Normal mouth opening can be considered to be the width of three fingers.

1.2.2 Trismus etiology

Trismus can be caused by many different factors and can be the result of both local processes affecting the jaw such as infections or tumours; it can also be the result of systemic disturbances in the body such as drug toxicity, *Table 1*. Trismus can also be classified as being of either organic genesis or of neurogenic genesis.

Organic genesis

Organic geneses are those conditions that cause trismus by interfering with the TMJ and inhibiting the free movement of the jaw. Examples of organic genesis are TMJ disc dislocation, fractures or hematomas of the TMJ, infiltrative tumour growth or fibrosis that mechanically restricts the jaw movements. Problems and symptoms related to the TMJ and the muscles of mastication can be termed temporomandibular disorders (TMD), and are common in the general population with an estimated prevalence of 10-50 % amongst adults¹⁴.

Neurogenic genesis

Neurogenic geneses include conditions with increased tonus of the muscles of mastication and can be caused either by systemic increased muscular tonus, such as in epileptic disease, or be the result of a muscular reflex of the trigeminal nerve. Such a reflex can be activated by an increase in the afferent sensory input, because of inflammation, contusions, or malignant processes in the oral cavity, pharynx, muscles of mastication, external auditory canal, infratemporal fossa, or the areas round the TMJ. This reflex is bilateral even if the afferent stimulus is unilateral (the tonus of the muscles of mastication will increase bilaterally), which results in what is referred to as reflectory trismus, *Figure 3*⁵.

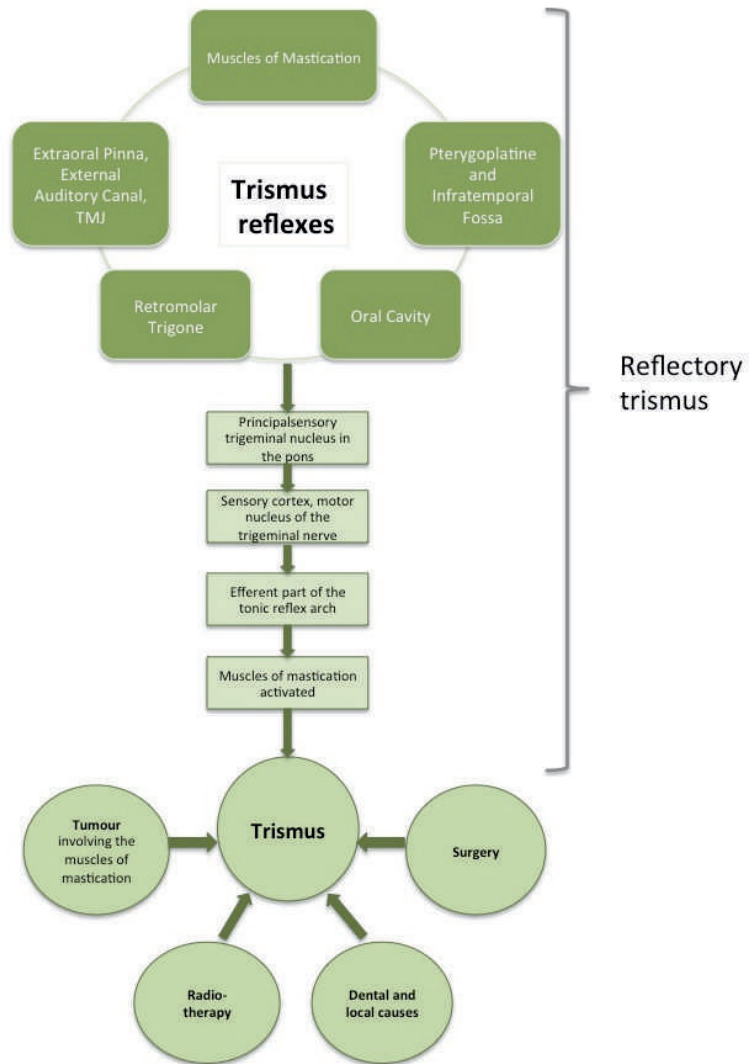


Figure 3. Pathogenesis of trismus. Adapted from Dr P S Satheeshkumar ¹⁵.

<u>Local factors:</u>	Example:
Chronic inflammation	Rheumatoid arthritis
Congenital disorders	Malformation of the mandibular condyle
Fibrosis	Radiation-induced fibrosis Surgical scarring
Infections	Odontogenic infections Peritonsillar abscess Masticatory space infections
TMD	TMJ disc displacement Muscle contracture
Trauma	Mandibular fractures Zygomatic fractures Haemarthrosis of the TMJ
Tumour growth	Head and neck cancer Sarcomas of the mandible
<u>Systemic factors:</u>	Example:
Drug toxicity	Strychnine, antihistamines Antipsychotic drugs
General muscle rigidity	Tetanus Parkinsonism Status epilepticus

Table 1. Example of local and systemic factors resulting in trismus. Adapted and modified from Tveteras et al. and Okeson^{5 14}

1.3 Head and neck cancer

Head and neck cancer (HNC) is a heterogeneous group of tumours situated in the larynx, nasal cavity, oral cavity, pharynx, paranasal sinuses, or salivary glands, *Figure 4*. Histopathologically squamous cell carcinoma is the most common type constituting more than 90% of the tumours whereas adenocarcinomas and adenoidecystic tumours are rare ¹⁶.

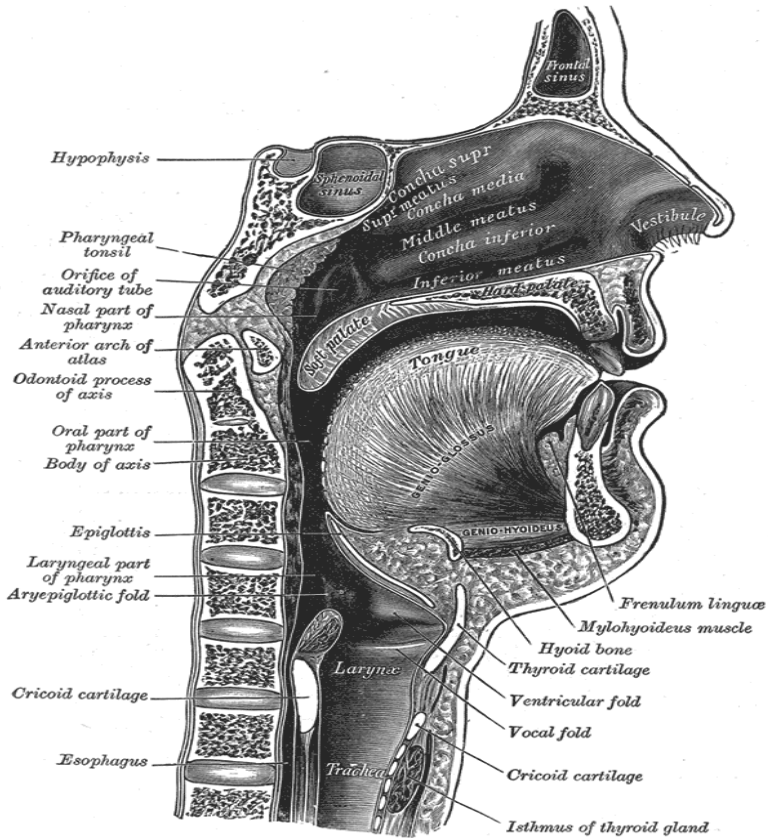


Figure 4. Head and neck anatomy, sagittal view, (source: Henri Gray, Gray's Anatomy).

1.3.1 Epidemiology

The estimated incidence of HNC is 650 000 new cases per year and it is the sixth most common type of cancer worldwide in men and the eighth most common type in women ¹⁷. In Sweden, about 1300 cases of HNC were reported during 2012 and more than two thirds of them were male ¹⁸. The incidence of HNC varies in different parts of the world, mostly due to different patterns of smoking behaviour, alcohol intake, and prevalence of HPV, but possibly also due to genetic differences ¹⁹.

Smoking and alcohol are well known risk factors for all HNC whereas Human Papilloma virus (HPV) is recently discovered as a risk factor for tumours of the tonsils and oral cavity ^{17, 20, 21}. The trend in Sweden, as well as in other parts of Europe and the US, is an increase in these kinds of tumours with the explanation being a rising incidence of HPV in the general population mainly HPV type 16) ^{18, 22, 23}. The HPV-associated tumours appear to have a better prognosis and are more sensitive to treatment than HPV-negative tumours ²⁴.

Smokeless tobacco and betel quid are other risk factors that are related to an increased risk of cancer of the oral cavity ²². Nasopharyngeal carcinoma is a tumour that differs from the rest of the HNCs both regarding incidence and risk factors. It is endemic in some parts of Asia and Alaska and is suggested to associate with genetics, dietary factors, and environmental exposure ²⁵.

The prognosis and overall survival of HNC differ substantially between tumour sites. The overall 5-year survival for all HNC in Sweden is approximately 50 %. In Sweden, lip cancer has a 5-year survival of more than 90 % whereas the prognosis for hypopharyngeal cancer is very poor with a 15 % 5-year survival. For oropharyngeal tumours, the 5 year survival about 70% ²⁶.

Staging

In Sweden, head and neck tumours are classified and staged according to the Tumour, Node, Metastasis (TNM) classification, developed by the International Union Against Cancer (UICC). The tumours are classified according to tumour size, anatomical site, involvement of regional lymph nodes and presence of distant metastasis²⁷. Stage categorization is a way of summarizing the TNM classification into a single score (Stage I-IV). Together, the classification and the staging guide the therapeutic decision-making. Example of the TNM classification and the stage categorization in oropharyngeal and hypopharyngeal cancer is shown in *Table 2*.

Stage categorization

	N0	N1	N2-3
T1	I	III	IV
T2	II	III	IV
T3	III	III	IV
T4	IV	IV	IV

Table 2. Stage categorization in oropharyngeal and hypopharyngeal cancer according to TNM-classification.

1.4 Treating head and neck cancer

The management and treatment of HNC is challenging due to the location of the tumours at close proximity to vital organs that carry out essential functions such as breathing, smelling, tasting and swallowing. Choice of treatment depends on the treatment site and if the tumour is surgically resectable. Early stage diseases (Stage I and II) are treated with surgery or radiotherapy and curative treatment is obtained in approximately 90 % and 70 % of the cases, respectively. However, the majority of the patients with HNC, about 70 %, are diagnosed at a more advanced disease stage (Stage III or IV). Reasons for this depends on tumour site and are related to initial absence of symptoms. For example, a tumour of the lip will typically be noted by the patient at an early stage whilst a hypopharyngeal tumour can grow without causing any symptoms until it has become locally advanced ²⁸. For stage III and IV disease (locally advanced tumours), unresectable tumours are generally treated with a combination of radiotherapy and chemotherapy (radiochemotherapy) whereas locally advanced resectable tumours are treated with primary surgery and postoperative radiochemotherapy ²².

1.4.1 Surgery

Primary surgical resection of HNC tumours is used as the standard treatment when possible. However, surgery is often infeasible or limited due to extensive tumour growth or risk for severe side effects and functional impairments post operatively with disfiguring tissue defects ²². Tumour resectability is judged from case to case, but tumours infiltrating the carotid artery, base of skull, or prevertebral fascia are often considered unresectable tumours²⁹. In addition to the removal of the primary tumour, neck dissection is often performed to remove regional lymph nodes and thus potential micro metastases from the areas draining the tumour. The result by neck dissection is used for staging and for identifying pathological lymph nodes. It is an important prognostic factor and it is also used to guide the therapy decision regarding the need for adjuvant therapy ³⁰.

1.4.2 Chemotherapy

Chemotherapy is used together with radiotherapy for curative treatment or can be used as a single treatment with palliative intent to reduce the tumour volume. Chemotherapy can be given before starting radiotherapy as inductive therapy, or during radiotherapy as concomitant therapy. An example of an inductive chemotherapy regimen in HNC is Cisplatin 100 mg/m² day one and 5-Fu 1000 mg/m² per day by continuous infusion day one through five before starting radiotherapy, with a cycle interval of 21 days; an example of a concomitant regimen is Cisplatin 40 mg/m² administered weekly throughout radiotherapy.

1.4.3 Radiotherapy

Radiotherapy is an important treatment modality in HNC. The anatomical location of HNC tumours close to the central nervous system (CNS), the brain stem, and the cranial nerves requires that the treatment is given with high precision to avoid severe radiation-induced complications such as paralysis.

Radiobiology & radiation-induced fibrosis

The effects of ionizing radiation on the human cells and tissues are complex. The therapeutically most commonly used type of radiation (photons) causes damage to the cells and tissues via two main mechanisms: 1) direct DNA-damage and subsequent cell death and 2) sub lethal damage of cells leading to a complex series of intra- and extracellular events and an excessive accumulation of extracellular matrix components.

Cell death in normal tissue in combination with excessive accumulation of fibrotic tissue can result in permanent damage with cell poor tissues and fibrosis altogether manifesting as radiation-induced fibrosis³¹.

The pathogenesis of radiation-induced fibrosis is not fully understood but it can be described as a dysregulation of the normal wound healing processes. It has been assumed that damage to the vascular endothelium plays a role with subsequent leakage of pro-inflammatory factors and stimulation of fibroblasts^{31, 32}.

Radiation-induced fibrosis in the head and neck region can lead to neuromuscular complications with musculoskeletal pain, spasm, and muscle weakness secondary to ectopic nerve activity and nerve atrophy.

In HNC, trismus, neck extensor weakness and cervical dystonia are examples of conditions relating to radiation-induced fibrosis ³². It has been described that magnetic resonance imaging (MRI) of patients with trismus, shows signs of fibrosis not just affecting the muscles of mastication but also affecting other surrounding tissues. The latter presenting as thickening of the TMJ capsule and as signs of osteoradionecrosis affecting the skull base and the mandible ^{33, 34}.

External beam radiotherapy

With external beam radiotherapy (EBRT) the radiation dose is delivered to the tumour volume from outside the body. In HNC there has been a shift during the last two decades from the use of conformal radiotherapy (3D CRT) to Intensity Modulated Radiotherapy (IMRT). With IMRT it is possible to modulate and shape the dose distribution to a greater extent than with 3D-CRT and thus better conform the dose to the tumour and reduce dose to surrounding normal tissue, Figure 5. The use of IMRT in HNC has led to decreased problems with toxicity without reduced loco-regional control, above all regarding parotid gland sparing and the reduction of xerostomia ^{35, 36}.

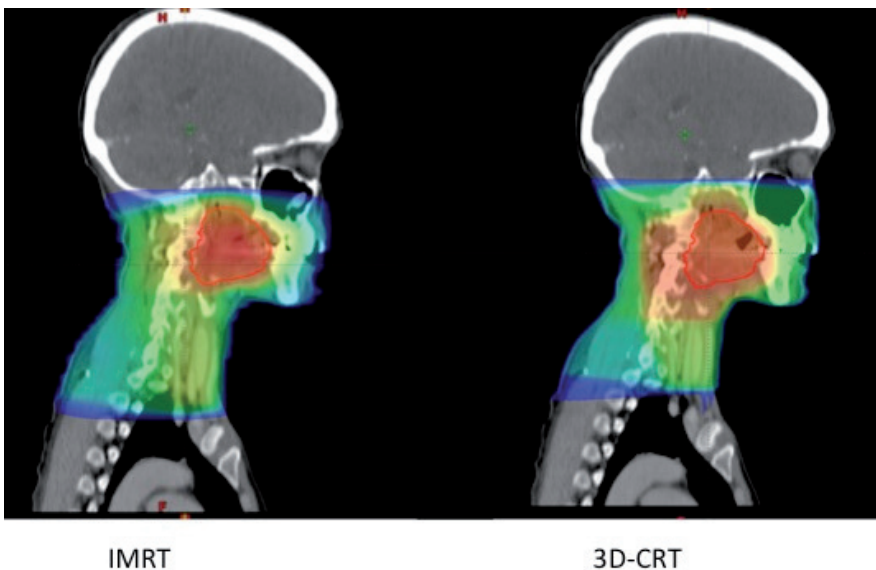


Figure 5. Comparison of dose distributions with IMRT and 3D-CRT technique for the treatment of tonsillar cancer, sagittal view. Red area=100 % of the prescribed dose to the tumour volume.

Brachytherapy

In brachytherapy or interstitial radiation therapy, radioactive sources are placed within or in close proximity to the tumour leading to a steep dose fall off outside the treated volume. Brachytherapy can be delivered with high-dose rate implants or with low-dose rate implants. These are typically administered through plastic catheter that are inserted into the tumour e.g. in the base of a tongue tumour. Brachytherapy is most often used as a complement to EBRT ³⁷.

Acute and late effects of ionizing radiation

The goal of radiotherapy is to eliminate tumour cells without causing too extensive damage in the normal tissue. Inevitable, normal tissue within the treated volume will be affected to some extent, and depending on the location in the body and the tissue type the symptoms for the patient will differ. Acute side effects or toxic effects are those appearing during the treatment course and up to about 3 months after finishing radiotherapy. Late side effects appear from 3 months up to years after finishing radiotherapy ³⁸.

Acute toxic effects after radiotherapy are predominantly seen in tissues with a rapid turnover of cells such as epithelial surfaces (skin, intestine, mucosa). Common acute oral toxic effects after HNC treatments are mucositis, often with secondary opportunistic fungal infections in the mouth, taste disturbance, and dysphagia. Some patients also react with dermatitis ^{22, 38, 39}.

Late effects of radiation occur more often in tissues with a slow cell turnover such as bone, muscle, brain, nervous system, fatty tissue and subcutaneous tissue ³⁸. In HNC, the brain, brainstem and spinal cord are structures that are carefully shielded from excessive radiation dose due to the severity of late toxic effects in this structures such as, brain edema, necrosis and spinal cord injury ⁴⁰. Another commonly recognized late radiation-induced toxicity in HNC is xerostomia (dry mouth) which, together with trismus causes substantial suffering and can be persistent or even worsening up to 5 years after completed radiotherapy ⁴¹. Other examples are osteoradionecrosis of the mandible, dental caries due to xerostomi, laryngeal edema and thyroid gland dysfunction ^{22, 39}.

Treatment schedules

During a radiotherapy treatment session, which takes about 10-30 min each, the patient is immobilized with an individually made thermoplastic head and neck mask which minimizes loss of precision due to patient's movements and treatment related positional changes. Radiotherapy is prescribed with the expectation that the patient is positioned the same way at every session, which makes the preparations before treatment of paramount importance, *Figure 6*.



Figure 6. Fitting a facemask for radiotherapy, (source: National Cancer Institute).

Radiotherapy treatment schedules and guidelines in HNC differ a lot from country to country but also within nations. In western region of Sweden, HNC patients treated with curative EBRT typically receive 64-70 Gray (Gy= joule per kilogram) whereas patients treated with pre-operative EBRT receive 47-50 Gy, both at 1.7-2.0 Gy per fraction²⁶.

During the study period of this thesis (2007-2012) two main fractionation schedules, conventionally fractionated radiotherapy and accelerated hyperfractionated radiotherapy, were used. Fractionation means that the total radiation dose is spread out over a period of weeks in a series of daily fractions instead of being administered as one single large dose.

Fractionating the dose spares the normal tissue and can at the same time increase tumour damage. Fraction size and overall treatment time can be altered and may result in different patterns of late and early toxicity⁴².

Conventionally fractionated radiotherapy is the general reference schedule for radiotherapy where the dose per fraction is around 2.0 Gy and the treatment is delivered in daily fractions five times per week during a five to seven-week period. The patients prescribed conventional fractionation in this thesis were treated to a total dose of 68 Gy.

With respect to conventionally fractionated radiotherapy, accelerated fractionated radiotherapy means that the overall treatment time is shorter; hyperfractionated radiotherapy means that the number of fractions per day is increased (and that the dose per fraction is lowered). The patients prescribed accelerated hyperfractionated radiotherapy in this thesis were treated at 1.7 Gy per fraction, two times per day, five days per week to a total dose of 64.6 Gy.

The outcome of these two fractionation schedules was studied in the randomized ARTSCAN study and no difference with respect to the incidence of trismus could be determined between the two study arms⁴³.

Treatment planning and organ-sparing radiotherapy

As earlier mentioned treating HNC with radiotherapy is challenging due to the tumours' locations close to critical anatomical structures. Planning of radiotherapy is done based on the information from the Computed Tomography (CT) scans and is performed in a treatment planning system. Besides the tumour and involved lymph nodes, critical structures; Organs At Risk (OAR:s), such as the spinal cord, the brain stem, the salivary glands and the mandible are identified and delineated in order to assure that absorbed doses in these structures are calculated. Knowing OAR dose tolerance limits is necessary when weighting the desired tumour effect against the risk of causing complications.

IMRT has facilitated the development of organ-sparing techniques. One such example is parotid gland sparing technique to reduce the risk of xerostomia after radiotherapy. In the treatment planning system, the parotid glands are identified and delineated and the dose to the glands is kept at lowest possible level without jeopardizing tumour eradication^{35,36}.

Investigating relationships between dose to an OAR and a specific complication is a complex process and identified links need to be

carefully evaluated in the clinic with respect to a secured locoregional tumour control. Research is now carried out in order to identify dose tolerance limits (dose-volume constraints) for anatomic structures related to dysphagia^{44, 45}. Dose-volume constraints relate to the absorbed dose that a certain volume (or anatomic structure) can tolerate without resulting in a complication. Dose-volume constraints for trismus and potential mastication structures have not yet been conclusively determined.

1.5 Patient-reported outcomes and Health-Related Quality of Life

Many different definitions of Health-Related Quality of Life (HRQL) have been suggested. On the whole, HRQL bears the meaning of issues that are of fundamental importance for an individual's well-being. One way to try to describe quality of life (QoL) is that QoL is a measure of the difference between the hopes and expectations of the individual and the individual's present experience⁴⁶. When using QoL in the healthcare context, it usually refers to HRQL.

The term Patient-Reported Outcome (PRO) covers both HRQL and other issues where information can be obtained from the patients, e.g. treatment compliance and treatment satisfaction¹⁷. Addressing HRQL and using PRO:s in clinical studies have become increasingly common. In HNC there has been a development towards tougher radiotherapy and chemotherapy treatment regimens over the last decades. This has resulted in improved loco-regional tumour control, but not in increased overall survival and the treatment-related symptom burden is significant⁴⁷. It is therefore important to address PRO and HRQL in clinical research to understand patients' experiences of treatment and treatment-related effects and to identify rehabilitation needs.

Trismus-related symptoms and HRQL

The research on trismus in HNC is scarce and existing studies with trismus as a primary endpoint are often small and of retrospective design. To date, the use of PRO and HRQL assessments in clinical studies on trismus are particularly rare⁴⁸ and the knowledge about its impact on HRQL is therefore poorly understood. After oncological treatment for HNC, trismus is a symptom that often co-exists with other symptoms such as dry mouth and dental problems, which together have a negative effect on the patient's nutritional status and HRQL⁴⁹. These are symptoms that in contrast to other treatment-related problems, do not resolve but seems to persist or even worsen years after finished treatment^{41, 50}. One of the few studies addressing trismus and HRQL found that HNC patients with trismus reported overall more HRQL-deficiencies as compared to patients without trismus, who had received the same treatment regimen⁵¹. Trismus can be associated with pain and patients with restricted mouth opening describe difficulties in eating, chewing and brushing their teeth. In addition trismus can hamper clinical follow-up at the dentist, oncologist or head and neck surgeon.

1.6 Trismus in head and neck cancer

Trismus in HNC can be caused by tumour invasion or tumour growth near the muscles of mastication, the oral cavity, or the TMJ. Trismus can be the result of surgical scarring after tumour removal or develop as a late effect after radiotherapy. In the case of radiation-induced trismus, it typically develops during the first 9 months after completed radiotherapy⁵². Trismus is described as a persistent problem and is one of the symptoms that HNC patients suffer from years after oncological treatment^{41, 50}. Studies have shown an incidence of trismus between 5-45 % in HNC patients treated with radiotherapy^{51, 53, 54}. For patients treated with both surgery and radiotherapy the incidence of trismus is up to 50 %, *Table 3*. The varying trismus incidence can partly be explained from the previous lack of a uniform trismus criterion. However, in recent years researchers have begun to use the same criterion for trismus i.e. the Maximal Interincisal Opening (MIO) ≤ 35 mm by Dijkstra *et al.*⁵⁵ as a criterion for trismus, which is expected to facilitate the comparing of results between different studies.

Author, year	No.	Treatment	Incidence	Tumour localisation	Follow-up	Trismus Criteria
Wetzels, 2014 ⁵³	143	Surgery	8 %	Oral cavity	1 year	MIO ≤35 mm
		Surgery + RT	50%			
		RT	35 %			
Lee, 2011 ⁵⁶	87	Surgery	71 %	HNC	6 months	MIO ≤35 mm
Johnson, 2010 ⁵⁴	69	RT	42 %	HNC	Retro-spective	MIO ≤35 mm
Bensadoun, 2010 ⁵⁷	NA	RT	25 %	HNC	Review of 12 studies	Varying
		IMRT	5 %			
		RT + Chemo	31 %			
Kent, 2007 ⁵¹	40	RT	45 %	HNC	Retro-spective	MIO ≤35 mm

Table 3. Incidence of trismus. Abbreviations: No.=number of patients, RT=radiotherapy, HNC= head and neck cancer, IMRT= intensity modulated radiotherapy, NA = not applicable, MIO= maximal interincisal opening

1.6.1 Risk factors for trismus in head and neck cancer

The risk of trismus in HNC depends on various factors. Studies on oral cancer have suggested that pre-treatment mouth opening, treatment modality, and tumour location are factors that can predict trismus after treatment. Tumours located close to the mandible or the maxilla and especially with a posterior location are related to an increased risk of trismus⁵³. Tumour size is another factor, where there is a stronger association with trismus for larger tumours (T3 and T4) than for smaller tumours⁵⁸. In addition, several studies show that the prescribed radiation dose to the tumour correlates with mouth opening after treatment^{54, 59-61}. When studying specific risk structures for trismus the pterygoid muscles, the TMJ and the masseter muscle have been given most attention^{43, 59-61}. More specifically Teguh *et al* showed that for every 10 Gy increase in prescribed dose to the pterygoid muscle, the risk of trismus increased with 24 %⁵⁹.

Other proposed risk factors for an increased risk of developing trismus after HNC treatment is smoking and comorbidity but none of these associations have been established conclusively. Surprisingly two independent studies have described that patients who report alcohol intake have a decreased risk of trismus^{53, 56}.

1.6.2 Treating trismus

Many methods to treat trismus have been described, but there are no large prospective randomized studies which evaluates the effect of the different approaches. There are neither any guidelines on how to design exercise programs nor are there comparisons between the efficacy of different intervention techniques. Furthermore, data is lacking on patient compliance to exercise.

Jaw exercise

Most treatment methods are based on stretching the muscles of mastication and the TMJ. The stretching can be performed either using a jaw exercise device, which assists mouth opening or unassisted using manual stretching with the fingers to force mouth opening.

There are several different jaw exercise devices available, the most commonly described are the TheraBite® device (*Figure 7*), and the

Dynasplint Trismus System (DTS). Two studies have reported that results by assisted stretching with a jaw exercise device is superior to unassisted stretching where no device is used^{62, 63}.

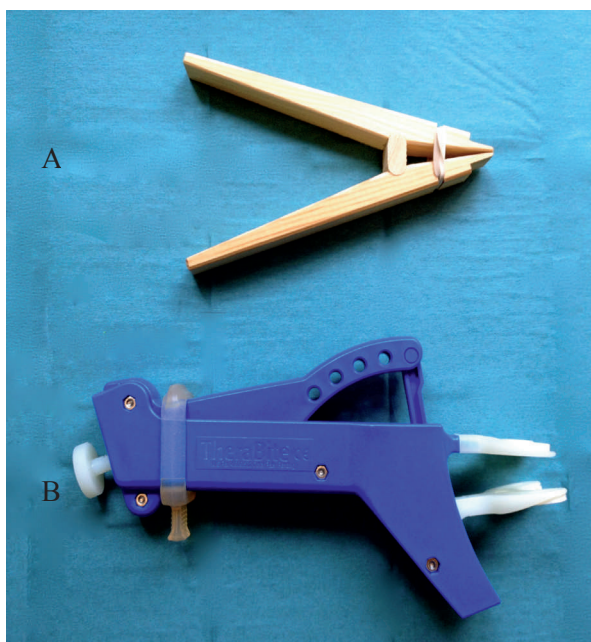


Figure 7. Example of jaw exercise devices. A) The Engström jaw device and B) The TheraBite® jaw Device (by Atos Medical AB, Hörby, Sweden).

Pharmacological treatment

Pharmacological treatment alternatives for the treatment of trismus have been described. Botulinum toxin, injected transcutaneous into the masseter muscles reduces pain in patients with trismus but does not improve mouth opening⁶⁴. Pentoxifylline, a drug with immunomodulating effects and a proposed inhibitor of radiation-induced fibrosis, has been evaluated in a small study on patients with nasopharyngeal carcinoma and trismus. It improved mouth opening for some patients but the results have not yet been reproduced⁶⁵.

Other mechanical alternatives

Numerous alternative treatments for trismus have been proposed. Examples are rubber plugs inserted between the jaws as screws or tongue depressors stacked in a pile to gradually force mouth opening. Another more peculiar method is found in a case report of a patient treating his own trismus with a sledgehammer that was tied to the lower gum with a tie, his mouth opening increased from 20 to 38 mm ⁶⁶.

Surgical treatment of trismus

Surgical release of radiation-induced trismus is sometimes applied but the results are inconclusive and not well studied. The procedure often includes local myotomi of muscles of mastication or corioidectomy ⁶⁷. Another approach described is to reduce the mandibular height ⁶⁸. Surgical release of trismus is more commonly used in cases of submucous fibrosis which is a condition related to betel-nut chewing and more commonly seen in parts of Asia ⁶⁹.

Aim

The overall aim of this thesis was to investigate the incidence of trismus in HNC and to assess the treatment of radiation-induced trismus with a structured exercise program using jaw mobilising devices. Another objective was to investigate anatomic risk structures related to the development of radiation-induced trismus.

Specific aims

Paper I: To investigate the incidence of trismus in patients undergoing treatment for HNC and to analyse the impact of restricted mouth opening on trismus-related symptoms and HRQL.

Paper II: To investigate the impact of a structured exercise program with jaw mobilizing devices on trismus in HNC patients and its effect on trismus-related symptoms and HRQL.

Paper III: To compare two different jaw exercise devices with respect to measured improvement in mouth opening, trismus-related symptoms and HRQL in HNC patients with trismus and to investigate the compliance to exercise.

Paper IV: To investigate relationships between the dose to structures of mastication and objectively and subjectively assessed radiation-induced trismus in HNC patients and to identify critical structures for this condition.

Patients and Methods

The HNC patients addressed in Papers I to IV were included at the multidisciplinary tumour board conference at the Sahlgrenska University Hospital, Gothenburg, Sweden from 2007 to January 2012. Descriptions of inclusion and exclusion criteria, and lost to follow-up, *Table 4*, patient characteristics in Papers I to IV, *Table 5*.

1.7 Study design

Paper I: A prospective longitudinal study with consecutive inclusion of 75 HNC patients during one year (2007). Assessments of mouth opening, trismus-related symptoms and HRQL were done at baseline, and at 3, 6 and 12 months after completed oncological treatment.

Paper II: A prospective study with consecutive inclusion of patients with HNC. Fifty patients who developed trismus were enrolled into an intervention group and results were compared with a control group of 50 patients matched according to established criteria. Assessments of mouth opening, trismus-related symptoms and HRQL were done before and after the 10-week intervention.

Paper III: A prospective randomised study on the effect of and compliance to exercise with two different jaw exercise devices. Fifty HNC patients who developed trismus from study II were randomised to one of two different jaw device interventions. Results for mouth opening, trismus-related symptoms, compliance to exercise and HRQL were compared. Patients were assessed before and after the 10-week intervention.

Paper IV: A Study with 216 prospectively included HNC patients where trismus was defined as any event, objectively or subjectively assessed, during the first 12 months after completed oncological treatment. Delineation of trismus risk structures in clinical treatment plans was retrospectively performed and calculated doses for these were investigated together with clinical data to identify critical structures for radiation-induced trismus.

Paper	No. elig.	No. incl.	Inclusion criteria	Exclusion criteria	Excluded and lost to follow -up
I	127	75	Tumour location; Oropharynx, Oral Cavity, Nasopharynx, Tumour Colli, Salivary glands, Sinonasal	Edentulous Difficulties in reading and understanding Swedish Poor general health Metastatic or relapsing disease	Deceased before first follow-up n=18, poor general health n=9, unspecified reasons n=8, declined participation n=7, did not attend board meeting n=5, edentulous n=4, dementia n=1
II	N/A	100	All of above Radiotherapy Trismus	All of above Surgical treatment	Deceased before intervention commenced n=1
III	51	50	All of above Radiotherapy Trismus	All of above Surgical treatment	Deceased before intervention commenced n=1
IV	308	216	All of above Followed up for at least 12 months	Trismus at baseline Significant dose contribution from Brachytherapy	Edentulous n=4, Palliative treatment n=3, language n=2, poor general health n=1,declined further participation n=42, deceased n=21, n=18 unspecified reasons.

Table 4. Overview of inclusion and exclusion criteria for Paper I-IV Abbreviations: No. elig. = number of eligible patients, No. incl. = number of included patients, N/A=Not applicable.

	Paper I	Paper II	Paper III	Paper IV
No. of patients	n= 75	n= 100	n= 50	n= 216
Female	30	38	19	62
Male	45	62	31	154
Age (mean)	62	58	58	60
Tumour localisation				
Salivary gland	10	-	-	-
Oral cavity	22	2	1	28
Oropharynx	29	76	38	144
Tumor colli	6	12	6	22
Nasopharynx	5	10	5	17
Other	3	-	-	5
Treatment regimen				
Radiotherapy	17	15	7	63
Surgery	8	0	0	0
Surgery + Radiotherapy	15	8	4	N/A
Radiochemotherapy	29	77	39	153
Surgery+ Radiochemotherapy	6	0	0	N/A
Stage classification				
I	9	1	1	8
II	20	12	8	40
III	16	20	8	44
IV	29	55	27	123
Missing	1	12	6	1

Table 5. Patient characteristics. Abbreviations: N/A=Not applicable.

1.8 Outcome measures

The primary endpoint in all four studies was mouth opening measured in millimetres. Secondary endpoints were assessed using PRO:s.



Figure 8. Measuring the Maximal Interincisal Opening (MIO).

1.8.1 Maximal Interincisal Opening

Measurement of mouth opening has been carried out the same in all four studies. MIO is measured as the distance between the edges of the incisors of the mandible and the maxilla, *Figure 8*. MIO was measured using a ruler with the patients seated in an upright position. All patients were measured twice and the largest MIO was noted. Trismus was defined as an MIO ≤ 35 mm as originally proposed by Dijkstra *et al.*⁵⁵.

1.8.2 Patient-reported outcome

In this thesis validated questionnaires was used in all four studies to assess PRO. In Paper IV, only single questions from the GTQ and EORTC QLQ-HN35 was used for analysis, *Table 6*.

Questionnaires	GTQ	EORTC QLQ-C30	EORTC QLQ-HN35	HADS
Paper I	X	X	X	X
Paper II	X	X	X	
Paper III	X		X	
Paper IV	X*		X*	

Table 6. PRO questionnaires used in Papers I-IV. *=single questions used for analysis. Abbreviations: GTQ= Gothenburg Trismus Questionnaire, EORTC QLQ- C30= European Organisation for Research and Treatment of Cancer Quality of life Questionnaire Core 30, EORTC QLQ-HN35=Head and Neck 35, HADS= Hospital Anxiety and Depression Scale

Gothenburg Trismus Questionnaire

GTQ is a validated symptom-specific questionnaire that focuses on trismus and trismus-related symptoms. GTQ is encouraged to be used as a screening tool in clinical work with patients at risk of trismus or to be used as an endpoint in clinical HNC trials. The GTQ consists of 21 questions in total divided into three main domains: Jaw Related Problems (six items), Eating Limitations (four items), and Muscular Tension (three items) and eight single items concerning facial pain, limitations in mouth opening and inabilities to function in social- and working contexts. The GTQ scale range from 0-100 where 0 equals to absence of symptom and 100 equals worst possible symptoms, *Appendix 1*. GTQ has been translated to English, Portuguese and French and has been used in clinical studies. It has shown good reliability and responsiveness to changes over time^{70, 71}.

European Organisation for Research and Treatment of Cancer Quality of life Questionnaire

To assess the HRQL of the patients in the studies, the European Organisation for Research and Treatment of Cancer Quality of life Questionnaire (EORTC QLQ-C30) was used. It is a widely used and validated HRQL questionnaire that has been translated into more than 80 different languages. It consists of 30 questions divided into six functional domains; (Physical functioning, Role functioning, Emotional functioning, Cognitive functioning, Social functioning and Global QoL), three symptom scales; (Fatigue, Nausea and Pain) and six single items; (Dyspnoea, Insomnia, Appetite loss, Constipation, Diarrhoea and Financial difficulties)⁷², *Appendix 2*.

The EORTC QLQ-C30 has a complementary HNC specific module, the EORTC QLQ-HN35 that consists of 35 questions regarding HNC-specific symptoms. The EORTC QLQ-HN35 is also a validated instrument and contains one question addressing trismus that was used for analysis in Paper IV; “Have you had problems opening your mouth wide?”⁷³, *Appendix 2*.

1.8.3 Comorbidity

Hospital Anxiety and Depression Scale

The patients were also assessed regarding signs and symptoms of anxiety and depression. This was done using the Hospital Anxiety and Depression Scale (HADS), which is a validated scale, for detecting mood disorders in patients with somatic comorbidity. HADS contains 14 questions and the score is divided into a depression score (seven questions), and an anxiety score (seven questions)⁷⁴, *Appendix 3*.

Adult Comorbidity Evaluation 27

The HNC patients were assessed with regards to coexisting somatic illnesses using the Adult Comorbidity Evaluation 27 (ACE-27) scale. The ACE-27 scale is a comorbidity scale based on information regarding the patient's physical health as retrieved from his or her medical record. The ACE-27 encompasses three levels of comorbidities, grade 1 (mild), grade 2 (moderate), and grade 3 (severe). The score is obtained by using a structured form where the condition of different organ systems of the body is systematically registered. The ACE-27 scale was developed by Picirillo *et al.* to supplement the TNM-staging system with patient-related information on comorbidity for improved assessments of disease outcome and prognosis^{75, 76}.

1.8.4 Exercise intervention

The intervention to improve the mouth opening ability was designed as a 10-week exercise program using jaw mobilising devices (The Engström and The TheraBite jaw devices, *Figure 7*). The program was to be carried out five times per day. The program was designed in four steps and included both unassisted and assisted stretching with the jaw device: (a) unassisted warm-up movements, jaw opening ten times and small sideway movements of the jaws ten times; (b) assisted stretching, 30 seconds (if possible), repeated five times; (c) active exercise, bite toward resistance, repeated five times; and (d) assisted stretching, the same as in (b).

1.8.5 Compliance to exercise

Compliance to exercise was assessed using information from diaries filled in by the patients during the intervention period. The total amount of exercise and associated comments were to be written down by the patients daily. Compliance to exercise was calculated as the average number of exercises per week for each patient.

1.8.6 Treatment related outcome

In Paper IV, the outcome analyses were based on calculated radiation doses to a number of risk structures of interest and their relationships to trismus. To calculate each structure's absorbed radiation dose, its volume must be known. For each patient, the volume of each risk structure was, therefore, defined by delineating its anatomical borders in the CT-based clinical treatment plan. The treatment planning system Eclipse[®] (version 10.0.39, Varian Medical Systems, Palo Alto, U.S.) at the Department of Medical Physics and Biomedical Engineering, Sahlgrenska University Hospital was used for this purpose. Hereafter, dose-volume histograms displaying the estimated absorbed dose in the risk structures could be created and used for further processing.

The anatomical risk structures of interest in trismus symptomatology were identified with support from a senior Neuroradiologist, *Figure 9 and 10*. These were: the muscles of mastication (masseter, lateral and medial pterygoids, and temporal muscle), the TMJ, the soft palate, and the pterygopalatine ganglion. The delineation guidelines used in Paper IV are attached as *Appendix 4*.

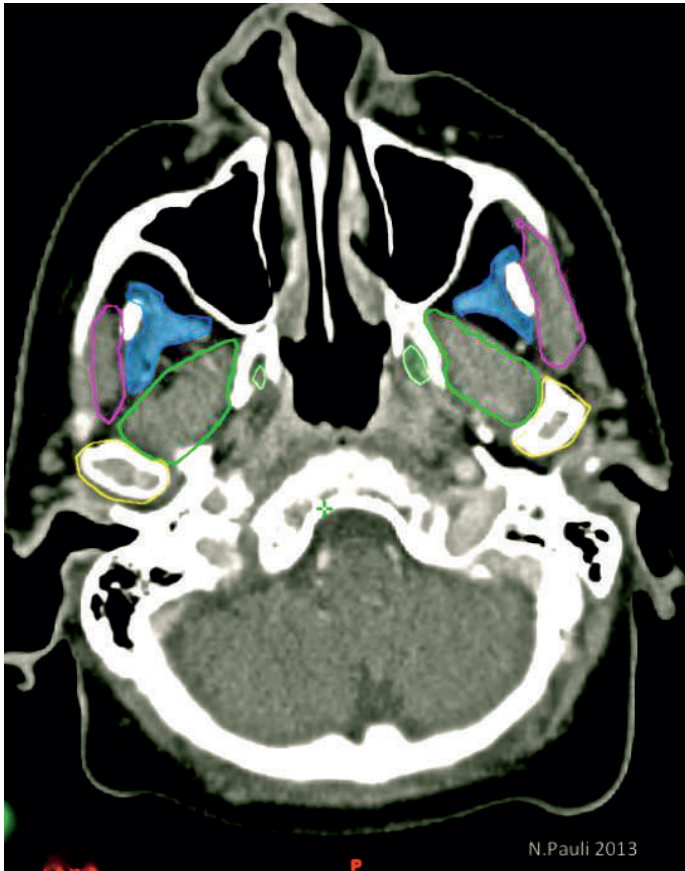


Figure 9. Delineation of trismus risk structures, transversal view. TMJ= yellow, Masseter muscle= purple, Temporal muscle= blue, Lateral pterygoid muscle= green and Medial pterygoid muscle= light green.

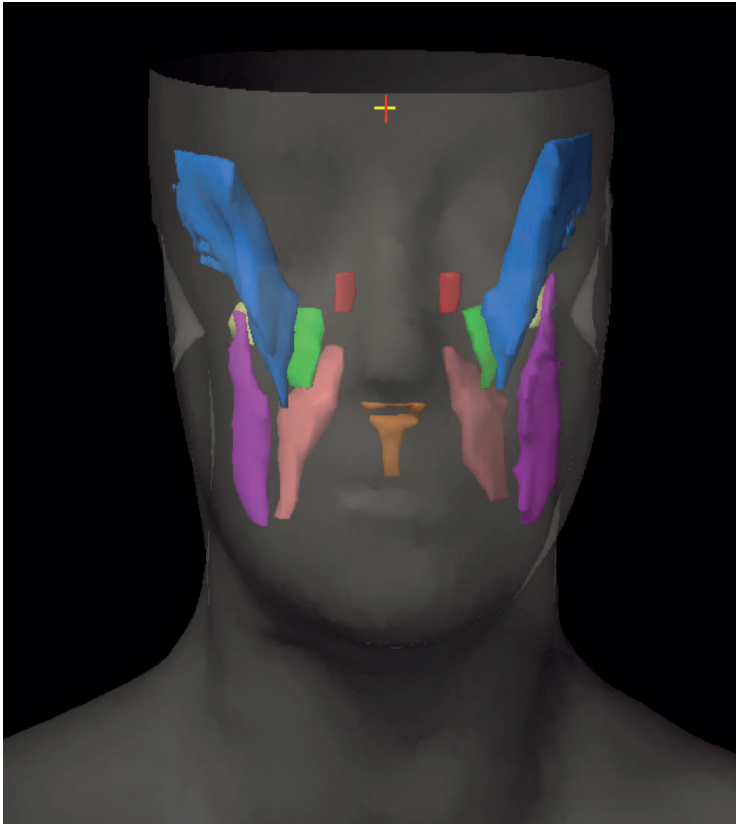


Figure 10. Delineated risk structures for trismus. 3D projection, frontal view. Masseter muscle=purple, Temporal muscle= blue, Lateral pterygoid muscle= green, Medial pterygoid muscle=pink, Soft palate= orange, Pterygopalatine ganglion= red and TMJ=yellow.

1.9 Statistics

For comparison between groups all tests were two-tailed and performed at a 5 % significance level. For data from quality of life questionnaires non-parametric methods were used.

Descriptive statistics

Descriptive statistics in Paper I-IV was presented using mean values and standard deviations for continuous variables, and frequency and percentage for categorical data, unless otherwise stated.

Comparison between groups

For comparison between groups, Fisher's exact test was used for dichotomous variables. For continuous variables Mann-Whitney U-test was used. The Mantel-Haenszel Chi square test was used for ordered categorical variables and Chi square exact test was used for non-ordered categorical variables.

Comparison within group over time

For comparison within groups the Wilcoxon signed rank test was used.

Randomisation and study dimension

In Paper III the randomisation procedure was performed using the Pocock allocation procedure⁷⁷. The calculation of the study dimension was done with the aim to be able to detect a 5 mm difference in MIO between the groups. The calculation was based on the assumption of a MIO variance of 5 mm, which yielded a group size of 23 patients in each group in order to obtain 80 % statistical power.

Regression analysis

In Paper I, multiple linear regressions analysis was performed, and in paper IV, logistic regression analyses were performed, to identify risk factors for trismus. In Paper IV, both univariable and multivariable analysis with forward selection were used.

1.10 Ethics

All studies were performed with permission from the Regional Ethical Review Board at the Gothenburg University and performed in accordance with the declaration of Helsinki. All patients gave their written informed consent to participate.

The findings

1.11 Paper I



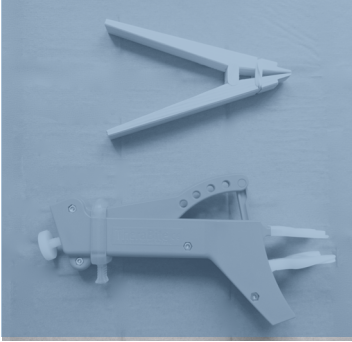
The incidence of trismus was 9% at baseline and 28% at the one-year follow-up post treatment. The highest incidence, 38%, was found six months post treatment. Compared to HNC patients without trismus, patients with trismus reported more problems with general and social eating, dry mouth, swallowing, appetite loss, and pain, as well as more jaw-related problems.

1.12 Paper II



The jaw exercise program improved mouth opening. Compared to the control group, the patients who underwent the exercise program after HNC treatment increased their MIO with 6.4 mm (CI: 4.8-8.0 mm) on average, reported improvements in HRQL, and less trismus-related symptoms.

1.13 Paper III



The largest increase in mouth opening was seen during the first four weeks of exercise. After the entire ten-week period, 84 % in the TheraBite® group (n=21) and 60 % in the Engström group (n=15) no longer fulfilled the trismus criteria ($MIO \leq 35$ mm). On average, patients exercised two to three times daily as opposed to the recommended five times per day.

1.14 Paper IV



The mean absorbed doses of the masseter muscle and the TMJ were significant predictors for both objectively and subjectively determined trismus. The predictive ability of the masseter muscle dose was somewhat superior to the TMJ dose and the masseter muscle may, therefore, be the more suitable candidate for future trismus-sparing techniques in cases where its dose can be safely lowered without jeopardizing tumour control.

“Oral health and problems with opening mouth has been pointed out as predictors for survival in HNC.”

Discussion and future directions

In the light of the developments and optimizations of oncological treatments and the rising incidence of HNC, increasing numbers of future patients can be expected to survive and live for many years with the aftermath of oncological treatments. This could lead to an increased need for preventive and rehabilitative actions to ameliorate functional impairments and lowered HRQL.

Incidence and impact of trismus

In Paper I, it was found that approximately one third of the HNC patients developed trismus (MIO \leq 35 mm) during the first year of follow up after completed oncological treatment. This result is comparable with other studies and it has been stated that trismus is one of the most commonly described symptoms after HNC treatments ⁷⁸.

In Paper I, the patients with trismus reported more problems with general and social eating, dry mouth, swallowing, appetite loss, and pain, as well as more jaw-related problems compared to the HNC patients without trismus. Trismus most often co-exists with other symptoms of the tumour treatment. Oral health and even more specifically, problems with opening mouth has been pointed out as predictors for survival in HNC ⁷⁹. Patients with a negatively affected oral health have an increased risk of malnutrition ⁸⁰ which in turn can lead to impaired recovery, prolonged rehabilitation process and to poor survival ⁸¹.

Trismus and trismus-related symptoms need to be given more attention together with the patients other symptoms and functional impairments after HNC treatments. It is important; both for the clinicians as well as for the HNC patients, to be aware of the high risk of developing trismus and trismus-related symptoms after radiotherapy in HNC, and therefore patients should be regularly assessed for mouth opening and oral health during follow-up. This is especially important during the first year after completed oncological treatment.

Treating trismus

In Papers II and III the effect of a structured exercise program using jaw mobilising devices for the treatment of trismus in HNC was investigated. It has earlier been shown that jaw device exercise can be effective, but the

studies have been small and the compliance to exercise has not been addressed. The demonstrated mouth opening improvement in Papers II and III was comparable with other studies and, likewise, in the order of 5-10 mm^{62, 63, 82-85}. The structured jaw device exercise also led to improvement in trismus-related symptoms and HRQL. The patients in the intervention group reported improvements both in symptoms directly related to the TMJ and trismus, such as jaw related problems and eating limitations, as well as improvements in Global QoL, social functioning, social eating and role functioning. Although a few millimetres might be considered a modest improvement, it seems to be of great importance for the patients. Earlier research on trismus, focus on objective clinical outcomes and primarily address mouth opening measured in millimetres without relating it to the patients ability to eat or function socially⁴⁸. The results from this thesis clearly demonstrate that the use of both objective and subjective assessment of trismus is important in order to acknowledge the patients experience.

Compared to other studies the patients in Papers II and III were included as soon as they developed trismus and, therefore they could start exercising at early onset. Such an early intervention has not previously been described in the scientific literature, but other studies have suggested that the results from jaw exercise therapy depend on the duration of trismus, and that it is easier to improve the mouth opening ability in earlier stages of trismus⁸⁵. In studies where trismus has been more manifest and of chronic nature, the treatment with jaw device exercise has been less successful. However, it is claimed that even in these cases exercise can be important since it seems to at least inhibit the progression of trismus⁸⁶. To initiate the treatment for trismus at an early onset, regular measurements and assessments of mouth opening during and after cancer treatments are necessary.

Another issue with the treatment of trismus has been how to design guidelines for exercise. Most studies have suggested exercise programs with five to ten exercise sessions per day^{63, 82, 85}. We instructed the patients to exercise five times per day, but in reality compliance to exercise turned out to be two to three times per day, indicating that this may be feasible for most patients. Based on the results from Papers II and III; a jaw exercise program three times per day during a four to six week period, followed by a gradual reduction to one session per day, in order to maintain mouth opening can be suggested for patients who develop radiation-induced trismus.

The two jaw exercise devices were found to function equally well in our intervention. There are, however practical and individual issues to take into account when deciding what device a patient should use. For instance, TheraBite device may be more suitable for patients who lack stable incisors since the broad mouthpieces distributes the pressure during exercise to a larger area compared to the Engström device. On the other hand the Engström device may be more suitable for patients with smaller mouths. To sum up, using a jaw mobilising device for the treatment of radiation-induced trismus is a non-invasive, feasible and affordable treatment method to improve the daily life for survivors of HNC.

Preventive treatment of trismus

Since trismus is a common symptom after HNC treatments and it has been stated that an early start of exercise rehabilitation is advantageous, it can be presumed that a preventive exercise program could be beneficiary for the patients. A few studies have looked into preventive measures to reduce both trismus and dysphagia after radiotherapy (regardless of pre-existing symptoms) but none have shown promising results. However, as for many studies on HNC, dropout rates are often high or the compliance to exercise low, making the results of the effect of the actual interventions more difficult to interpret⁸⁷⁻⁹¹. Still, one interpretation of the modest results by preventive efforts could be that the patients are approached at the time of diagnosis and are emotionally and cognitively occupied in coping with the cancer diagnosis and the upcoming oncological treatment. Suggestions of a preventive exercise could be interpreted as an unnecessary action. An early intervention that targets symptomatic patients can, therefore, be expected to be more successful.

The complex movements of the TMJ are performed mainly by the muscles of mastication, but the digastric muscles, the infra- and suprahyoid muscles, as well as the sternocleidomastoid muscle, not normally referred to as muscles of mastication, are also involved¹⁴. These structures are also important for the swallowing process. With that said, it is tempting to believe that an early intervention approach focusing on both mouth opening and swallowing problems, could lead to a more successful overall treatment result of radiation-induced side effects in HNC. This needs to be further researched.

Predictors and risk factors for trismus

In Paper I, results from regression analysis revealed that having a low MIO (smaller mouth opening) at baseline was predictive for trismus. In Paper IV, height turned out to be a significant risk factor for trismus, were shorter individuals being at higher than taller individuals. MIO and height, are most probably related, since mouth opening and general stature are correlated to one another¹¹. Some patients will therefore, be at higher risk for trismus due to shorter height and length of the mandible^{11, 12}. If these patients also will be at higher risk for trismus-related symptoms and subsequent functional impairment is currently not clear. Using a uniform criterion for trismus for all patients may, however, not be optimal. Some authors have suggested that different trismus criteria for men and women can be used to address expected differences in normal mouth opening⁵⁶. Either way, MIO can be assessed together with a PRO instrument to investigate the effect of trismus on eating and drinking ability/functioning and HRQL.

In Paper IV, comorbidity and smoking were predictive for trismus. Both these factors have previously been shown to predict treatment outcome in HNC. Comorbidity is related to more symptoms during radiotherapy and can increase the risk of late radiation effects^{92, 93}. Smokers suffer from more late side effects after radiotherapy compared to non-smokers especially with regards to dysphagia, trismus, and fibrosis⁹⁴.

It is important to try to identify the patients who are at risk of trismus as early as possible. In addition to the identified risk factors in Papers I and IV (low MIO at start, height, comorbidity and smoking), tumour location, and tumour size are related to the risk for trismus^{53, 58}. Furthermore, treatment regimens with high radiation dose towards the TMJ and the muscles of mastication, as well as surgery in combination with radiotherapy increases the risk for trismus⁵⁹⁻⁶¹. Altogether, there are several clinical and patient-related factors that must be taken into account to make reasonable risk estimations for trismus.

In addition to the known risk factors for radiation-induced trismus, there are of course other important factors that currently not are fully understood. One such example is the difference in individual radiosensitivity. Lately, there has been some data indicating that there might be genetic differences that could be predisposing for trismus⁹⁵. This is an area for future research on trismus. Furthermore, given that there is a high prevalence of TMD in the population, it is reasonable to believe that TMD can be a relevant risk factor for trismus in patients who

are symptomatic long before their cancer diagnosis. The prevalence of TMD in HNC patients before treatment and its relation to symptoms and HRQL after treatment is unknown. Together, these are interesting areas worth further studying in future research on trismus.

Anatomic risk structures

In Paper IV, doses to the masseter muscle and TMJ were predictive for trismus in the regression analysis of trismus risk structures. Earlier research has revealed that irradiation of the muscles of mastication and the TMJ are critical for trismus development^{43, 59-61}. In Paper IV, seven different anatomical structures were investigated. In contrast to earlier research, the muscles of mastication were analysed separately and the soft palate and the pterygopalatine ganglion were also included as potential risk structures. The medial pterygoid and the masseter muscle are the two largest muscles of mastication. As for the TMJ and the lateral pterygoid the mean doses to these structures were highly correlated, meaning that a high dose to the TMJ resulted in a high dose to the lateral pterygoid given its proximity. This was also the case for the medial pterygoid and the masseter muscle. Such a strong correlation makes it difficult to draw any certain conclusion about the role of each individual mastication structure for the development of radiation-induced trismus. Still, the dose to the masseter muscle, in line with a few other studies also using dose-volume information from radiotherapy^{43, 61} provided the strongest statistical model for predicting trismus. It would, however, be of great interest to investigate how the radiation dose to different combinations of mastication structures relate to trismus in future studies.

The masseter muscle imparts a strong bite force and has, compared to the other mastication structures, the most lateral position, which makes it distant from many HNC tumours. It is large in volume and it is anatomically uncomplicated to delineate on CT scans. Together with the findings in Paper IV, this promotes the masseter muscle to be a candidate for future investigations on dose-volume constraints for trismus and in developments of trismus-sparing techniques.

Limitations

It is important to keep in mind that this all results of this thesis are based on study populations which are generated from one centre and which depend on the local treatment regimens during the study period. This may limit the generalizability of the results to other situations.

In the studies of Papers II and III, where the jaw exercise intervention is investigated, the short follow-up time is a limitation and the long-term effect of the proposed exercise intervention needs further studying. Furthermore, only patients living in the Gothenburg catchment area were intervened due to practical and logistical reasons. To reduce the risk of selection bias, the matching procedure for the control group acknowledged individual characteristics such as gender, age, tumour localisation and stage.

The assessment of compliance to exercise in Paper III could have been analysed with a qualitative method to better understand why some patient exercised more frequently and to identify factors that influence compliance. Finally, a larger study population might have revealed differences in results between the two investigated jaw mobilising devices.

Conclusions

Trismus is a symptom affecting about one third of the patients treated with radiotherapy for HNC during the first year after completed oncological treatment. Patients with trismus suffer from jaw-related problems, eating limitations, and pain, which in turn affects HRQL negatively. The use of both objective and subjective methods to assess trismus is recommended in clinical studies on HNC in order to relate mouth opening to functioning and trismus-related symptoms. A structured jaw exercise program with a jaw mobilising device is effective when initiated during early onset of trismus. It improves mouth opening, trismus-related symptoms, and leads to improved HRQL. The choice of jaw mobilising device should be made according to individual factors such as dental health. Among the potential risk structures for radiation-induced trismus, the masseter muscle is a promising candidate for further research on predictive models for trismus.

- Regular measurements and assessments of mouth opening is important during the first year after completed oncological treatment in order to identify patients with trismus
- A structured exercise program with a jaw exercise device in the treatment of trismus is non-invasive and effective when initiated during early onset of trismus

Sammanfattning på svenska

Tumörer i huvudhalsregionen påverkar grundläggande funktioner, såsom andning, födointag, sväljningsförmåga, lukt- och smaksinnet. Behandlingen av tumörerna är utmanande eftersom risken för allvarliga biverkningar är stor. Patienter med huvudhalscancer behandlas med kirurgi, strålbehandling och cytostatika kombinerat eller var för sig beroende på tumörens storlek, lokalisering och spridning.

Gapsvårigheter (trismus) efter huvudhalscancerbehandling är ett symptom som tidigare inte studerats eller beskrivits i någon större utsträckning i den vetenskapliga litteraturen. Det är sedan tidigare känt att patienterna under och efter pågående behandling har en försämrad hälsorelaterad livskvalitet (Health Related Quality of Life, HRQL). För många förbättras HRQL succesivt efter avslutad behandling och efter ca ett år har de flesta funktionerna återgått till de nivåer som patienterna beskrev före tumörbehandlingen. För en del patienter sker dock ingen förbättring gällande vissa organfunktioner, vilket innebär att dessa patienter står inför mångåriga, kanske livslånga funktionsnedsättningar. Detta gäller framförallt muntorrhet och sväljningssvårigheter men även för gapsvårigheter.

Avhandlingen behandlar incidensen av trismus och dess påverkan på HRQL hos patienter med huvudhalscancer. Huvudhalscancerpatienter har prospektivt följts avseende gapförmåga och symptom relaterade till nedsatt gapförmåga samt HRQL. Vidare undersöktes i en klinisk interventionsstudie hur trismus kan behandlas. I denna studie har 50 patienter med trismus genomgått ett strukturerat träningsprogram och jämförts med en matchad kontrollgrupp som ej genomgått någon strukturerad träning. I interventionsstudien undersöktes effekten av träning på gapförmågan samt på relaterade symptom och HRQL. Patienterna randomiserades till två olika gapträningsinstrument och resultaten analyserades dels avseende effektivitet och dels avseende följsamhet till träningsprogrammet. Avhandlingen behandlar också vilka anatomiska strukturer som kan anses vara av vikt för utveckling av trismus genom att relatera information från strålbehandlingsplaner till kliniska data av både objektiv och subjektiv trismus.

Sammanfattningsvis är trismus ett symptom som drabbar var tredje patient med huvudhalscancer under de första 12 månaderna efter onkologisk behandling. Trismus och trismusrelaterade symptom påverkar funktioner som är kritiska för upplevd HRQL, där strukturerad träning med gaptänjande instrument effektivt

förbättrade gapförmågan. Den objektiva effekten på gapförmågan konfirmeras även i patienternas upplevelse av sina besvär, där gruppen som genomgick strukturerad gapträning rapporterade förbättrad HRQL och färre trismusrelaterade symtom jämfört med kontrollgruppen. I analyserna av anatomiska riskstrukturer för trismus tycks stråldosen till massetermuskeln vara kritisk för utvecklandet av trismus och det kan därför vara viktigt att fortsätta studera massetermuskeln i framtida trismus-sparande strålbehandlingsstudier.

Konklusioner av avhandlingsarbetet:

- Trismus drabbar var tredje patient med huvudhalscancer under de första 12 månaderna efter onkologisk behandling
- Trismus kan med fördel utvärderas med både ett objektivt och ett subjektivt patientrapporterat mått i kliniska studier
- Ett strukturerat träningsprogram för behandling av trismus vid huvudhalscancer kan rekommenderas till patienter med trismus där valet av träningsinstrument med fördel individanpassas
- Stråldosen till massetermuskeln tycks vara kritisk för utvecklandet av trismus

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Appendix

Appendix 1

GTQ

Göteborg Trismus Questionnaire (GTQ)

Detta formulär innehåller frågor i samband med gapsvårigheter och käkbesvär. Besvara frågorna genom att markera det svarsalternativ du tycker stämmer bäst. Om du är osäker, markera det alternativ som känns riktigast.

Har Du under den **senaste veckan** haft:

	Inte alls	Lite	Måttligt	Mycket	Väldigt mycket
	1	2	3	4	5
1. trötthets/stelhetskänslor i käkarna	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. smärtor eller värk i ansikte och käkar	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. smärtor vid rörelse av käken (gapning/tuggning)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. problem med att gapa stort eller bita över stor tugga	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. värk eller ömhet i käkmuskler	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. problem med att gäspa	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. käkledsljud	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

I vilken utsträckning begränsas eller omöjliggörs följande aktivitet av Dina käkbesvär?

	Inte alls	Lite	Måttligt	Mycket	Väldigt mycket
	1	2	3	4	5
8. äta hård föda	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. föra in mat i munnen	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10. äta mjuk föda	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
11. bita av	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Brukar Du:

	Inte alls	Lite	Måttligt	Mycket	Väldigt mycket
	1	2	3	4	5
12. bita ihop hårt	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
13. pressa med tungan	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

14. Hur mycket ansiktssmärta har Du **just nu**?

Har inte ansiktssmärta	Mycket lätt	Lätt	Måttlig	Svår	Mycket svår	Outhärdlig
<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅	<input type="checkbox"/> ₆	<input type="checkbox"/> ₇

15. Hur intensiv har smärtan varit när den var som värst den **senaste månaden**?

Har inte haft ansiktssmärta	Mycket lätt	Lätt	Måttlig	Svår	Mycket svår	Outhärdlig
<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅	<input type="checkbox"/> ₆	<input type="checkbox"/> ₇

16. Hur intensiv har smärtan varit i genomsnitt den **senaste månaden**?

Har inte haft ansiktssmärta	Mycket lätt	Lätt	Måttlig	Svår	Mycket svår	Outhärdlig
<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅	<input type="checkbox"/> ₆	<input type="checkbox"/> ₇

17. Har ansiktssmärtan stört Din förmåga att delta i sociala, fritids- och familjeaktiviteter den **senaste månaden**?

Inte alls	Lite	Måttligt	Mycket	Väldigt mycket	Har inte haft ansiktssmärta
<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅	<input type="checkbox"/> ₀

18. Har ansiktssmärtan förändrat Din förmåga att arbeta (innefattar både förvärvsarbete och hushållssysslor) den **senaste månaden**?

Inte alls	Lite	Måttligt	Mycket	Väldigt mycket	Har inte haft ansiktssmärta
<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅	<input type="checkbox"/> ₀

19. Hur begränsad är Din förmåga att gapa nu?

Inte alls	Lite	Måttligt	Mycket	Väldigt mycket
<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅

20. Har Din begränsade gapförmåga stört Din förmåga att delta i sociala, fritids- och familjeaktiviteter den **senaste månaden**?

Inte alls	Lite	Måttligt	Mycket	Väldigt mycket	Har inte haft begränsad gapförmåga
<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅	<input type="checkbox"/> ₀

21. Har Din begränsade gapförmåga förändrat Din förmåga att arbeta (innefattar både förvärvsarbete och hushållssysslor) den **senaste månaden**?

Inte alls	Lite	Måttligt	Mycket	Väldigt mycket	Har inte haft begränsad gapförmåga
<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅	<input type="checkbox"/> ₀

Appendix 2
EORTC QLQ-C30 and EORTC QLQ-HN 35

EORTC QLQ C30 (version 3.0.)

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

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

Den information Du lämnar kommer att hållas strikt konfidentiell.

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

Fortsätt på nästa sida

Patienter uppger ibland att de har följande symptom eller problem.

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

Sätt en ring runt den siffra som stämmer för Dig.

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

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

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

Appendix 3

HADS

HAD

(självskattningsskala)

Namn

Datum

Läs igenom varje påstående och ringa in det alternativ som bäst beskriver hur du har känt dig den senaste veckan. Fundera inte för länge över dina svar; din spontana reaktion inför varje påstående är förmodligen mer korrekt än ett svar som du tänkt på länge.

1. Jag känner mig spänd eller nervös:

- 3 Mestadels
- 2 Ofta
- 1 Av och till
- 0 Inte alls

2. Jag uppskattar fortfarande saker jag tidigare uppskattat:

- 0 Definitivt lika mycket
- 1 Inte lika mycket
- 2 Endast delvis
- 3 Nästan inte alls

3. Jag har en känsla av att något hemskt kommer att hända:

- 3 Mycket klart och obehagligt
- 2 Inte så starkt nu
- 1 Betydligt svagare nu
- 0 Inte alls

4. Jag kan skratta och se det roliga i saker och ting:

- 0 Lika ofta som tidigare
- 1 Inte lika ofta nu
- 2 Betydligt mer sällan nu
- 3 Aldrig

5. Jag bekymrar mig över saker:

- 3 Mestadels
- 2 Ganska ofta
- 1 Av och till
- 0 Någon enstaka gång

6. Jag känner mig på gott humör:

- 3 Aldrig
- 2 Sällan
- 1 Ibland
- 0 Mestadels

7. Jag kan sitta stilla och känna mig avslappnad:

- 0 Definitivt
- 1 Vanligtvis
- 2 Sällan
- 3 Aldrig

8. Allting känns trögt:

- 3 Nästan alltid
- 2 Ofta
- 1 Ibland
- 0 Aldrig

9. Jag känner mig orolig, som om jag hade "fjärilar" i magen:

- 0 Aldrig
- 1 Ibland
- 2 Ganska ofta
- 3 Våldigt ofta

10. Jag har tappat intresset för hur jag ser ut:

- 3 Fullständigt
- 2 Till stor del
- 1 Delvis
- 0 Inte alls

11. Jag känner mig rastlös:

- 3 Våldigt ofta
- 2 Ganska ofta
- 1 Sällan
- 0 Inte alls

12. Jag ser med glädje fram emot saker och ting:

- 0 Lika mycket som tidigare
- 1 Mindre än tidigare
- 2 Mycket mindre än tidigare
- 3 Knappast alls

13. Jag får plötsliga panikkänslor:

- 3 Våldigt ofta
- 2 Ganska ofta
- 1 Sällan
- 0 Aldrig

14. Jag kan uppskatta en god bok, ett TV- eller radioprogram:

- 0 Ofta
- 1 Ibland
- 2 Sällan
- 3 Mycket sällan

Poängen på frågorna med udda nummer (1 tom 13) visar totalpoängen för ångest. Poängen på frågorna med jämna nummer (2 tom 14) visar totalpoängen för depression. Lägg samman poängen från *båda sidor* av formuläret och ange summan för depression och ångest i respektive ruta.

Ångest
(udda frågenummer)

Depression
(jämna frågenummer)

Appendix 4
Delineation guidelines for risk structures

Descriptions of trismus risk structures contours.

Structures	Definition
Masseter muscle	Muscle visible from the zygomatic arch and process to the insertion on the lateral surface of the mandible.
Medial pterygoid muscle	Muscle visible from the pterygoid process of the maxilla to the insertion on the medial surface of the mandible.
Lateral pterygoid muscle	Muscle visible from the pterygoid process of the maxilla to the insertion on the anterior surface of the temporomandibular joint
Temporal muscle	Muscle visible from the coronoid process to the level of the most superior aspect of the orbit.
Temporomandibular joint	Temporomandibular joint delineated where mandibular caput and fossa/cave are visible.
Soft palate	Soft palate contoured including the uvula.
Pterygopalatine fossa	Fossa visible between the posterior aspect of the maxillary sinus and the inferior most aspect of the infraorbital fissura



Example contours for trismus risk structures.