Chapter 1
General introduction and outline of this thesis
General introduction

Head and neck cancer

Head and neck cancer includes tumors of the of the lip, oral cavity, nasopharynx, oropharynx, hypopharynx, larynx, and salivary glands. Over 90% of the tumors of the head and neck are squamous cell carcinomas of these locations. The incidence of head and neck cancer in the Netherlands in 2000 was 2,481 persons. The incidence increased with almost 20% to 2,964 persons in 2013. In the Netherlands, 816 patients died because of their head and neck cancer in 2000, this were 875 patients in 2013. An increase of about 7%. Etiological factors for squamous cell carcinomas of the upper aerodigestive tract are the use of tobacco and alcohol. In oropharyngeal cancer, the human papillomavirus (HPV) is also an important etiological factor. Overall prognosis of patients with a tumor associated with HPV is better than of patients who have a tumor that is not.

Treatment modalities for head and neck cancer includes surgery and radiotherapy. Radiotherapy can be combined with chemotherapy and biologicals. During and after treatment, patients can suffer from side effects such as trismus, mucositis, and xerostomia. These side effects can be a burden for patients and can impede on quality of life (QoL). Treatment of head and neck cancer can also impede on mandibular function. Mandibular function includes speaking, eating, laughing, yawning, and social activities. Side effects and impairment of mandibular function are related to location and classification of the tumor and the treatment modalities applied. Since the number of patients who are successfully treated for their head and neck cancer is increasing, the number of patients with impaired mandibular function and QoL is also increasing.

Trismus

Head and neck cancer patients frequently suffer from trismus, a limited ability to open the mouth. A mouth opening of 35 mm or less is a commonly used cut-off point for trismus. Trismus can be present before treatment because of invasion of the tumor in the masticatory muscles and temporomandibular joint, or their surrounded tissues. Surgery may lead to trismus because of scar formation in or near the masticatory muscles. Radiotherapy may cause fibrosis of the masticatory muscles, temporomandibular joint, and cheek, which can also lead to trismus. When the medial pterygoid muscle is included in the irradiated region, the risk of developing trismus increases. Trismus usually occurs 3 to 6 months post-radiotherapy and can continue up to 2 years post-radiotherapy. Trismus usually occurs 3 to 6 months post-radiotherapy and a progressive decrease in mouth opening can be observed up to 2 years post-radiotherapy. Large differences in prevalence and incidence of trismus in head and neck cancer patients have been reported: between the 5 and 42%. Trismus can impair oral hygiene, dental treatment, and oncological follow-up. Trismus can also, in addition to other side effects after head and neck cancer, impact negatively on mandibular function and QoL.
Prevention and treatment of trismus
A decrease in mouth opening of head and neck cancer patients cannot always be prevented by exercise therapy. Therefore, preventive exercises are only advised for patients with a high risk for developing trismus. When trismus is present, generally a limited increase in mouth opening can be achieved following different types of therapies, including exercise therapy and administration of pentoxifylline. There is no standard treatment for trismus; many different types of therapy have been described in literature and are clinically applied. Stretching techniques are used as exercise therapy, for example conventional range of motion exercises that are sometimes combined with tools as dynamic bite openers, tongue depressors, and rubber plugs. Many (unusual) stretching techniques have been described in case reports and case series, for example stretching with a home-made sledgehammer device. Advanced stretching devices as the Dynasplint Trismus System® (DTS) and the TheraBite® Jaw Motion Rehabilitation System™ (TheraBite) can be used to treat trismus. Trismus can also be treated by surgical procedures that are mainly used if exercise therapy has failed. Tissue release, a coronoidectomy, or lowering the height of the mandible are applied to obtain a larger mouth opening.
Outline of this thesis

General aims of this thesis are to analyze the burden of side effects after treatment of oral and oropharyngeal cancer and their influence on mandibular function, to identify risk factors for trismus after head and neck cancer, and to evaluate exercise therapy for trismus after head and neck cancer.

Side effects after treatment of oral and oropharyngeal cancer
Of all side effects oral and oropharyngeal cancer patients may experience after treatment, it is unclear which oral symptoms are most burdensome for patients and which factors have the largest impact on mandibular function. This information may be used to prioritize preventive measures for oral symptoms in order to maintain or improve mandibular function. In Chapter 2, the oral symptoms related to oral and oropharyngeal cancer, their burden, and their association with mandibular function were analyzed. In this cross-sectional study, 89 patients who had completed their oral and oropharyngeal cancer treatment for at least 6 months were included.

Risk factors for trismus after head and neck cancer
Previous studies that aimed to identify risk factors for trismus are limited by their retrospective design and relatively small sample sizes. The longitudinal course of mouth opening up to 1 year following surgery and/or radiotherapy (with or without chemotherapy) has been described in 4 studies with small sample sizes, limited number of primary tumor sites, or no radiotherapy applied as part of the treatment. Consequently, when several risk factors are present, it has been impossible to predict mouth opening of head and neck cancer patients after radiotherapy because of lack of statistical power. In Chapter 3.1, the longitudinal course of mouth opening up to 48 months post-radiotherapy and risk factors predicting mouth opening were analyzed. A multivariate prediction model for change in mouth opening was developed. This multivariate prediction model for mouth opening had a limited clinical application because of its complexity. In Chapter 3.2, the incidence of trismus and risk factors for developing trismus at different time points post-radiotherapy were analyzed for adequate prediction of trismus, during and post-radiotherapy. In these prospective longitudinal cohort studies described in Chapter 3.1 and Chapter 3.2, 641 patients irradiated for head and neck cancer were included.

Exercise therapy for trismus after head and neck cancer
In recent years, numerous studies have been published regarding exercise therapy for trismus, which have not been evaluated in a systematic review yet. In Chapter 4.1, studies regarding exercise therapy interventions for trismus secondary to head and neck cancer were identified, their methodological quality was analyzed, and the results of these studies were summarized. In this systematic review, 20 studies were included.

The effects of TheraBite exercises for the treatment of trismus in head and neck cancer patients have been described in several studies, whether or not as part of a mul-
timodal treatment. Reported increase in mouth opening ranges between -1.9 and 13.6 mm.\textsuperscript{35-37} However, factors influencing the effect of TheraBite exercises are unknown. In Chapter 4.2, the clinical effect (as change in mouth opening in mm) of TheraBite exercise therapy for trismus secondary to head and neck cancer and factors influencing this effect were analyzed. In this chart review study, 69 head and neck cancer patients of 2 medical centers were included.

The effects of DTS exercises as change in mouth opening have been described in 3 retrospective studies. Reported increase in mouth opening ranges between 6.2 and 13.6 mm.\textsuperscript{32-34} The patients' perception of DTS exercises has not been described. In Chapter 4.3, DTS exercises in head and neck cancer patients with trismus were analyzed. Effects on mouth opening, pain, mandibular function, QoL, and symptomatology and patients' perspective regarding DTS exercises, including user-satisfaction, experiences, comfort, and compliance were analyzed. In this prospective mixed methods study, 18 patients were included.
References


3. Integraal Kanker Centrum Nederland.


