CHAPTER 1
General introduction
Head and neck cancer and treatment

Head and neck cancer (HNC) is a relatively rare malignancy with approximately 2,900 newly diagnosed patients per year in the Netherlands, which is around 3% of the total number of newly diagnosed malignancies each year. It is the seventh most common malignancy in men, and the ninth in women. The majority of the patients are male and over 60 years of age.

HNC refers to a heterogeneous group of cancers originating from the mucosal areas of the oral cavity, nasal cavity, paranasal sinuses, nasopharynx, oropharynx, hypopharynx and larynx. More than 90% of HNCs are squamous cell carcinoma (HNSCC). Other histological tumor types include adenoid cystic carcinoma, adenocarcinoma, malignant melanoma, lymphoma and sarcoma.

The major risk factors for developing HNSCC have been known for several decades and include excessive use of tobacco and alcohol. The use of tobacco and alcohol together results in a synergistic effect. More recently, the human papilloma virus (HPV) has been identified as an increasingly important risk factor for the development of HNSCC. This is particularly true for HNSC originating in the oropharynx. The incidence of HPV related HNSCC is increasing rapidly, especially in younger males. In some countries, such as Sweden and in the United States, HPV-positive HNSCC accounts for approximately 70% of all oropharyngeal cancers. Between 1990 and 2010, the occurrence of HPV-positive HNSCC in the Netherlands rose from 5.1% to 29.0%.

Treatment of HNC may consist of surgery, radiotherapy (RT), chemotherapy, biological agents (cetuximab) or various combinations of these modalities. For patients with limited disease, single modality treatment (surgery or RT) is sufficient and preferred, with high locoregional control and high overall survival rates. However, in most cases patients present with advanced-stage disease, with large, bulky primary tumors and unilateral or bilateral cervical lymph node metastases. These more advanced-stage cases are generally treated with multiple modalities. Multimodality treatment primarily aims at achieving locoregional tumor control either by surgical resection of the tumor and affected (or potentially affected) lymph nodes, followed by postoperative RT or chemoradiation (CHRT) in case of adverse prognostic factors, or by definitive RT combined with concurrent chemotherapy or cetuximab to enhance radiation efficacy. In recent decades, RT has been used increasingly, in particular as part of organ preservation strategies. The meta-analysis of the MACH-HN group showed that, compared to RT alone, concurrent CHRT significantly improved locoregional control and overall survival. It has therefore become the standard of care for younger patients (< 70 years) with locally advanced HNSCC. However, some patients are not considered fit for CHRT. For this group, RT with concurrent cetuximab is a good alternative, with improved locoregional tumor control and overall survival rates as compared to RT alone. Another strategy for patients unfit for CHRT is hyperfractionated or accelerated RT, which significantly improved locoregional tumor control compared to standard fractionation.
Radiotherapy and radiation-induced side effects

Interaction of ionizing radiation with tissue cells causes damage (sometimes irreversible) to the cellular DNA, which kills cells and therefore damage tissue. Tumor cells are generally more sensitive to radiation compared to normal tissue cells; nevertheless the main objective of RT is to administer a lethal dose to the tumor, while avoiding the surrounding normal tissues as much as possible.

In head and neck cancer, treatment with definitive RT or CHRT is generally associated with complex-shaped, large target volumes surrounded by various critical and vital structures (e.g. the spinal cord, salivary glands, optic structures and structures involved in swallowing). Therefore, a variety of side effects may occur during and after RT or CHRT that may significantly and permanently affect health-related quality of life (HRQoL). Acute side effects affect the skin (erythema, desquamation, edema), mucous membranes (mucositis, ulceration), salivary glands (dryness (or xerostomia), thick and sticky saliva), larynx (hoarseness, cough), and pharynx and esophagus (mild to severe dysphagia, requiring a feeding tube). Late side effects may occur in the skin (atrophy, telangiectasia), subcutaneous tissue (fibrosis, loss of subcutaneous tissue), mucous membranes (atrophy, dryness, telangiectasia), salivary glands (xerostomia, fibrosis), spinal cord (L’Hermitte’s syndrome), optic pathway structures (visual deficits), larynx (hoarseness, arytenoid edema), thyroid gland (hypothyroidism), and pharynx and esophagus (fibrosis, swallowing dysfunction, aspiration).

The most devastating side effects after RT or CHRT for HNSCC are xerostomia - the most frequently reported grade 2 or higher side effect and radiation-induced swallowing dysfunction - the most frequently reported grade 3 or higher side effect, with an even larger impact on HRQoL than xerostomia. Swallowing dysfunction may subsequently result in malnutrition, dehydration, feeding tube dependency, aspiration and pneumonia. The incidence of radiation-induced swallowing dysfunction has increased significantly after the clinical introduction of more intensified treatment regimens, such as the addition of concurrent chemotherapy to radiotherapy and accelerated radiotherapy. After CHRT, swallowing dysfunction occurs in 40-80% of patients, depending on the time interval after treatment, the method of measurement and the definition of swallowing dysfunction. Similar to recovery from acute toxicity such as mucositis, pain and edema, patients with swallowing dysfunction recover as well. However, 2 years after CHRT, 4-13% of the patients still suffer from moderate to severe swallowing dysfunction.

Normal swallowing process, swallowing dysfunction and evaluation of the literature

Swallowing involves a precise coordination of multiple muscles and other structures (such as the hard and soft palate, the uvula, saliva of the salivary glands, the hyoid bone,
epiglottis, true and false vocal folds) in the oral cavity, pharynx, larynx, and esophagus (Figure 1). The swallowing process can be divided into four phases. During the first phase, the oral preparation phase, a food bolus is formed from chewed food mixed with saliva. Subsequently, during the oral phase, the bolus is transported to the pharynx, due to pressure from the base of tongue. The third phase of swallowing, the pharyngeal phase, results in the food bolus to passing into the esophagus by 1) contraction from superior to inferior of the pharyngeal musculature, including the circular constrictors and longitudinal muscles; 2) laryngeal elevation and glottic closure caused by the glottic adductor muscles and supraglottic adductors; 3) opening of the cricopharyngeal sphincter by relaxation of the cricopharyngeal muscle, upward and forward motion of the cricoid cartilage by the suprathyroid muscles, and the pressure generated on the bolus which widens both the cricopharyngeal sphincter and the inlet muscles of the esophagus. In the final phase the bolus moves into the stomach by peristalsis of the esophageal muscles.

Since swallowing is such a complex physical activity involving numerous anatomical structures, swallowing dysfunction may result from a variety of radiation-induced normal tissue reactions, such as mucosal swelling, vascular damage, neural damage, fibrosis of the muscles involved in swallowing and xerostomia.

Figure 1. Four phases of the swallowing process: (1) the oral preparation phase, (2) the oral phase, (3) the pharyngeal phase, (4) the esophageal phase. The following reference anatomical structures are shown: (a) soft palate, (b) base of tongue, (c) epiglottis, (d) cricopharyngeal sphincter. The colors indicate the oral cavity (orange), pharynx (blue), larynx (green), and esophagus (red).
Given the relatively high incidence of radiation-induced swallowing dysfunction and its major impact on HRQoL, it has become increasingly important to minimize this problem. Preventative measures for swallowing dysfunction may include exercises to improve swallowing ability by strengthening the musculature and increasing the precision of movement of the food bolus. It is generally believed that these exercises should start prior to cancer treatment and should be continued during and after treatment, even if patients have a feeding tube. Therapeutic interventions after swallowing dysfunction has developed include 1) dietary modifications (e.g. softer food, thickening agents for thinner liquids when there is aspiration); 2) pharyngeal or esophageal dilatation; 3) exercises for muscle strength; 4) swallowing manoeuvres (e.g. Mendelsohn Manoeuvre, super-supraglottic swallow); 5) postural strategies (e.g. head positioning), and; 6) prosthetics (e.g. palatal obturators to prevent food from entering the nose).

Although swallowing rehabilitation can be successful when started soon after treatment and will help to improve HRQoL for patients, the efficacy is rather disappointing. It is therefore generally assumed that the emphasis should be on prevention. Prophylactic swallowing exercises may improve some swallowing functions after CHRT, but the efficacy is hampered by poor compliance during treatment.

Another preventative approach could be to decrease the radiation dose delivered to the swallowing-related structures, assuming that a dose-effect relationship exists between functional status and the dose distribution to these structures. Several authors have reported on swallowing dysfunction after RT or CHRT and the potential involved organs at risk. The outcomes of these studies varied widely. The superior pharyngeal constrictor muscle (PCM) was a significant prognostic factor for radiation-induced swallowing dysfunction in many studies, as were the middle PCM and the inferior PCM. But the cricopharyngeal muscle, the esophageal inlet muscle, the cervical esophagus and the supraglottic and glottic larynx were significant predictors for swallowing dysfunction only a few studies. The dose to the base of tongue was not a significant risk factor in any of these studies.

Definition of organs at risk

In order to analyse the dose received to relevant organs at risk (OARs), candidate OARs have to be delineated on computed tomography scans that are used for radiotherapy treatment planning (planning CT scans). Delineation of target volumes and OARs is prone to inter- and intra-observer variability. Minimizing these variabilities may improve reporting and interpreting RT results. For HNSCC, guidelines are available for the delineation of target volumes and OARs involved, or potentially involved, in salivary dysfunction and xerostomia. However, no guidelines are available for OARs related to swallowing dysfunction.

The aforementioned 14 papers reporting on swallowing dysfunction after RT or CHRT differed in their definition and delineation of the various potential swallowing organs at risk.
risk (SWOARs)\textsuperscript{22,32,58–69}. The delineation of the SWOARs was well described in some studies, though most studies provided only cranial and caudal borders of the SWOARs, which may lead to differences in dose-volume histogram (DVH) parameters from the same treatment plan. This is particularly the case regarding structures for which the definitions differed widely (e.g., using the PCM as one structure versus dividing the PCM into a superior, middle and inferior part). Therefore, in this thesis (Chapter 2), the first step included the development of guidelines for delineation of the OARs involved, or potentially involved, in swallowing dysfunction. This would enable unambiguous reporting of DVHs for these OARs.

**Normal tissue complication probability models**

When comparing treatment plans, differences in dose distributions may result in a difference in complication probabilities, which cannot be determined directly from the differences in the dose distributions. Normal Tissue Complication Probability (NTCP) models describe the relationships between 3-dimensional dose distributions and the risk of expected toxicities. For HNSCC, various NTCP models describe the relationship between the dose to the parotid and/or submandibular salivary glands and xerostomia-related endpoints\textsuperscript{77–82}. These studies used different input parameters and different endpoints, leading to different NTCP models. Most of these studies only reported on univariate associations between one dose distribution factor (e.g. mean parotid dose) and a clinical endpoint (e.g. severe xerostomia). However, these univariate models have limitations because they assume that the development of a given side effect relies on a single dose-volume parameter, which is very unlikely. Multivariable analytic methodologies for the development of NTCP models, which take into account the effect of multiple potential prognostic factors (e.g. age, tumor stage, co-morbidity and dose distributions), are potentially more accurate and reproducible\textsuperscript{77,78,83}.

Interpretation of the results of the published studies on swallowing dysfunction after RT or CHRT is hampered by a number of methodological problems\textsuperscript{22,32,58–69}. First, these studies generally included small numbers of patients, so they did not have sufficient power to detect all clinically relevant associations, especially when many potential prognostic factors have to be taken into account. These factors consisted of a variety of dose-volume histogram parameters from multiple potential SWOARs and multiple other possible prognostic factors such as primary tumor site, fractionation schedule and the effect of adding concomitant chemotherapy to radiation. Moreover, given this high number of potential prognostic factors, their mutual correlations and the possibility of interactions between the pre-treatment determinants, more sophisticated statistical methods are required to detect the most important dose-volume histogram parameters related to swallowing dysfunction. Second, as the primary endpoint was swallowing dysfunction induced by radiation treatment, patients with swallowing dysfunction at baseline should have been ex-
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cluded from the analysis. Because some of the aforementioned studies had a retrospective or cross-sectional design, baseline swallowing dysfunction was not always taken into account. Third, the various studies used different endpoints, leading to different associations with prognostic factors for swallowing dysfunction. Patient-rated endpoints, measured on quality of life questionnaires, could lead to different associations with the SWOARs than physician-rated swallowing dysfunction. At the same time, different SWOARs could be involved in different endpoints, e.g. aspiration and tube feeding dependency.

In the studies reported in this thesis (Chapters 3, 5 and 6), we tried to avoid these methodological problems. We aimed at developing multivariable prediction models for physician-rated and patient-rated swallowing endpoints based on prospective longitudinal sufficiently powered studies in order to design Level 2 (or higher) prediction models.

Aims of this thesis

The main aims of this thesis were:

1. to develop multivariable prediction models for radiation-induced swallowing dysfunction;
2. to develop radiation delivery techniques aiming at reduction of the risk of swallowing dysfunction using information from the prediction model, and:
3. to clinically validate this swallowing sparing radiation delivery technique.

Chapter 2 reports on the first step: the development of guidelines for delineation of the organs at risk (OARs) involved in swallowing dysfunction (SWOARs) that would permit unambiguous reporting of dose-volume histograms (DVHs) for these SWOARs.

Chapter 3 presents the results of a prospective observational study of 354 consecutive patients with head and neck cancer treated with definitive radiotherapy (RT) or chemoradiation (CHRT). In this chapter we report on the results of the development of prediction models for physician-rated and patient-rated swallowing dysfunction after RT or CHRT. More specifically, we describe the identification of the SWOARs, i.e. the anatomical structures which dose distributions are significantly associated with radiation-induced swallowing dysfunction and which DVH parameters and other factors (and confounders) are important to predict radiation-induced swallowing dysfunction. This resulted in a number of multivariable NTCP models for radiation-induced swallowing dysfunction.

The next step was the development of a radiation delivery technique aiming at reduction of swallowing dysfunction by reducing the dose to the SWOARs considered most relevant in these multivariate predictive models. In Chapter 4, the potential benefit of swallowing sparing intensity modulated radiotherapy (SW-IMRT) was tested in an in silico planning comparative study.
Subsequently, we started treating patients with SW-IMRT with treatment planning optimisation using dose constraints based on the NTCP models developed in Chapter 3, and performed a new prospective cohort study to clinically validate this new technology (Chapter 5).

Chapters 3, 4 and 5 focus on swallowing dysfunction assessed 6 months after RT or CHRT. Other investigators showed that swallowing dysfunction may improve or deteriorate beyond 6 months\textsuperscript{43,44}, indicating that patients may show different patterns of swallowing dysfunction over time. These patterns may reflect various underlying radiobiological mechanisms. After the initial analysis of swallowing dysfunction at 6 months, all patients continued in a standard follow-up program, which included a subsequent prospective assessment of swallowing dysfunction up to 60 months after completion of treatment.

In Chapter 6, we report on the results of this prospective study, with a follow-up time of 24 months, identifying patterns of long-term, radiation-induced swallowing dysfunction after completion of definitive RT or CHRT.

The findings of this thesis are discussed and summarized in Chapter 7. A Dutch translation of the summary is provided in Chapter 8.

References

1. www.cijfersoverkanker.nl.
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