Prediction of patient-rated radiation-induced xerostomia

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CHAPTER 1

General introduction

Introduction

Head and neck cancer is a relatively rare malignancy that covers a heterogeneous group of cancers. Most head and neck cancers (> 90%) are squamous cell carcinoma (HNSCC) with varying degrees of differentiation originating from the mucosal areas of the oral cavity, oropharynx, nasopharynx, hypopharynx and larynx. Other histological tumour types such as adenoid cystic carcinoma and adenocarcinoma arising from salivary gland tissue, malignant melanoma, lymphoma and primary tumours arising from bone, soft tissue and skin may be found as well but their incidences are much lower.

In the Netherlands, approximately 2.500 new cases of head and neck cancer per annum are diagnosed and the incidence is gradually rising. The median age at diagnosis is approximately 65 years and the vast majority of patients are male (www.ikcnet.nl). Smoking tobacco was first described in 1957 as independent risk factor for the development of head and neck cancer located in the oropharynx en oral cavity (1). Later on, numerous studies established the use of alcohol as independent risk factor or as risk factor in combination with the use of tobacco (2-4). More recently, the association between different types of human papilloma virus (HPV) and the development of squamous cell carcinoma in the HNSCC has been described (5). Carriers of HPV are more prone to develop squamous cell carcinoma, in particular in the oropharynx.

Diagnostic procedures and tumour classification

This thesis reports on the results of radiotherapy and chemoradiation in patients treated at the departments of Radiation Oncology at the University Medical Centre Groningen (UMCG), Groningen and the VU University Medical Centre (VU*mc*), Amsterdam, the Netherlands.

In the Netherlands, all patients with proven or suspected head and neck cancer are currently referred to dedicated Head and Neck Oncology Centres (HNOC) or their preferred partners. The multidisciplinary head and neck tumour boards

of both the UMCG and VU*mc* are officially recognized as HNOC. These institutions meet the quality criteria as defined by the Dutch Head and Neck Society.

In these centres, all patients are evaluated by a multidisciplinary team consisting of head and neck surgeons, maxillofacial surgeons, radiation-oncologists, radiologists, nuclear medicine physicians, pathologists, psychologists, dieticians, oral hygienists and medical oncologists. The standard diagnostic work up procedure included physical examination (including also flexible endoscopy), CT- or MRI-scan of the head and neck area and thorax to exclude distant metastases and examination under general anaesthesia to determine the locoregional extension of the primary site. Diagnosis is normally confirmed by biopsy and subsequent histological examination. When indicated, ultrasound of the neck either or not with fine needle aspiration is performed. ^{18}F-FDG PET-CT and MRI are increasingly used to further determine locoregional tumour extension and/or distant metastases and as routine standard in specific cases, such as in case of lymph node metastases from squamous cell carcinoma from unknown primary origin. Finally, all patients are classified according to the TNM international staging system and discussed in a multidisciplinary panel to determine the most appropriate treatment approach.

Treatment and prognosis

The main treatment modalities in patients with head and neck cancer are surgery, radiotherapy and chemotherapy. For the majority of patients with limited disease, single modality treatment (surgery or radiotherapy) is generally sufficient resulting in high loco-regional control and overall survival rates (6-8). In case of more advanced disease, patients are generally treated with multiple modalities.

Patients with locally advanced HNSCC can either be treated with primary surgical or non-surgical approaches. In the last decade, non-surgical approaches have gained popularity, in particular for patients with resectable

laryngeal and hypopharyngeal squamous cell carcinoma in order to prevent total laryngectomy and to preserve a functional larynx (6,9-11). A number of prospective studies in which patients with resectable locally advanced laryngeal or hypopharyngeal squamous cell carcinoma were randomly assigned to receive primary surgery (total laryngectomy followed by postoperative radiotherapy) versus induction chemotherapy followed by radiotherapy showed that larynx preservation can be safely obtained in approximately 50-60% of the patients without jeopardizing overall survival (12)

Currently, based on the results of the meta-analysis of chemotherapy in head and neck cancer (MACH-NC), concurrent chemoradiation is considered standard of care for patients with locally advanced HNSCC (i.e. stage III-IV) in case of a non-surgical approach (13). For patients considered unfit for chemoradiation, accelerated radiotherapy with or without the concurrent use of cetuximab is a good alternative, as this combined treatment modality showed to significantly improve locoregional tumour control and overall survival as compared to radiotherapy alone (14). In the Netherlands, many patients with locally advanced HNSCC are treated with accelerated radiotherapy, which significantly improved outcome in terms of locoregional tumour control as compared to standard fractionation (15).

After primary surgery, postoperative radiotherapy or concurrent chemoradiation is indicated in the presence of adverse prognostic factors, such as advanced T-stage (T3-T4), multiple lymph node metastases, perineural growth, extranodal spread and close or positive surgical margins. Recent studies showed that the addition of concurrent chemotherapy in the postoperative setting improved locoregional tumour control as well as the overall survival, in particular in case of high risk factors for locoregional recurrence, including positive surgical margins and lymph node metastases with extra nodal spread (16,17).

In summary, radiotherapy plays a pivotal role in the primary and postoperative curative treatment of patients with HNSCC and has contributed to a significant improvement of locoregional tumour control and overall survival.

Radiation-induced side effects

The head and neck region harbours numerous delicate organs that are essential for basic physiological functions such as vision, speech, swallowing and saliva production. Besides the benefits with regard to tumour control and life expectancy, radiation treatment in this area may also result in a wide variety of radiation-induced side effects. One of the most common side effects after curative radiation for head and neck cancer is salivary dysfunction.

Normal physiology of saliva production and pathophysiology of radiation-induced hyposalivation

The saliva in the oral cavity is produced by a number of major and minor salivary glands. The three paired major salivary glands, including the parotid, submandibular and sublingual glands together contribute for about 90% of the whole saliva production. The largest salivary glands are the parotid glands, located pre-auricular around the mandible, while the submandibular glands are located in the submandibular region at the level of the hyoid bone (Figure 1)(18).

The sublingual glands are located under the tongue in the floor of mouth. Besides these major salivary glands, there are large numbers of minor salivary glands lining the mucosa of the oral cavity.

Saliva is produced by the acinar cells located in the secretory ends and is transferred through the intercalated ducts and striated ducts to the excretory ducts. The striated ducts consist of columnar cells that modify the composition of the primary saliva as formed by the acinar cells to the saliva as it is secreted into the oral cavity.

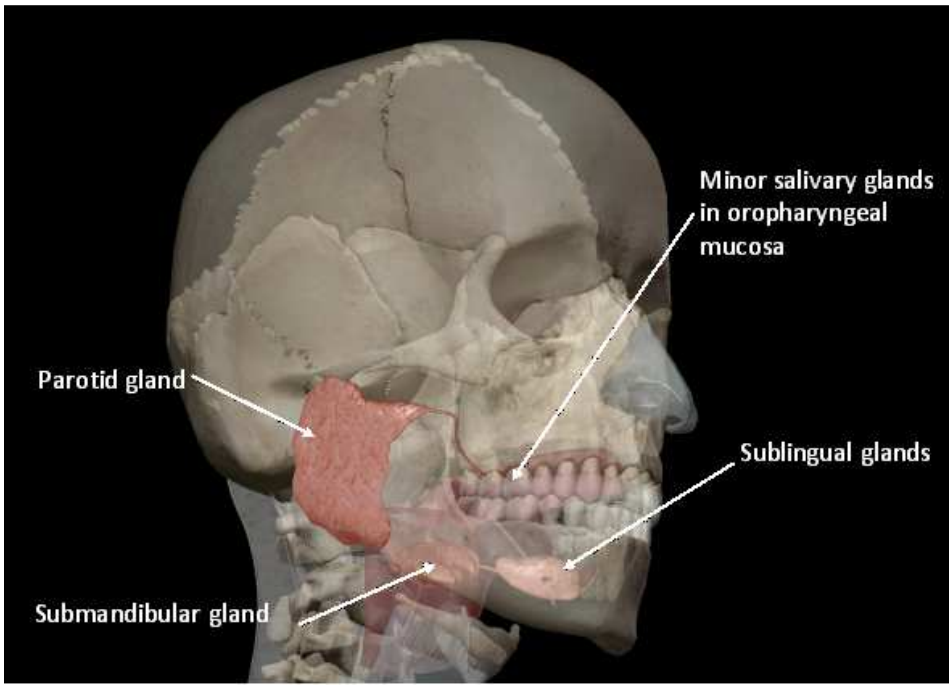

Figure 1 The anatomical positioning of the most important salivary glands.

The regulation of salivary secretion by reflexes involves the autonomic nervous system, both the sympathetic and the parasympathetic nerves. Afferent nerves carry impulses to salivary nucleus in the medulla. From here, efferent signals are directed to the salivary glands. Also afferents arising from the olfactorium and stretch of the stomach can initiate salivation. The sympathetic nerves run from the sympathetic trunk, follow the blood vessels supplying the glands and then separately innervate the glands. The parotid gland receives parasympathetic signals from the glossopharyngeal nerve; the submandibular and sublingual glands receive parasympathetic signals from the facial nerve. The blood vessels are controlled by the sympathetic nerves that make them constrict. Parasympathetic stimulation overcomes this vasoconstriction and gives vasodilatation.

Based on the findings in preclinical studies in rats, four different phases of radiation-induced damage to the salivary glands have been proposed. The acute phase (0-10 days after irradiation) is characterised by a reduced function

of the acinar cells resulting in impaired water excretion rather than a loss in acinar cell (19,20). In the second phase (10-60 days after irradiation), there is a significant loss of acinar cells and secretion of amylase, corresponding with the tissue turnover time (19,21). The third phase (60-120 days after irradiation) is characterised by stabilization of damage, followed by a fourth phase (120-140 after irradiation) in which there is a further progression of both acinar cell and function loss (19).
In patients, radiation-induced cellular and tissue effects may eventually result in the clinical signs. Hyposalivation (i.e. decreased saliva production) is still one of the most frequently reported side effects of radiation treatment in the head and neck area (22-27). Hyposalivation may result in the subjective sensation of a dry mouth (i.e. xerostomia). Radiation to the salivary glands may also change the composition of saliva resulting in the sensation of sticky saliva. In addition, changes in the extend and composition of saliva may also lead to altered taste, swallowing problems and speech problems. Eventually, a number of studies showed that xerostomia has a significant impact on the more general dimensions of health-related quality of life (QOL) (22,28-36).

Current measures to prevent hyposalivation

So far, studies on salivary dysfunction mainly focused on the univariate relationship between parotid gland dose distribution parameters and stimulated and/or unstimulated parotid salivary flow and thus on hyposalivation rather than on the effects of hyposalivation as experienced by patients (37-39). The common finding of these studies is that the mean parotid dose is the most important prognostic factor for developing hyposalivation. Based on the results of these studies, the Quantative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) Study Group updated and refined guidelines to prevent hyposalivation after radiation treatment for head and neck cancer (40,41) by defining dose constraints for the parotid glands for radiotherapy treatment planning. These QUANTEC-criteria are currently used in routine clinical practice to avoid hyposalivation and subsequent xerostomia and are

defined as follows: mean dose to one parotid gland at least less than 20 Gy or mean dose to both parotid glands at least less than 26 Gy (42).

Patient-rated xerostomia and sticky saliva

As mentioned in the previous paragraph, most studies focussed on the relationship between the parotid dose and the risk of hyposalivation. However, patients' awareness of xerostomia and sticky saliva is not only caused by hyposalivation of the major salivary glands but may also result from insufficient mucosal wetting for which mainly the minor salivary glands located in the oral cavity, soft palate, buccal mucosa and lower and upper lips are responsible (43,44). There are a number of reasons why it is important to focus more on patient-rated endpoints related to salivary dysfunction.

First, some studies showed discrepancies between different endpoints related to salivary dysfunction (45-48). It is important to notice that the correlation between salivary flow and patient-rated xerostomia is relatively weak. A decrease in salivary flow does not always correspond with an increase in xerostomia as reported by patients (45,49).

Jensen et al. also showed that physician-rated physical evaluation of treatment outcome was inferior to the patients' own assessments about post treatment toxicity (50). In general physicians tended to underestimate xerostomia as scored by patients (50). Other studies also showed that health-related quality of life (HRQOL) as scored by physicians poorly correlate to HRQOL as scored by patients (51,52). From this point of view, xerostomia and sticky saliva as reported by patients may provide important additional information in the assessment of post-radiotherapy salivary gland dysfunction.

The discrepancies between hyposalivation and patient-rated xerostomia may have an impact on the beneficial effect of radiation techniques aming at reducing the dose to the parotid glands as illustrated by Kam et al. (46). They reported on the results of a phase III study in which patients with nasopharyngeal carcinoma were randomly assigned to receive IMRT or 2-dimensional radiotherapy (2D-RT). In that study, significant differences in

stimulated parotid salivary flow, whole saliva flow and physician-rated xerostomia according to the RTOG criteria were found in favour of IMRT. However, no significant difference in patient-rated xerostomia at any time point was found (46). These findings suggest that patient-rated xerostomia cannot only be explained by changes in parotid flow due to radiation of the parotid glands, but that irradiation to other salivary glands are of importance as well. Moreover, these results also illustrate that prevention of parotid hyposalivation does not necesarilly translate into less xerostomia as experienced by patients. One of the explanations could be that function of other salivary glands play a role in patient-rated xerostomia as well. Indeed, the importance of radiation dose to salivary glands other than the parotid glands has been confirmed by the findings of other investigators (45,48). Jellema et al. found that the risk of moderate-to-severe patient-rated xerostomia not only depended on the mean dose in the parotid glands but also on the mean dose in the submandibular glands (48). Eisbruch et al.(45) also showed that the radiation dose to the minor salivary glands, such as the sublingual gland and the minor salivary glands lining the oral cavity are important as well with regard to patient-rated xerostomia.

In other words, parotid hyposalivation, which can be measured relatively easy by salivary flow measurements, is a usefull endpoint to evaluate the relationship between parotid dose and parotid function. However, from a clinical perspective, hyposalivation as such is probably less relevant.

Apart from radiation to the salivary glands, hyposalivation and patient-rated xerostomia and sticky saliva may be due by many other causes, such as medication, poor health, age and gender (Figure 2). Moreover, based on the currently available literature, the effect of more advanced treatment modalities, such as the addition of concurrent chemotherapy to radiation and the increasing use of accelerated radiotherapy, which are nowadays commonly used in routine clinical practice, on radiation-induced patient-rated xerostomia and sticky saliva remains unclear.

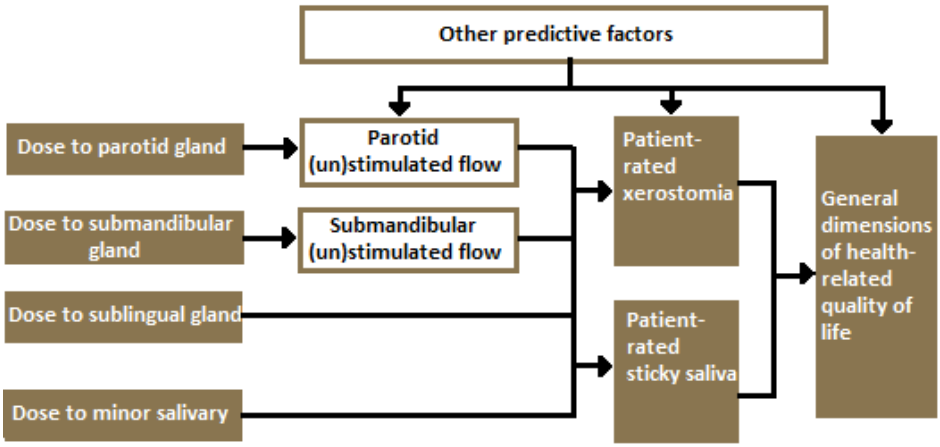

Figure 2 Theoretical model relating the salivary glands and potential demographic, tumor-related and treatment-related factors involved in the development of patient-rated xerostomia and its impact on the general dimensions of health-related quality of life.

Taking these considerations into account, in order to prevent radiation-induced patient-rated xerostomia and sticky saliva, multiple factors have to be taken into account. This requires another methodological approach than has been done so far.

Predictive modeling for radiation-induced side effects

New radiation delivery techniques, such as Intensity Modulated Radiation Therapy (IMRT), involve optimization of treatment plans using physical criteria, i.e., adequate target dose coverage and minimization of doses to organs at risk (OARs). In order to optimize the dose distribution, it should be clear which dose volume parameters to which organs at risk (OARs) are most important for the development of a given side effect. So-called Normal Tissue Complication Probability (NTCP) models generally describe the relationships between dose distribution parameters and the probability of side effects. The most commonly used NTCP-model in radiation oncology is the Lyman-Kutcher-

Burman (LKB) model. The Lyman model was originally defined for uniform irradiation. However, in particular in the era of modern radiation delivery techniques, normal tissues are rarely irradiated uniformly. Therefore, several algorithms to convert heterogeneous dose distributions into a uniform dose resulting in the same NTCP-value have been designed (53,54). The dose-volume-histogram (DVH) reduction proposed by Kutcher and Burman is the most commonly used (55). The combined formalism is often referred to as the LKB-model in the literature (56). Other examples of commonly used NTCP-models include the relative seriality and critical volume models (39).

As mentioned before, the QUANTEC study group defined guidelines to minimize the radiation dose to the parotid glands aiming to reduce xerostomia as much possible after radiation treatment for head and neck cancer. These dose constraints have been based on NTCP-modelling studies describing univariate relationships between radiation dose to the parotid glands and xerostomia (41).

One of the main disadvantages of the commonly used NTCP-models is that they only describe the direct relationship between a dose-volume parameter and a given side effect. In their original form these models do not take into account other candidate prognostic factors, such as the addition of chemotherapy, age and pre-existing co-morbidity. Similarly, these models do not take into account the possible existence of confounding and effect modulation by other factors. Another aspect that has not been taken into account so far is that for some side-effects, the risk may depend on dose distributions in multiple organs at risk, which is the case for example for swallowing dysfunction, which involves multiple anatomical structures and regions (57). Other examples of such endpoints are patient-rated xerostomia and sticky saliva, which developments may depend on dose distributions in a number of different salivary glands [see: Figure 2]. In order to identify which OARs are most relevant for the risk on such side effects and subsequently to describe a prognostic model for side effects that depends on multiple prognostic factors (including both dose volume parameters and other clinical and demographic factors), other statistical methods are required. Therefore, in

this thesis a multivariable logistic regression analysis was used with forward variable selection and bootstrapping as described by Van der Schaaf et al. (58).

The clinical validation of new radiation techniques aiming at reduction of side effects

The studies reported on in this thesis were part of the ALLEGRO (EArLy and Late hEalth risks to normal/healthy tissues from the use of existing and emerGing techniques for RadiatiOn therapy) project, a multicentre European Union research project. One of the aims of this project was to develop and validate NTCP-models for head and neck radiotherapy and to estimate the potential clinical benefit of existing (e.g. IMRT) and emerging radiation techniques (e.g. protons). For this purpose, a new methodology was developed. This methodology consists of three consecutive phases: phase 1, aiming at the development and external validation of NTCP-models; phase 2, aiming at the definition of cohorts of patients who may benefit most from new radiation techniques (e.g. protons) using the combination of NTCP-models and in silico planning comparative studies, and: phase 3 aiming at the clinical validation of new radiation techniques of these model-based indications, either through RCT's or prospective observational cohort studies using historical comparisons as a reference, whenever appropriate.

Phase 1: The development of NTCP models

The basic principle in the development of new radiation delivery techniques is the existence of validated relationships between dose distributions in OARs and the estimated risk on a given radiation-induced side effects (i.e. NTCP-value). In general, the NTCP value will increase with increasing dose and increasing volume that receives a certain dose (Figure 3).

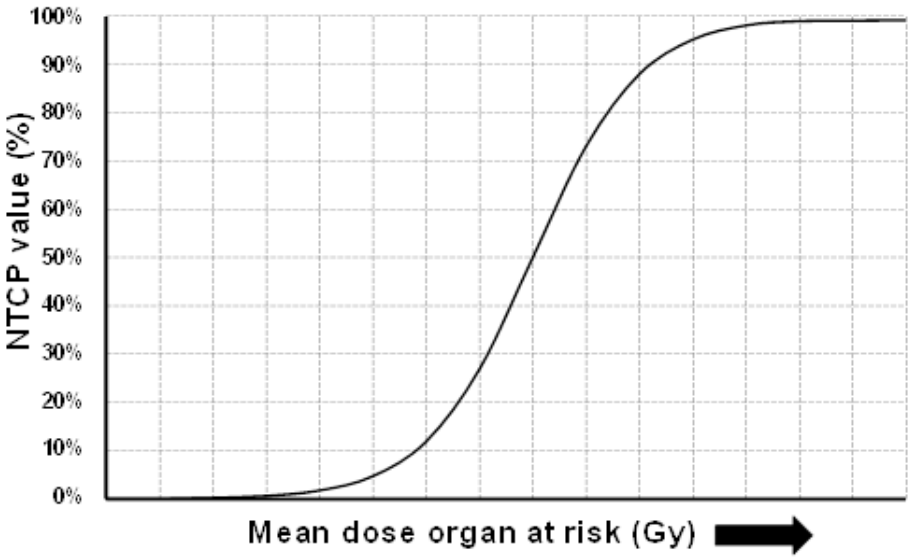

Figure 3 Normal Tissue Complication Probability as function of an increasing dose to a specific organ at risk

For the purpose of this thesis we decided to initially develop NTCP-models among patients treated with conventional 3D-conformal radiotherapy (3D-CRT) and, subsequently, to test these NTCP-models among patient populations treated with IMRT. This was done in order to test if the radiation technique itself affected the NTCP-model as was illustrated by Dijkema *et al.* (59). In that study, the NTCP-curve for salivary flow dysfunction after head and neck radiotherapy as a function of the mean parotid dose shifted to the left, indicating a higher probability of salivary dysfunction after IMRT reference to 3D-CRT with the same mean parotid dose. Therefore, if the NTCP-curve for a given side effect is similar after 3D-CRT to that after IMRT, this would further support the validity of the NTCP-model when treated with other techniques as well. For the purpose of this methodology, a prerequisite is that at least one dose distribution parameter will be significantly associated with the risk on a given side effect. If this is the case, this parameter can be used for optimisation of the radiation technique in phase 2.

Phase 2: Estimation of the clinical benefit

NTCP-models typically contain dose distribution parameters that can be used to optimize treatment planning for radiation with photons or protons. From this point of view, the question is which patients are likely to benefit from emerging radiation techniques. These subgroups must be identified from computer-based studies in which the dose distributions that can be achieved with new radiation delivery techniques are simulated and compared with the current standard in each individual patient. These kinds of studies are often referred to as *in silico planning comparative (ISPC) studies.*

The final step in phase 2 is to determine to what extent the optimised physical dose distributions will translate into a clinically relevant beneficial effect, using the combination of data from existing NTCP-models and ISPC-studies. This step is required as similar reductions in the most relevant dose distribution parameters will not always translate into the same amount of reduction in NTCP values as illustrated in Figure 4 depending on the shape of the NTCP curve and the initial value of the dose distribution parameter. In this way, the NTCP-value reduction for each individual patient can be estimated.

Phase 3: Clinical validation

The outcome of the two first phases can then be used to generate hypotheses for clinical studies aiming at the validation of these model-based indications, either through RCT's or prospective observational cohort studies using historical comparisons as a reference, whenever appropriate.

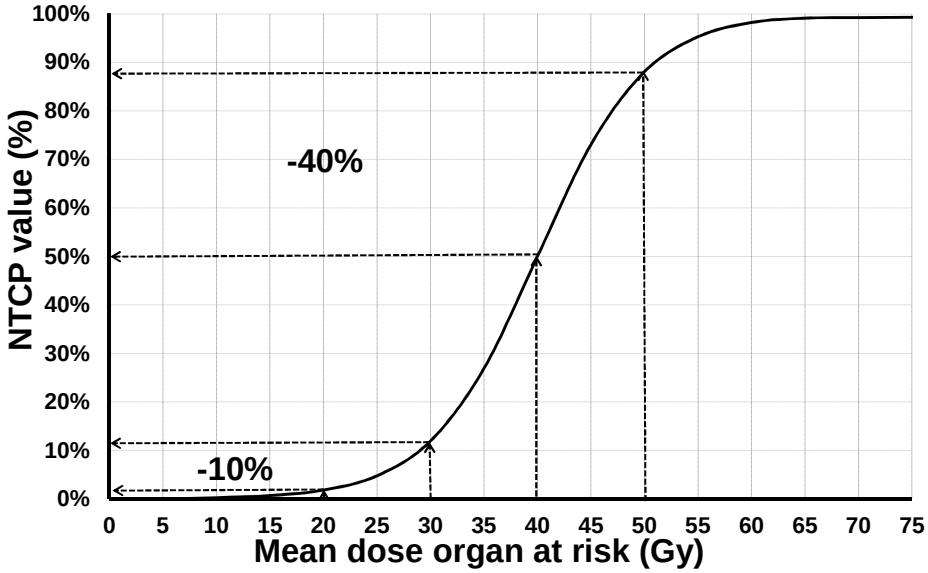

Figure 4 In this particular case, two radiation techniques were compared (IMRT versus 3D-CRT). With IMRT, the mean dose to the parotid glands could be reduced with 10 Gy from 50 Gy to 40 Gy. According to the NTCP-model, this dose reduction would result in an estimated NTCP-value reduction of 40%. However, a dose reduction of 10 Gy from 30 Gy to 20 Gy would result in an estimated NTCP-value reduction of approximately 10%.

Circadian rhythm of saliva production

Content and production of saliva varies among different salivary glands and at different time points during the day (60,61). The parotid glands are mainly responsible for the serous secretion of saliva, while the other major (submandibular and sublingual) glands and minor salivary glands (the salivary glands in the inner surface of the lips, cheeks and soft palate) produce saliva with a (much) higher viscosity (18,61-63). Although the minor salivary glands produce only a small proportion of the saliva, the saliva from these glands contains high levels of salivary proteins and thus plays a very important role in the lubrication of the mucosa. The parotid and submandibular glands are

responsible for the main stimulated saliva production and the production of saliva at rest, while during sleep the submandibular, sublingual glands and the minor salivary glands lining the oral cavity predominantly produce the saliva. In contrast, during sleep the saliva production by the parotid glands is almost zero and is negligible in relation to the total saliva production during the night (18).

Given the circadian rhythm of saliva production of the different glands over the day, some patients mainly will suffer from xerostomia at night while others have complaints predominantly during the day (64). Therefore, it is not unlikely, that multivariable NTCP-models for patient-rated xerostomia and sticky saliva differ are different during the night and during the day. This issue will also be addressed in the current thesis.

Aim of the thesis

The overall aim of this thesis was to develop and validate multivariable NTCP-models for different aspects of patient-rated complaints related to radiation-induced hyposalivation, taking into account the possible role of dose distributions in different salivary glands as well as other factors. The outcome of the studies described in this thesis was thus part of phase 1 of the aforementioned methodology.

The specific aims of this PhD project were:

- To develop multivariable NTCP-models for patient-rated xerostomia and sticky saliva among patients treated with 3D-conformal radiotherapy (*Chapter 2*)
- To test the validity of the NTCP-models developed in the study described in *Chapter 2* in a patient population treated with IMRT, taking into account dose distributions in all major and minor salivary glands as well as clinical and treatment related factors (*Chapter 3*).
- To develop IMRT specific predictive models (*Chapter 4*).

- To investigate the validity of the dose constraints as defined by the QUANTEC group to prevent xerostomia after radiation treatment in the long term (*Chapter 5*).
- To develop and validate the Groningen Radiotherapy Induced Xerostomia questionnaire, to score the different aspects of xerostomia and sticky saliva as reported by patients (*Chapter 6*). This questionnaire was specifically developed to differentiate between complaints during the day and complaints during the night.
- To investigate the role of the dose to all salivary glands for patient-rated xerostomia and sticky saliva for complaints during the day as well as during the night (*Chapter 7*).

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CHAPTER

2

Development of NTCP models for head and neck cancer patients treated with 3 dimensional conformal radiotherapy for xerostomia and sticky saliva: The role of dosimetric and clinical factors

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Abstract

Purpose:

The purpose of this multicenter prospective study was to investigate the significance of the radiation dose in the major and minor salivary glands, and other pre-treatment and treatment factors, with regard to the development of patient-rated xerostomia and sticky saliva among head and neck cancer (HNC) patients treated with primary (chemo-) radiotherapy ((CH)RT).

Methods and Materials:

The study population was composed of 167 consecutive HNC patients treated with 3 dimensional conformal (3D-CRT) (CH)RT. The primary endpoint was moderate to severe xerostomia (XER6m) as assessed by the EORTC QLQ-H&N35 at 6 months after completing (CH)RT. The secondary endpoint was moderate to severe sticky saliva at 6 months (STIC6m). All organs at risk (OARs) potentially involved in salivary function were delineated on planning-CT, including the parotid, submandibular and sublingual glands and the minor glands in the soft palate, cheeks and lips. Patients with moderate to severe xerostomia or sticky saliva at baseline were excluded. The optimum number of variables for a multivariate logistic regression model was determined using a bootstrapping method.

Results:

The multivariate analysis showed the mean parotid dose, age and baseline xerostomia (none versus a bit) to be the most important predictors for XER6m. The risk of developing xerostomia increased with age and was higher when minor baseline xerostomia was present in comparison with patients without any xerostomia complaints at baseline. Model performance was good with an Area Under the Curve (AUC) of 0.82.

For STIC6m, the mean submandibular dose, age, the mean sublingual dose and baseline sticky saliva (none versus a bit) were most predictive for sticky saliva. The risk of developing STIC6m increased with age and was higher when minor baseline sticky saliva was present in comparison with patients without any sticky saliva complaints at baseline. Model performance was good with an AUC of 0.84.

Conclusion:

Dose distributions in the minor salivary glands in patients receiving 3D-CRT have limited significance with regard to patient-rated symptoms related to salivary dysfunction. Besides the parotid and submandibular glands, only the sublingual glands were significantly associated with sticky saliva. In addition, reliable risk estimation also requires information from other factors such as age and baseline subjective scores. When these selected factors are included in predictive models, instead of only dose volume histogram parameters, model performance can be improved significantly.

Introduction

In patients with head and neck cancer (HNC), radiotherapy includes irradiation of parts of the salivary glands. This might result in salivary dysfunction and subsequent xerostomia, which is one of the most frequently reported side effects of radiation treatment in the head and neck area (1-6). In addition, salivary dysfunction may lead to additional effects, such as sensation of a dry mouth, altered taste, swallowing problems and speech problems which have a significant impact on the general dimensions of health-related quality of life (HRQOL) (1,7-15).

Content and production of saliva may differ between different salivary glands and different time points (16-22). The parotid and submandibular glands are responsible for the main stimulated saliva production and the production of saliva at rest, while during sleep saliva is predominantly produced by the sublingual and the minor salivary glands located at the inner surface of the lower lip, upper lip and both cheeks and the submandibular glands (18). In contrast, during sleep the saliva production of the parotid glands declines almost to zero.

Until now, most investigators mainly focused on the univariate relationship between parotid gland dose and stimulated and/or unstimulated parotid salivary flow (23-25). However, the development of xerostomia as reported by patients most likely depends on a variety of prognostic factors, such as radiation dose distributions in the salivary glands as well as demographic, tumour-related and treatment-related factors (26). Therefore, large prospective cohort studies are required to determine which factors are most important in predicting patient-rated xerostomia after a curative course of radiation in which all these factors can also be taken into account.

The study reported on in this paper is part of the ALLEGRO project (EArLy and Late hEalth risks to normal/healthy tissues from the use of existing and emerGing techniques for RadiatiOn therapy) which is funded by the European Union (27). The three general objectives of the ALLEGRO project are: (1) investigation of the magnitude and distribution of radiation doses in normal tissues (from all causes, adjusted where necessary for biological effect)

received in treatments with current and emerging radiation technologies; (2) investigation of the risk of second cancers from the radiation exposure of normal tissues, and: (3) modelling of the risk of normal tissue damage in common cancer treatments and estimation of the beneficial effects of emerging radiation delivery techniques (e.g., radiation with protons).
In the work package regarding normal tissue complication probability (NTCP) modelling, a 4-step approach is applied. Step 1 includes the development of predictive models among patients treated with 3D conformal radiotherapy (3D-CRT). In step 2 the validity of these predictive models will be tested among patients treated with Intensity Modulated Radiotherapy (IMRT). In step 3, we will investigate as to whether new radiation techniques could be further optimized in terms of physical dose distributions using the most relevant dose volume histogram (DVH) parameters from the predictive models from step 1 and 2, also referred to as in silico planning comparative (ISPC) studies. Finally, the aim is to estimate the potential benefit of these new techniques by combining the results of the predictive models and the ISPC-studies in order to see if, and to what extent, differences in physical dose distributions translate into reductions in NTCP-values.
The main objective of the current paper was to report on the results of the first step, i.e., the development of predictive models for patient-rated symptoms related to salivary dysfunction (i.e., xerostomia and sticky saliva) taking into account dose distributions in all salivary glands (i.e., major as well as minor salivary glands) as well as taking into account other potential clinical and treatment-related determinants.

Methods and Materials

The standardised follow up program

Since 1997, all patients referred for radiotherapy for HNC to the department of Radiation Oncology of the VU University Medical Center, Amsterdam, the Netherlands (VU*mc*), were included in a standardised follow up program (SFP). Since March 2007, the same SFP was established at the department of

Radiation Oncology of the University Medical Center Groningen, Groningen, the Netherlands (UMCG). Until the end of 2007, the majority of patients were treated with 3D-CRT, while since 2008 patients were increasingly treated with IMRT. The SFP includes a prospective evaluation of toxicity and HRQOL on a routine base, prior to, during and at regular intervals after curative (chemo-) radiotherapy ((CH) RT). HRQOL was assessed using the EORTC QLQ-C30 and the additional head and neck cancer module, the EORTC QLQ-H&N35 at baseline, 6 weeks post-treatment and at 6 month intervals thereafter (28-30).

Patients

To be included in the analysis, patients had to fulfil the following eligibility criteria: (1) HNC originating in the oral cavity, oropharynx, larynx, hypopharynx or nasopharynx; (2) treated with curative 3D-CRT either alone or in combination with chemotherapy or cetuximab; (3) no previous surgery, radiotherapy and/or chemotherapy; (4) no previous malignancies; (5) no distant metastases; (6) planning-CT and 3D-dose distributions available in DICOM-format, and: (7) HRQOL assessments available prior to and 6 months after completion of (CH)RT. Eventually, the prospective cohort used for this analysis was composed of 205 patients who fulfilled all these eligibility criteria.

Endpoints

For the evaluation of patient-rated xerostomia and sticky saliva, the EORTC QLQ-H&N35 questionnaire was used 6 months after treatment. Six months was chosen because former studies indicated that after 3D-CRT the assessment on this time point is predictive for subsequent time points (5,11,31). For all questions, including those regarding xerostomia and sticky saliva, a 4-point Likert scale was used varying from none, a bit, quite a bit and a lot. For the purpose of this study, the primary endpoint was defined as moderate to severe xerostomia at 6 months after completion of radiotherapy, which corresponds with the two highest scores on the 4-point scale. Patients

with moderate to severe xerostomia or sticky saliva at baseline were excluded from the analysis. This was done, as we were primarily interested in xerostomia and sticky saliva induced by radiation treatment itself. Thirty three patients suffered from moderate to severe xerostomia at baseline and were excluded for further analysis. From these 172 patients, 165 (96%) completed the EORTC QLQ HN35 at 6 months after treatment and were included in the analysis.
Similarly, for the analysis of sticky saliva, only those with no or minimal complaints at baseline were included. Twenty-eight of all 205 included patients suffered from moderate to severe sticky saliva and were excluded from further analysis. From the remaining 177 patients, 167 (94%) completed the EORTC QLQ-HN35 at 6 months after treatment.
The majority of patients were male (76%) and the mean age of the study population was 63.8 years, ranging from 41 to 92 years for patients included in both the xerostomia and sticky saliva analysis. Most of the patients were treated with radiotherapy alone (78%). The demographic and tumour characteristics of these two study populations are listed in Table 1.

Treatment

Radiotherapy was delivered using megavoltage equipment (6 MV linear accelerator). In all patients, a planning CT scan was made in supine position. All patients were treated with 3D-CRT, without attempts to spare the salivary glands. Patient position was fixed with a five point individual thermoplastic mask (Posicast® thermoplastics, CIVCO) in combination with a standard head support (Posifix® supine headrest, CIVCO). Position verification was carried out by using a shrinking action level correction protocol (SAL-protocol), using an electronic portal imaging device (EPID).
Patients with early glottic carcinoma were treated with a fraction dose of 2.5 Gy (5 times/week) up to a total dose of 60 Gy in 5 weeks or with a fraction dose of 2.0 Gy (5 or 6 times/week) up to a total dose of 66 Gy. These patients were only irradiated at the primary site.

Table 1 Demographic and disease-related characteristics for the patients included in the xerostomia (165) and sticky saliva analysis (n=167).

Characteristics	Xerostomia (n=165)	%	Sticky saliva (n=167)	%
Sex				
Male	126	76	124	74
Female	39	24	43	26
Age				
≤65	101	61	99	59
≥65	64	39	68	41
Chemotherapy				
Yes	36	22	36	22
No	129	78	131	78
Tumour classification				
T0	5	3	6	4
T1	27	16	28	17
T2	85	52	87	52
T3	25	15	22	13
T4	23	14	24	14
Node classification				
N0	113	69	118	70
N1	10	6	9	5
N2a	5	3	5	3
N2b	17	10	16	10
N2c	16	10	16	10
N3	4	2	3	2
Site				
Oropharynx	47	29	46	28
Sinuses and nasopharynx	6	4	7	4
Hypopharynx	10	6	9	5
Larynx	93	69	100	60
Miscelaneous	4	2	5	3
Bilateral neck irradation				
yes	111	67	110	66
no	54	33	57	34
Medical center				
UMCG	43	26	43	26
VU*mc*	122	74	124	74

Patients treated with concomitant CHRT were treated with conventional fractionation (2.0 Gy per fraction, 5 times per week up to 70 Gy in 7 weeks). In case of primary radiotherapy of the more advanced cases, which were considered not eligible for CHRT, an accelerated schedule with concomitant boost technique was used, either or not combined with cetuximab. These patients were generally treated with 6 fractions per week with a second fraction on Friday afternoon with a minimum interval of 6 hours, up to a total dose of 70 Gy in 6 weeks. Most patients received bilateral elective irradiation of the neck nodes to a total dose of 46 Gy and a boost on the primary tumour and pathological lymph nodes to a total dose of 70 Gy. In some cases, radiotherapy only with conventional fractionation was used.

Contouring of organs at risk

Organs at risk (OARs) potentially involved in salivary function related symptoms were delineated according to the guidelines for OARs potentially involved in radiation-induced salivary dysfunction and xerostomia as described by Van de Water et al. (26), including the parotid, submandibular and sublingual glands, as well as the minor salivary glands located in the soft palate, the inner surface of the lower and upper lip and the minor salivary glands in the inner surface of the cheeks. All OARs were delineated by an expert in head and neck radiation (JL). For this purpose, all planning-CT scans were transferred to the Pinnacle Treatment Planning System (TPS) (version 8.0 h, Philips Radiation Oncology Systems, Fitchburg, WI). After completing OARs contouring, all data were transferred to the VODCA platform (VODCA Company: viewer version 4.2.2. and database version 4.1.1). The VODCA platform is a software program which allows for dose distribution evaluation of different TPS's.

Dose distribution calculations

The dose distributions from the original treatment planning systems (Pinnacle, Masterplan, Eclipse, CadPlan) used were transferred to the VODCA platform in DICOM format. The original dose distributions in all aforementioned potential OARs could be reconstructed and DVHs could be generated.

Statistics

For the development of the predictive models for patient-rated xerostomia and sticky saliva, a multivariate logistic regression analysis was used with an extended bootstrapping technique and forward variable selection as described by El Naqa et al. (32). In contrast to the El Naqa method, our method uses the likelihood criterion, instead of correlation measures. The average likelihood is calculated over all test datasets for each combination of variables. The model which gives the highest average likelihood was selected as the most predictive model.

Before carrying out the regression analysis, a correlation matrix was produced to check for high correlations between potential prognostic determinants, in particular between DVH-parameters. In case of Pearson correlation coefficients ≥0.8 between potential prognostic determinants, these variables were combined into a single variable to avoid the problem of multicollinearity which may negatively affect the generalisability of the model. Finally, all DVH data were transferred to MATLAB (version R2009b) and connected to all other potential pre-treatment prognostic factors for each individual patient.

The variables initially included in the multivariate model are listed in Table 2. After reducing the number of variables based on the correlation coefficient analysis, a multivariate logistic regression with forward selection and an extended bootstrapping technique was carried out. We used 2000 bootstraps for each analysis. For every model order, the average likelihood of predictions was calculated and the number of variables selected with the highest average likelihood was selected for the definite predictive model for patient-rated xerostomia and sticky saliva.

After selecting the combination of variables with the highest performance in MATLAB, the analysis was repeated in SPSS for windows (version 16.0; SPSS, Chigaco, Il) using exactly the same dataset and selected variables. Adjusted Odd's ratios (OR) and 95% confidence intervals (95% CI) were calculated in SPSS for the selected variables in the model. For each patient, predictive values (i.e., NTCP values) were calculated for each set of prognostic variables based on the regression coefficients according to the formula:

$$NTCP = \left(1 + e^{-S}\right)^{-1}$$,in which

In SPSS, model performance was then determined by calculating the area under the curves (AUC) based on Receiver Operating Characteristics.

$$S = \beta_0 + \sum_{i=1}^{n} \beta_i \cdot x_i$$

Results

Variable reduction and dose distribution procedure

In order to reduce the number of variables in the model, we first produced a correlation matrix to identify DVH-parameters of all OARs that were strongly correlated (i.e., Pearson correlation coefficient > 0.8) (Figure 1). There was a very strong correlation between all DVH parameters within each OAR and the mean dose of that OAR. Therefore, we decided to only include the mean doses of all OARs in the multivariate model to prevent the problem of multicollinearity. In addition, we also found a very strong correlation between the mean dose in the ipsilateral and contralateral parotid, submandibular and sublingual glands and the ipsi- and contralateral glands in the cheek (Pearson r > 0.8). Therefore, we decided to use the mean dose in these ipsi- and contralateral glands as one single variable.

		Parotid gland ipsilateral							Partoid gland contralateral						
		Mean dose	Max dose	V5	V10	V20	V40	V60	Mean dose	Max dose	V5	V10	V20	V40	V60
Parotid gland ipsilateral	Mean dose		0.89	0.88	0.90	0.95	0.97	0.83	0.81	0.71	0.79	0.74	0.73	0.76	0.63
	maximum dose	0.89		0.91	0.92	0.90	0.85	0.63	0.74	0.83	0.83	0.76	0.71	0.67	0.49
	V5	0.88	0.91		0.99	0.95	0.87	0.57	0.75	0.77	0.90	0.84	0.77	0.71	0.46
	V10	0.90	0.92	0.99		0.97	0.91	0.61	0.75	0.75	0.89	0.82	0.77	0.72	0.49
	V20	0.95	0.90	0.95	0.97		0.96	0.69	0.78	0.73	0.86	0.80	0.77	0.76	0.55
	V40	0.97	0.85	0.87	0.91	0.96		0.80	0.78	0.67	0.79	0.74	0.75	0.79	0.63
	V60	0.83	0.63	0.57	0.61	0.69	0.80		0.64	0.49	0.52	0.49	0.54	0.62	0.76
Parotid gland contralateral	Mean dose	0.81	0.74	0.75	0.75	0.78	0.78	0.64		0.89	0.85	0.91	0.96	0.97	0.75
	maximum dose	0.71	0.83	0.77	0.75	0.73	0.67	0.49	0.89		0.87	0.91	0.90	0.84	0.56
	V5	0.79	0.83	0.90	0.89	0.86	0.79	0.52	0.85	0.87		0.96	0.89	0.82	0.50
	V10	0.74	0.76	0.84	0.82	0.80	0.74	0.49	0.91	0.91	0.96		0.95	0.89	0.54
	V20	0.73	0.71	0.77	0.77	0.77	0.75	0.54	0.96	0.90	0.89	0.95		0.97	0.63
	V40	0.76	0.67	0.71	0.72	0.76	0.79	0.62	0.97	0.84	0.82	0.89	0.97		0.73
	V60	0.63	0.49	0.46	0.49	0.55	0.63	0.76	0.75	0.56	0.50	0.54	0.63	0.73	

Correlation < 0.7
Correlation >0.7 <0.8
Correlation >0.8

Figure 1 Paerson correlation coefficients between the ipsi- and contralateral parotid gland. Part of the correlation matrix. Strong correlations between two variables (>0.8) are colored in red. Very strong correlations within and between ipsi- and contralateral salivary glands were observed and therefore analyses were carried out with pairs of ipsi- and contralateral glands, to avoid multicollinearity.

Prevalences of patient rated xerostomia and sticky saliva

At 6 months after treatment, 52% of the patients reported moderate to severe xerostomia. After 12, 18 and 24 months, 38%, 35% and 35%, respectively, reported moderate to severe xerostomia. At 6 months after treatment, 43% of the patients reported moderate to severe sticky saliva. At 12, 18 and 24 months after treatment, 28%, 33% and 27%, respectively reported moderate/severe sticky saliva. Additional analysis showed that the 6 month assessments were very predictive for these endpoints at subsequent time points. Therefore, we decided to use the 6 months assessments as primary outcome measure for the current analysis.

Xerostomia

In the univariate analysis, the mean dose in the parotid, submandibular and sublingual glands, the minor glands in the cheeks, the minor glands in the soft palate, chemotherapy, bilateral neck irradiation and baseline xerostomia and sticky saliva score (none versus a bit) and the treatment centre were significantly associated with patient-rated xerostomia 6 months after treatment (Table 2). Average likelihood of bootstrap prediction in the multivariate logistic regression analysis was optimal with a model consisting of three variables (Figure 2). Increasing the number of variables to four did not further increase the average likelihood of the model compared to the 3-factor model.

Table 2 Univariate logistic regression coefficients for all possible predictors for xerostomia and sticky saliva.

Predictor	Xerostomia					Sticky saliva				
	β	*OR*	*95% CI*	*p-value*	*AUC*	*β*	*OR*	*95% CI*	*p-value*	*AUC*
Mean dose parotid glands (Gy)	0.06	1.06	1.04 - 1.08	<0.01	0.79	0.03	1.03	1.02 - 1.05	<0.01	0.69
Mean dose submandibular glands (Gy)	0.05	1.05	1.03 - 1.07	<0.01	0.75	0.04	1.04	1.02 - 1.05	<0.01	0.68
Mean dose sublingual glands (Gy)	0.02	1.02	1.01 - 1.04	<0.01	0.72	0.00	1.00	0.99 - 1.01	0.67	0.57
Mean dose cheeks (Gy)	0.04	1.04	1.02 - 1.07	<0.01	0.72	0.00	1.00	0.99 - 1.02	0.77	0.55
Mean dose inner surface lower lip (Gy)	0.02	1.02	1.00 - 1.05	0.07	0.67	-0.13	0.99	0.97 - 1.01	0.21	0.51
Mean dose inner surface upper lip (Gy)	0.03	1.03	1.00 - 1.07	0.06	0.65	-0.15	0.99	0.96 - 1.01	0.30	0.52
Mean dose soft palate (Gy)	0.03	1.03	1.02 -1.05	<0.01	0.75	0.01	1.01	1.00 - 1.02	0.06	0.61
Sex	0.24	1.27	0.67 - 2.40	0.46	0.56	0.31	1.37	0.68 - 2.74	0.38	0.53
Age	0.01	1.01	0.98 - 1.04	0.54	0.51	0.03	1.03	1.00 - 1.06	0.06	0.57
Chemotherapy	0.93	2.53	1.15 - 5.58	0.02	0.58	0.21	1.24	0.59 - 2.59	0.57	0.52
Accelerated radiotherapy	-0.29	0.75	0.40 - 1.42	0.38	0.53	0.02	1.02	0.54 - 1.91	0.96	0.50
Baseline xerostomia score	1.01	2.75	1.39 - 5.47	<0.01	0.61	0.63	1.87	1.15 - 3.04	0.01	0.61
Baseline sticky saliva score	0.59	1.81	1.01 -3.23	0.05	0.57	0.94	2.57	1.27 - 5.17	<0.01	0.59
Bilateral neck irradiation	1.80	6.06	2.90 - 12.66	<0.01	0.68	1.97	7.15	3.19 - 16.01	<0.01	0.69
Medical centre (UMCG *vs* VUMC)	1.09	2.98	1.43 - 6.21	<0.01	0.60	1.54	4.67	2.0 - 10.9	<0.01	0.63

Table 3 Distributions of the mean dose for the selected organs at risk for the patient-rated xerostomia NTCP model (parotid glands) and for the NTCP model for patient-rated sticky saliva (submandibular glands and sublingual glands). The analysis for patient-rated xerostomia included 165 patients and for sticky saliva 167 patients.

	Mean dose parotid glands (n=165)		Mean dose submandibular glands (n=167)		Mean dose sublingual glands (n=167)	
Dose (Gy)	Number of patients	%	Number of patients	%	Number of patients	%
0-10	45	27	25	15	80	48
10-20	9	5	13	8	12	7
20-30	35	21	9	5	7	4
30-40	29	18	11	7	11	7
40-50	13	8	29	17	17	10
50-60	11	7	19	11	14	8
60-70	23	14	31	19	19	11
>70	0	0	30	18	7	4

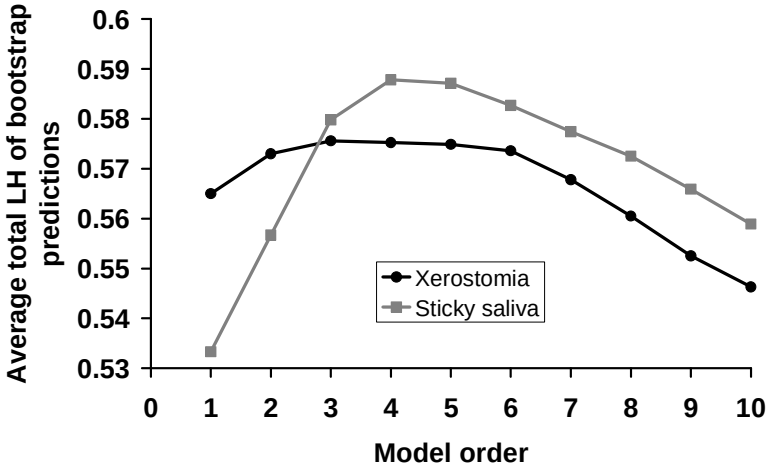

Figure 2 Average likelihood for bootstrapping technique for each number of selected variables in the multivariate logistic regression analysis for each model order. Best model performance is observed with a model order with the highest average of total likelihood of bootstrap predictions. For respectively xerostomia and sticky saliva best model performance was seen with three and four selected variables.

The three variables selected were the mean dose to the parotid glands, age and baseline xerostomia (none versus a bit). AUC for this 3-factor model was 0.82 (95% CI 0.76 – 0.89). This model describes the relation for a mean dose of the parotid glands ranged from low dose to high dose (table 3). The OR's for each of the 3 selected variables are shown in Table 4. The NTCP-value for each individual patient can be calculated by the following logistic regression formula:

$$NTCP = \left(1 + e^{-S}\right)^{-1}$$, in which

S= -5.27 + (*mean dose parotid gland* * 0.066) +
(*age* * 0.050) + (*baseline xerostomia score* * 0.916)

Sticky saliva

In the univariate analysis, the mean dose to the parotid and submandibular glands, bilateral neck irradiation, baseline sticky saliva score and xerostomia score (none versus a bit) and the treatment centre were significantly associated with patient-rated sticky saliva 6 months after treatment (Table 2). In the multivariate analysis with bootstrapping, the average likelihood was maximal with a model consisting of 4 variables (Figure 2).
The four factor model included the following variables: the mean dose to the submandibular glands, age, the mean dose in the sublingual glands and sticky saliva at baseline. AUC for this four factor model was 0.84 (95% CI 0.78 – 0.90). This model describes the relation for a mean dose of the submandibular and sublingual glands ranged from low dose to high dose (table 3). Odd's ratios for each selected variable are listed in Table 4.
A negative logistic regression coefficient (-0.041) was found for the mean dose of the sublingual glands and the OR was 0.96 for each Gray increase in dose (95 % CI 0.94 – 0.98). Elderly patients suffered more from sticky saliva 6 months after treatment and patients with minor sticky saliva at baseline are more prone to develop moderate to severe sticky saliva as compared to those

without any complaints of sticky saliva. The NTCP-value for each individual patient can be calculated by the following logistic regression formula:

$$NTCP = \left(1 + e^{-S}\right)^{-1}$$, in which

S= -10.70 + (*mean dose submandibular glands* * 0.091) + (*age* * 0.107) + (*baseline sticky saliva score* * 1.218) + (*mean dose sublingual glands* * -0.041)

Table 4 Multivariate logistic regression model for patient-rated xerostomia and sticky saliva 6 months after treatment.

Predictor	β	*p-value*	Odds ratio	95%CI
Xerostomia model				
Mean dose parotid glands (Gy)	0.066	<0.001	1.07	1.05 - 1.09
Age (years)	0.050	0.014	1.05	1.01 - 1.09
Baseline xerostomia score (none vs a bit)	0.916	0.024	2.50	1.13 - 5.55
Constant	-5.27	<0.001		
Sticky saliva model				
Mean dose submandibular glands (Gy)	0.091	<0.001	1.10	1.06 - 1.13
Age (years)	0.107	<0.001	1.11	1.06 - 1.17
Mean dose sublingual glands (Gy)	-0.041	<0.001	0.96	0.94 - 0.98
Baseline sticky saliva score (none vs a bit)	1.218	0.006	3.38	1.42 - 8.06
Constant	-10.70	<0.001		

Discussion

In this study, we investigated the significance of radiation dose distributions in the major and minor salivary glands in relation to patient-rated xerostomia and sticky saliva among patients treated with 3D-CRT. The results revealed that dose distributions in the minor salivary glands have limited significance for the development of patient-rated symptoms related to salivary dysfunction among patients treated with 3D-CRT. Besides the dose distributions in the parotid glands and the submandibular glands, only the dose distributions in the sublingual glands were significantly associated with patient-rated sticky saliva. For both xerostomia and sticky saliva the risk was higher with increasing age and pre-existing minor complaints at baseline. This multivariate analysis of

patient-rated xerostomia and sticky saliva clearly indicates, that the estimation of the risk on developing these endpoints cannot be described by a simple univariate relationship between the dose in one OAR and these patient-rated endpoints.

In an earlier report, Jellema et al reported on the results of a similar prospective study (31). It should be noted that approximately two-third of the patients included in the study of Jellema were also used in this study. The main differences was that in the current study, we only included patients treated with primary (CH) RT while patients treated with surgery were excluded. The reason for this was that we were primarily interested in radiation-induced changes and preferred to only include patients with all salivary glands in situ. Another difference with the study of Jellema et al. was that instead of using the oral cavity dose as a surrogate for the dose in all individual minor glands in the cheeks, soft palate and lips, the dose distributions in all minor salivary glands were taken into account separately.

In the multivariate analysis the role of the minor salivary glands was limited and only the sublingual glands were selected as possible predictor for patient-rated sticky saliva. In the univariate analysis for xerostomia the minor salivary glands in the soft palate were significantly associated with the development of patient rated xerostomia. Similar results were found by Jellema et al. They also found a significant association between the dose in the oral cavity in the univariate analysis which however disappeared in the multivariate analysis if the mean parotid dose was entered in the multivariate model (31). It should be stressed that these patients were all treated with 3D-CRT with consequently high correlations between the dose distribution parameters of the salivary glands included in the analysis.

We decided to analyze the parotid glands, submandibular glands, sublingual glands and the minor salivary glands separately because the content of saliva production of these glands is different from each other (16-22). It is not unlikely that with IMRT, in which the dose to the parotid glands is significantly lower, the relative importance of the dose distributions to the submandibular glands and the minor glands increases. Therefore, the findings of the current

study based on patients treated with 3D-CRT should be externally validated among those treated with more advanced techniques such as IMRT.

In the univariate analysis the treatment centre appeared as a possible independent predictor for as well patient-rated xerostomia and sticky saliva. The majority of patients treated in the University Medical Centre Groningen were treated with primary radiotherapy for laryngeal tumours and therefore had relatively low dose to the salivary glands located in the oral cavity. In contrast, patients treated in the VU Medical Centre were mainly included before 2007 and consisted of relatively more patients with oropharyngeal and oral cavity tumours. Therefore the patients included from the VU*mc* had on average higher doses to the salivary glands. After correcting for these differences in case mix in the multivariate analysis, treatment centre itself was not significantly associated with any of the endpoints anymore.

This study investigated the relationship between patient-rated xerostomia and sticky saliva and the dose distributions in a variety of salivary glands as well as other potential predictive factors. Until now, most studies focused on the univariate relationship between dose and stimulated parotid flow (23-25). Several NTCP models were used to describe this relationship. The Lyman-Kutcher-Burman model is currently the most commonly used NTCP model (33,34). This model assumes a dose volume dependent and tolerance dose relation between a specific OAR and a specific endpoint. Other models also used information about dose distributions and fractionation (35,36). El Naqa et al. was the first study published describing a model not only based on dose volume characteristics, but also took other potential prognostic clinical factors into account (32).

Some studies showed discrepancies between different endpoints related to salivary dysfunction (13,31,37-39). Kam et al. showed significant differences in stimulated parotid salivary flow, whole saliva flow and physician-rated xerostomia according to the RTOG criteria in a patient population treated for head and neck cancer with IMRT compared with a patient population treated with 2-dimensional radiotherapy (2D-RT). However, no significant difference in patient-rated xerostomia was found (38). These findings suggest that patient-rated xerostomia can not only be explained by changes in parotid flow due to

radiation of the parotid glands, but other clinical factors are of importance as well.

The parotid glands are responsible for the serous secretion of saliva, while the other major and minor salivary glands produce saliva with a (much) higher viscosity (16,18,40,41). Radiation damage of the acinar cells in the parotid glands diminish the saliva production (8,18). Due to irradiation of the submandibular glands and parotid glands the serous secretion of saliva is diminished more then the mucus secretion (8,17,18,40,41). The viscosity and pH of the saliva will change in such a way that patients will be more aware of sticky saliva (8,17,18,40,41).

An important finding was the inverse relationship between the mean dose to the sublingual glands and patient-rated sticky saliva. A possible explanation for this apparent protective effect of irradiation could be related to the composition of the saliva produced by the sublingual glands. The sublingual glands only produce highly viscous mucous saliva (18), while irradiation of the parotid and submandibular glands will mainly reduce production of serous saliva production. Irradiation of the latter major glands with sparing of the sublingual glands may increase the ratio between mucous saliva and serous saliva, resulting in higher viscosity of saliva and thus more sticky saliva. Irradiation to the sublingual glands will reduce the mucous saliva production resulting in a more balanced ratio between mucous and serous saliva production.

Another important finding was that elderly patients have a higher probability of suffering from xerostomia and sticky saliva than younger patients. This is completely in agreement with the fact that the prevalence of hyposalivation and xerostomia and sticky saliva in a healthy population is higher in patients beyond 50 year (42). Older patients are more likely to use medication and to have co-morbidity that may influence and reduce the saliva production at rest (43,44). Therefore older patients are more prone to develop xerostomia and sticky saliva due to reduced secretory reserve (45). Only small influences on the secretion of saliva of the salivary glands, like medication and radiation dose, is needed to develop hyposalivation (45,46).

The development of the NTCP models for patient-rated xerostomia and sticky saliva in patients treated for head and neck cancer with 3D-CRT was the first study in the four-step ALLEGRO approach to build validated predictive models which can be used in the estimation which patients will benefit from new radiation techniques. The next step in the ALLEGRO project will be the validation of these models in a population treated with IMRT. It is not self-evident that predictive models developed among patients treated with 3D-CRT are per definition valid among patients treated with other radiation delivery techniques, such as IMRT, due to the fact that the dose distributions in the salivary glands will show much more variability with IMRT. This was very nicely illustrated by Dijkema et al. who showed that the NTCP model for salivary flow among patients treated with 3D-CRT differed from that among patients treated with IMRT (47). Moreover, with IMRT, the correlation between the dose distributions in the paired glands will differ much more, which means that both glands will probably be selected for inclusion in the multivariate analysis, which was not the case in the present study.

Recently, we reported on the validation of a new xerostomia questionnaire (the Groningen Radiotherapy-Induced Xerostomia questionnaire (GRIX)), which can distinguish between patient-rated xerostomia and sticky saliva in different situations, such as complaints during the day or during the night (48). As during the night, the minor saliva glands and submandibular glands play a more important role in production of saliva than the parotid glands, it could be hypothesized that predictive models for these complaints change in correspondence with circadian rhythms of salivary productions of the different salivary glands (18).

In conclusion, we developed predictive models for patient-rated xerostomia and sticky saliva treated with 3D-CRT for head and neck cancer, using multivariate bootstrap logistic regression analysis. The results of our study illustrate that these endpoints cannot be predicted with one simple relationship between the dose distribution in an OAR and an endpoint but that other factors than DVH parameters are important as well. However, the role of the dose distributions to the minor salivary glands (the sublingual glands, the salivary glands in the soft palate and the inner surface of the cheeks and lips)

on the development of these factors appears limited when treated with 3D-CRT. These results should be validated among patients treated with IMRT.

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CHAPTER 3

External validation of three dimensional conformal radiotherapy based NTCP models for patient-rated xerostomia and sticky saliva among patients treated with intensity modulated radiotherapy

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Abstract

Purpose

The purpose of this study was to investigate the ability of predictive models for patient-rated xerostomia (XER_{6M}) and sticky saliva ($STIC_{6M}$) at 6 months after completion of primary (chemo)radiation developed in head and neck cancer patients treated with 3D-conformal radiotherapy (3D-CRT) to predict outcome in patients treated with intensity modulated radiotherapy (IMRT).

Methods and materials

Recently, we published the results of a prospective study on predictive models for patient-rated xerostomia and sticky saliva in head and neck cancer patients treated with 3D-CRT (3D-CRT based NTCP models). The 3D-CRT based model for XER_{6M} consisted of 3 factors, including the mean parotid dose, age, and baseline xerostomia (none versus a bit). The 3D-CRT based model for $STIC_{6M}$ consisted of the mean submandibular dose, age, the mean sublingual dose, and baseline sticky saliva (none versus a bit).
In the current study, a population consisting of 162 patients treated with IMRT was used to test the external validity of these 3D-CRT based models. External validity was described by the explained variation (R^2 Nagelkerke) and the Brier score. The discriminative abilities of the models were calculated using the area under the Receiver Operating Curve (AUC) and calibration (i.e. the agreement between predicted and observed outcome) was assessed with the Hosmer-Lemeshow “goodness-of-fit” test.

Results

Overall model performance of the 3D-CRT based predictive models for XER_{6M} and $STIC_{6M}$ was significantly worse in terms of the Brier score and R^2 Nagelkerke among patients treated with IMRT. Moreover the AUC for both 3D-CRT based models in the IMRT treated patients were markedly lower. The

Hosmer Lemeshow test showed a significant disagreement for both models between predicted risk and observed outcome.

Conclusion

3D-CRT based models for patient-rated xerostomia and sticky saliva among head and neck cancer patients treated with primary radiotherapy or chemoradiation turned out to be less valid for patients treated with IMRT. The main message from these findings is that models developed in a population treated with a specific technique cannot be generalized and extrapolated to a population treated with another technique without external validation.

Introduction

Treatment of patients with head and neck cancer (HNC) generally includes radiotherapy as either primary or postoperative modality which causes irradiation of at least some parts of the salivary glands. Irradiation of the salivary glands may result in salivary dysfunction and subsequent xerostomia, which is one of the most frequent reported side effects of radiation treatment in the head and neck area (1-8).

Since the risk of normal tissue complications depends on the volume of irradiated normal tissue, developments in radiotherapy are focusing on the reduction of the amount of normal tissue that is co-irradiated (9). For optimization of radiotherapy treatment planning, predictive models that describe the relationship between dose distributions in organs at risk and the probability of radiation-induced complications are required.

As such, we recently reported on the development of predictive models for patient-rated xerostomia and sticky saliva among patients with head and neck cancer (HNC) treated with 3D-conformal radiotherapy (3D-CRT) (10). The predictive model for patient-rated moderate to severe xerostomia at 6 months after completing (chemo)radiation ((CH)RT) was composed of the mean dose to both parotid glands, age and baseline xerostomia. The predictive model for moderate to severe patient-rated sticky saliva at the same time point was composed of the mean dose to both submandibular glands, the mean dose to both sublingual glands, age and baseline sticky saliva as reported by patients.

Based on the results of a number of randomised controlled trials (11-14), intensity modulated radiotherapy (IMRT) can now be considered as the standard of care in patients irradiated for head and neck cancer. As a result, the dose distributions in relevant organs at risk, in particular in the parotid glands, are different to those obtained with 3D-CRT. This might be relevant for predictive models related to salivary dysfunction as preclinical animal studies in the rat parotid gland showed that dose to different sub-volumes of the gland resulted in different responses (15). While irradiation of the caudal 50% of the parotid gland resulted in damage limited to the irradiated volume and a corresponding loss of function, irradiation of the cranial 50% of the gland

resulted in degradation of the entire gland and more severe loss of function (15,16). As such, a response of the parotid gland after irradiation with a non-uniform dose distribution such as given with IMRT may differ from the response after a more uniform irradiation such as given in 3D-CRT. From this point of view, the question arises as to whether predictive models developed among patients with 3D-CRT are also valid among those treated with IMRT.
Therefore, the main purpose of this study was to test if the 3D-CRT-based models for patient-rated xerostomia and sticky saliva can also make valid predictions among patients treated with IMRT.

Methods and Materials

Patients

In the current prospective study, we only included patients treated with IMRT. The additional patient selection criteria were exactly the same as the selection criteria mentioned in the previous paper reporting on the results obtained among patients treated with 3D-CRT (10), These criteria include: 1) HNC originating in the oral cavity, oropharynx, larynx, hypopharynx, nasopharynx, paranasal sinuses or cervical lymph node metastases from unknown primary tumours; 2) curative radiotherapy either alone or in combination with chemotherapy or cetuximab; 3) no previous surgery, radiotherapy and/or chemotherapy; 4) no previous malignancies; 5) no distant metastases, and: 6) HRQOL assessments available prior to and at 6 months after completion of (CH)RT. The study was conducted according to the regular procedures of the local ethical committee of the University Medical Centre Groningen and VU University Medical Centre, Amsterdam.

The standard follow-up program

All patients included in this analysis were subjected to a standard follow-up program (SFP) as previously described (10,17). The SFP includes a prospective

evaluation of toxicity and HRQOL on a routine base, prior to, during and at regular intervals after curative CH(RT). HRQOL was assessed using the EORTC QLQ-C30 and the additional head and neck cancer module, the EORTC QLQ-H&N35 at baseline, 6 weeks post-treatment and at 6 month intervals thereafter (18-20).

Endpoints

For the evaluation of patient-rated xerostomia and sticky saliva, the EORTC QLQ-H&N35 questionnaire was used. For the purpose of this study, the primary endpoint was defined in exactly the same way as in the previous study, i.e., as moderate to severe xerostomia and sticky saliva at 6 months after completion of radiotherapy (10). Patients with moderate to severe xerostomia or sticky saliva at baseline were excluded from the corresponding analyses.

Treatment

In all patients, a planning CT-scan with contrast-enhancement was performed in treatment position. Radiotherapy was delivered using a 6 MV linear accelerator. The target volumes for the initial fields and boosts were similar as described for the 3D-CRT patients (10). In summary, the clinical target volume of the initial field (CTV1) was composed of the primary tumour and pathological lymph nodes plus a 1.0 cm margin, and the elective nodal areas on both sides of the neck, selected according to the guidelines reported by Gregoire, et al. (21). The CTV for the boost irradiation (CTV2) consisted of the primary tumour and pathological lymph nodes with a 0.5 cm margin. In all cases, a 0.5 cm margin was applied for the planning target volumes (PTV1 and PTV2). The mean dose to both parotid glands was reduced as much as possible without compromising the required dose to the target volumes.
Patients in the validation cohort were treated with dynamic IMRT with a sliding window technique, as well as with step-and-shoot IMRT. In general, a seven-

field equidistant, non-opposing beam configuration was used. Step-and-shoot IMRT treatment planning was performed on the Pinnacle Treatment Planning System (TPS) (version 8.0 h, Philips Radiation Oncology Systems, Fitchburg, WI). The dynamic IMRT treatment planning was performed on Eclipse (version 7.1.31 , Varian Medical Systems Inc., USA). All patients were treated with a simultaneous integrated boost (SIB) technique. PTV1 was treated with 35 fractions of 1.55 Gy up to a total dose of 54.25 Gy. The PTV2 was treated with 35 fractions of 2 Gy up to a total dose of 70 Gy.

Contouring of organs at risk

Organs at risk (OARs) potentially involved in salivary function related symptoms were delineated according to the guidelines for OARs potentially involved in radiation-induced hyposalivation and xerostomia as described by van de Water et al. (22), including the parotid, submandibular and sublingual glands.

The 3D-CRT-based normal tissue complication logistic regression models

The NTCP values for each individual patient can be estimated using the equation from the 3D-CRT-based logistic regression model (10):

$$NTCP = \left(1 + e^{-S}\right)^{-1},$$

with S the linear prediction for xerostomia and sticky saliva given by

S (*patient rated xerostomia*) = -5.27 + (*mean dose parotid gland* * 0.066) +
(*age* * 0.050) + (*baseline xerostomia score* * 0.916)

and

S (patient rated sticky saliva) = -10.70 + (mean dose submandibular glands *
0.091) + (age * 0.107) +(baseline sticky saliva score * 1.218) +
(mean dose sublingual glands * -0.041)

Statistics

Differences between the 3D-CRT test cohort and IMRT validation cohort were described with an independent sample t-test for continuous variables and chi-square test for dichotomous variables.
For each individual patient the NTCP values for patient-rated xerostomia and sticky saliva were calculated using the aforementioned equations.
In the current study, various measures for model performance were used (23,24). The overall performance was measured by Nagelkerke's R^2, which quantifies the amount of explained variation by the model, and the scaled Brier score (25). The Brier score is a quadratic scoring rule, where the differences between actual outcome and predictions are calculated. The Brier score for a model can range from 0 for a perfect model to 0.25 for a non-informative model. The scaled Brier score is a recalculated Brier score which has a maximum value of 1.
In addition, model performance was evaluated using measures for discriminative ability, including the area under the Receiver Operating curve (AUC) (26,27) and by calculating the discrimination slope, defined as the absolute difference between the mean predicted NTCP values of patients with the primary endpoint and those without.
Performance was further assessed in terms of calibration, i.e. the agreement between predicted and observed outcome in the IMRT cohort, while the Hosmer-Lemeshow "goodness-of-fit" test (28) was used to test the hypothesis that the model and the observed outcomes were in agreement with each other.
The predictive performance of the model was also determined in the IMRT cohort, using the same measures as for the 3D cohort. The performance in the IMRT cohort can be different from the performance in the 3D cohort because of a difference in case-mix (23). The case mix refers to the distribution of included predictors as well as of the predictors not selected for the predictive model but of influence to outcome. To correct for a difference in case-mix, the expected performance (i.e. performance of the model in the IMRT cohort, assuming that the model gives correct, predictions) was determined. To this

end, 40.000 simulated IMRT datasets, of respectively 162 and 149 subjects for patient-rated xerostomia and sticky saliva, were generated, in which the endpoints were obtained with Monte Carlo simulations based on the calculated NTCP values in the IMRT validation dataset. For each simulated dataset the AUC, Brier score, Nagelkerke R2, and discrimination slope were calculated. The performance averaged over all simulated datasets is the performance expected to be found if the original model describes the outcome correctly for the case-mix of the IMRT cohort. The same simulations were performed for the 3D-CRT cohort, and the same performance measures were determined. The expected performance values for the IMRT-cohort were compared with the actual performance values in the IMRT cohort and the expected values for the 3D-CRT cohort as described above. A difference between the expected values of the 3D and IMRT cohorts is caused only by differences in case-mix. In contrast, a difference between expected and actual model performance cannot be explained exclusively by a difference in case-mix, but must be caused by a true difference in model performance.

The regression coefficients of the included variables may be different in development and validation datasets. Differences in regression coefficients can be due to statistical overfitting. Overfitted models may fit the test dataset perfectly, but will predict the outcome too extreme in the validation dataset. To determine whether a model was overfitted or contained incorrect variables, the regression coefficients of the predictors selected in the 3D-CRT dataset were refitted to the IMRT validation dataset. The different model performance measures were also calculated for this refitted model. If the performance of the refitted model would be significantly worse than the expected performance, it will be concluded that the variables in the model are inadequate.

Results

The demographic and tumour characteristics of the IMRT cohort and 3D-CRT cohorts as reported earlier are listed in Table 1 (10). In the IMRT cohort, the majority of patients were male and the mean age was 59.7 years. There were significant differences between the 3D-CRT cohort and the IMRT cohort. In the IMRT cohort significantly more oropharyngeal and hypopharyngeal tumours and less laryngeal tumours were observed. In addition, patients treated with IMRT had more extensive disease and were treated more frequently in combination with chemotherapy than patients treated with 3D-CRT. Finally, the dose range of the mean dose to both the parotid, submandibular and sublingual glands was smaller in the IMRT cohort as compared to that observed in the 3D-CRT cohort (Figure 1).

From the 179 initially included patients treated with IMRT, 17 already suffered from moderate to severe xerostomia prior to treatment, these patients were excluded from the analysis for patient-rated xerostomia. Twenty-three patients suffered from moderate to severe sticky saliva and were excluded from the analysis for patient-rated sticky saliva. Out of the remaining 156 patients for the analysis of sticky saliva, 149 (96%) completed the EORTC QLQ-HN35 at 6 months after treatment and were eventually analysed.

As compared to the 3D-CRT cohort, overall model performance of the 3D-CRT based patient-rated xerostomia NTCP model for the IMRT cohort was significantly worse in terms of the scaled *Brier score* and *Nagelkerke* R^2 (Table 2). In addition, discrimination in terms of AUC (Figure 2) and discrimination slope was markedly lower in the IMRT cohort. The expected values (3rd column in Table 2) refer to the expected difference in model performance in the IMRT cohort when case-mix differences are taken into account. As can be observed, the expected model performance was somewhat worse resulting from the differences in case mix. However, the actually observed results (4th column in Table 2) were much worse as compared to the expected results, indicating that the differences in performance as observed in the 3D-CRT and IMRT cohort cannot be explained only by case-mix differences.

Table 1 Baseline characteristics for the 3D-CRT cohort (test set) and the IMRT cohort (validation set). (Between the brackets for age, mean age and corresponding standard deviation are given.)

Characteristics	Xerostomia 3D-CRT (n=165)	%	Xerostomia IMRT (n=162)	%	p-value	Sticky saliva 3D-CRT (n=167)	%	Sticky saliva IMRT (n=149)	%	P-value
Sex					0.27					0.56
Male	126	76	115	71		124	74	106	71	
Female	39	24	47	29		43	26	43	29	
Age					0.08					0.034
≤ 65	101 (57.0 ± 5.70)	61	114 (54.9 ± 7.27)	70		99 (56.75 ± 5.76)	59	105 (55.2 ± 7.05)	71	
> 65	64 (74.4 ± 6.79)	39	48 (71.3 ± 5.20)	30		68 (74.37 ± 6.37)	41	44 (71.3 ± 5.10)	29	
Chemotherapy					<0.01					<0.01
Yes	36	22	73	45		36	22	66	44	
No	129	78	89	55		131	78	83	56	
Tumour classification					<0.01					<0.01
T0	5	3	6	4		6	4	6	4	
T1	27	16	14	9		28	17	14	9	
T2	85	52	50	31		87	52	47	32	
T3	25	15	51	31		22	13	45	30	
T4	23	14	41	25		24	14	37	25	
Node classification					<0.01					<0.01
positive	52	31	100	38		49	29	84	56	
negative	113	69	62	62		118	71	65	44	
Site					<0.01					<0.01
Oral cavity	10	6	57	35		12	7	50	34	
Oropharynx	37	22	13	8		35	21	12	8	
Larynx	98	59	59	36		100	60	55	37	
Hypopharynx	10	6	20	12		9	6	20	13	
Nasopharynx	3	2	1	1		3	2	1	1	
Sinuses	3	2	8	5		4	2	7	5	
Unknown primary	4	3	4	3		4	2	4	2	
Bilateral neck irradiation					<0.01					<0.01
yes	111	67	140	86		110	66	129	87	
no	54	33	22	14		57	34	20	13	
Xerostomia/Sticky saliva 6 months after treatment					0.87					0.16
No	79	48	79	48.8		95	57	97	65	
moderate/severe	86	52	83	51		72	43	52	35	

The Hosmer-Lemeshow test showed a significant disagreement between predicted risk and observed outcome (Table 2). The calibration slope decreased from 1.03 in the 3D-CRT cohort (an almost perfect fit) to 0.53 in the IMRT cohort (Figure 3), referring to a much lower agreement between predicted risk and observed outcome.

Some model performance measures, including the scaled Brier score and R^2 Nagelkerke and calibration, slightly improved after refitting the regression coefficients of the predictors of the 3D-CRT based model in the IMRT cohort. These results indicate that the differences in model performance of the 3D-

CRT based model in the 3D-CRT and IMRT cohorts can only partly be explained by overfitting.

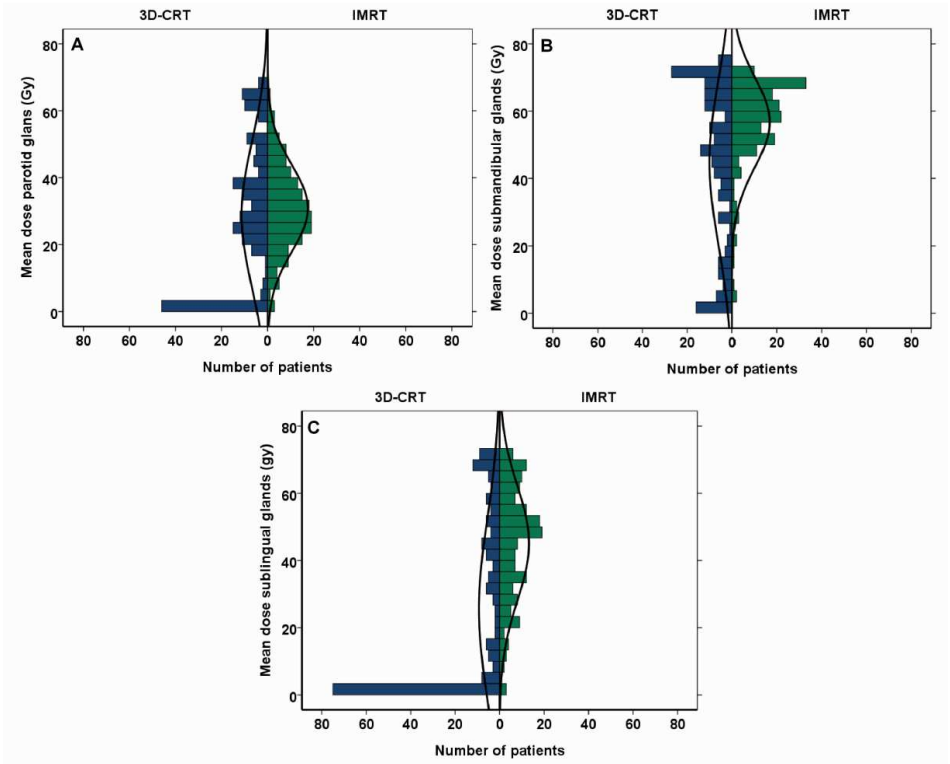

Figure 1: Differences in dose distributions to the parotid (a), submandibular (b) and sublingual (c) glands between the 3D-CRT test dataset and the IMRT validation dataset.

Overall performance of the 3D-CRT based NTCP model for patient-rated sticky saliva in terms of scaled Brier score and Nagelkerke R^2 markedly decreased and did not correspond with the expected values (Table 2). Also the AUC and the discrimination slope of the 3D-CRT based model were worse in the IMRT cohort and did not correspond with the expected values (Table 2 and Figure 2), indicating that overall performance and the discriminative abilities of the 3D-CRT based model cannot be explained only by differences in case mix alone.

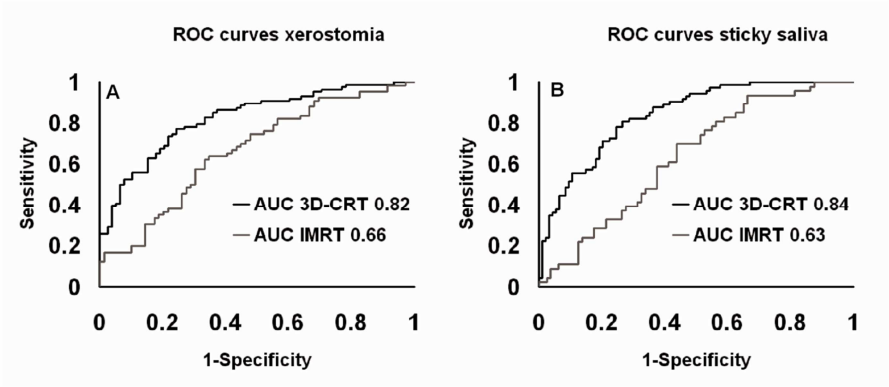

Figure 2: Discriminative abilities of the predictive models for patient-rated xerostomia (a) and sticky saliva (b) based on the area under the receiver operating curve; the difference between the 3D-CRT test dataset and the IMRT validation dataset.

The Hosmer-Lemeshow test showed a significant disagreement between predicted risk and observed outcome, which indicates a disagreement between predicted and observed outcome (Table 2). The slope of calibration decreased to 0.39 in the IMRT cohort (Figure 3).

To test for overfitting, we fitted the regression coefficients of the selected variables of the 3D-CRT model to the IMRT cohort. Overall performance and discrimination for this refitted model were similar to the actual 3D-CRT based model in the IMRT cohort, while the calibration parameters were somewhat better than the actual results. Based on these results, it is not very likely that the performance differences of the original 3D-CRT model among IMRT treated patients can be explained by overfitting alone.

Table 2 Performance of the 3D-CRT based predictive models for patient-rated moderate-to-severe xerostomia and sticky saliva at 6 months after completing (CH) RT in the IMRT treated cohort.

Performance measure	Xerostomia Treatment technique					Sticky saliva Treatment technique				
	3D-CRT	Expected in 3D-CRT	Expected in IMRT	Actual in IMRT	Refitted in IMRT	3D-CRT	Expected in 3D-CRT	Expected in IMRT	Actual in IMRT	Refitted in IMRT
Overall										
Brier (scaled)	0.313	0.314	0.209	0.039	0.088	0.340	0.339	0.240	-0.046	0.113
R^2 Nagelkerke	0.400	0.394	0.270	0.046	0.119	0.442	0.435	0.310	0.082	0.134
Discrimination										
Area under thecurve	0.824 (0.761-0.866)	0.826	0.768	0.657 (0.573-0.740)	0.664	0.840 (0.782-0.898)	0.840	0.790	0.644 (0.555 – 0.733)	0.681
Discrimination slope	0.315	0.318	0.215	0.126	0.089	0.342	0.343	0.250	0.107	0.103
Calibration										
Hosmer-Lemeshow test	x^2=7.6 *p=0. 47*			x^2=17.41 *p=0.04*	x^2=5.48 *p=0.79*	x^2=5.16 *p=0.74*			x^2=30.3 *p=0.04*	x^2=7.32 *p=0.502*
Intercept of calibration curve	0.010			0.033	-0.012	0.028			-0.411	-0.071
Slope of calibration curve	1.034			0.530	0.992	1.067			0.389	1.203

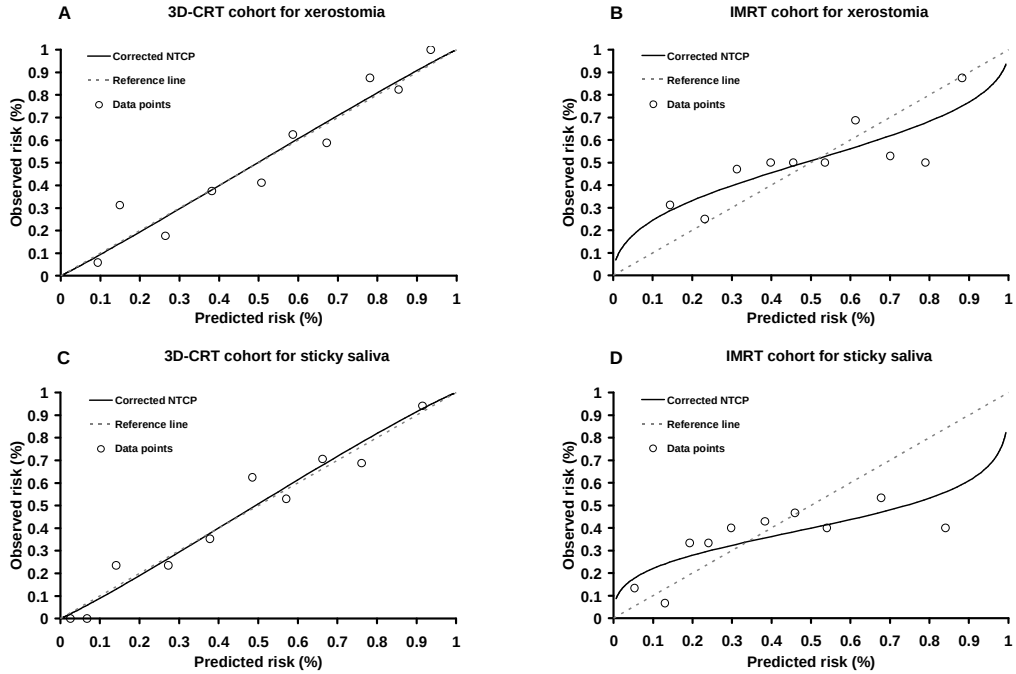

Figure 3: Calibration of a predictive model for patient-rated xerostomia developed in patients treated with 3D-CRT (A) and validated in a population treated with IMRT (B) and the calibration of a predictive model for patient-rated sticky saliva developed in patients treated with 3D-CRT (C) and validated in a population treated with IMRT (D). The plots show the relation between predicted risk and real outcome for as well the 3D-CRT test dataset and the IMRT validation dataset. The dots represent groups of patients with a specific mean calculated probability. The corrected NTCP is the trendline between the data points compared with the reference line, which indicates a perfect calibration between predicted risk and real outcome.

Discussion

The results of the current study showed that 3D-CRT-based prognostic models for patient-rated xerostomia and sticky saliva 6 months after primary radiotherapy for head and neck cancer cannot be generalised to patients treated with IMRT.

In the current study, we found differences in case mix between the 3D-CRT and IMRT cohorts (Table 1). The case mix refers to the distribution of the predictors selected and not selected for the predictive model but of influence to the outcome measure. In general, as illustrated by Vergouwe *et al*, differences in case mix between a test cohort and a validation cohort may well explain differences in model performance (23). In the current analysis, the distributions of a number of variables in the two cohorts were significantly imbalanced. More specifically, the distribution of the mean doses to the parotid glands, submandibular glands and sublingual glands differed. This was partly due to the fact that the 3D-CRT cohort also included patients locally irradiated for early glottic cancer and due to a significant reduction of the mean dose to the parotid glands among those with bilateral neck irradiation using IMRT. However, the estimated case-mix corrected performance measures were somewhat worse but still much better than those actually observed, indicating that these differences in case-mix cannot explain the markedly worse model performance in the IMRT cohort alone. Therefore, what other hypotheses could explain the worse performance of the 3D-CRT-based models in the IMRT cohort?

First, among patients treated with 3D-CRT, high correlations were found between the dose distribution parameters of all ipsilateral and contralateral paired salivary glands. Therefore, these variables were analysed as paired glands in the development of the 3D-CRT based NTCP models for patient-rated xerostomia and sticky saliva (10). However, in the IMRT cohort, the correlations between the dose distributions in the paired glands were much lower. As a consequence, when we would decide to model development rather than model validation in the IMRT cohort, the dose distributions in the ipsilateral and contralateral glands should in fact be included as separate

candidate variables. These so-called hidden candidate variables may become more important when patients are treated with IMRT instead of with 3D-CRT. This shifting importance of hidden variables may also be true for dose volume parameters of salivary glands other than the parotid glands. The importance of dose distributions for patient-rated xerostomia in other salivary glands was very well illustrated by Jellema et al. (29). In that study, the mean dose to both the parotid and submandibular glands were significantly associated with patient-rated xerostomia at 6 months.

Second, it should be noted that the dose distributions in general to the parotid glands in the 3D-CRT cohort were markedly different from that observed in the IMRT-cohort. With 3D-CRT, all parts of the salivary glands were co-irradiated more uniformly, resulting in steep dose volume histograms. From this point of view, the question arises as to whether the mean dose to both parotid glands is the most optimal candidate variable representing the dose to these glands when treating with IMRT. Preclinical animal studies in the rat parotid gland showed that dose to different sub-volumes of the gland resulted in different responses (15). Although IMRT reduces the mean dose to the parotid glands, spared parts of the glands still receive low to intermediate doses. Since in earlier work in the rat spinal cord these low doses were shown to have a huge impact on the tolerance for irradiation of a small volume (30-32), additional studies were performed to verify whether this also occurred in the rat parotid gland. In these studies irradiation of the caudal 50% of the parotid gland to an ablative dose of 30 Gy (single dose) lead to a reduction in saliva production of 15% during the first 4 months. Surprisingly, however, the addition of 1 Gy (single dose) to the cranial 50% resulted in an additional loss of 30% (33). This disproportionate effect of low dose can not be described by only the mean dose to the parotid gland. In line with these results, Dijkema et al. found that even though the use of IMRT reduced loss of parotid gland function, the dose response curve had shifted to lower doses as compared to 3D-CRT at 6 months after treatment (34). These effects may partly explain why the 3D-CRT-based model, also containing the mean dose to both parotid glands as predictor for radiation-induced xerostomia, showed worse performance. Improving the present models for parotid gland dysfunction and xerostomia may be possible

by identifying the sub-structures within the parotid gland that are more responsible for the effects observed in the rat parotid gland and both clinical studies.

The current analysis indicates that 3D-CRT-based multivariable predictive models for patient-rated xerostomia and sticky saliva cannot be generalized to patients treated with IMRT. It should be noted that these findings do not imply that the mean dose to the parotid glands is of no importance in the development of patient-rated xerostomia and sticky saliva. These findings only indicate that predictions based on multiple logistic regression models developed in a population treated with 3D-CRT are not automatically valid for IMRT treated patients. We refitted the original 3D-CRT models to the IMRT dataset to show that these models were not overfitted. We also performed a refit with only the selected salivary glands included to the IMRT dataset and model performance was similar to the model performance as described of the refitted models with the baseline score and age included. This indicates that the selected salivary glands in the original 3D-CRT test population are of main importance of the model performance in the IMRT treated population. To reach a more accurate model performance in the IMRT cohort, other predictors not selected in the 3D-CRT training dataset or predictors not yet known may be more important and, therefore, model updating for IMRT treated patients is subject of a future study.

In conclusion, 3D-CRT based models for patient-rated xerostomia and sticky saliva turned out to perform markedly worse and not useful among patients treated with IMRT. These findings include an important message, i.e. that prognostic models developed in a population treated with a specific radiation technique cannot be generalised to a population treated with another technique without external validation.

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CHAPTER

4

NTCP models for patient-rated xerostomia and sticky saliva after treatment with intensity modulated radiotherapy for head and neck cancer: The role of dosimetric and clinical factors

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Abstract

Purpose

The purpose of this multicenter prospective study was to develop multivariable logistic regression models to make valid predictions about the risk of moderate-to-severe patient-rated xerostomia (XER_{M6}) and sticky saliva 6 months ($STIC_{M6}$) after primary treatment with intensity modulated radiotherapy (IMRT) with or without chemotherapy for head and neck cancer (HNC).

Methods and materials

The study population was composed of 178 consecutive HNC patients treated with IMRT. All patients were included in a standard follow up program in which acute and late side effects and quality of life were prospectively assessed, prior to, during and after treatment.
The primary endpoints were XER_{M6} and $STIC_{M6}$ as assessed by the EORTC QLQ-H&N35 after completing IMRT. Organs at risk (OARs) potentially involved in salivary function were delineated on planning-CT, including the parotid, submandibular and sublingual glands and the minor glands in the soft palate, cheeks and lips. Patients with moderate-to-severe xerostomia or sticky saliva, respectively, at baseline were excluded.
The optimal number of variables for a multivariate logistic regression model was determined using a bootstrapping method.

Results

Eventually, 51.6% of the cases suffered from XER_{M6}.The multivariate analysis showed that the mean contralateral parotid gland dose and baseline xerostomia (none versus a bit) were the most important predictors for XER_{M6}. For the multivariate NTCP model, the area under the receiver operating curve

(AUC) was 0.68 (95% CI 0.60 – 0.76) and the discrimination slope was 0.10 respectively. Calibration was good with a calibration slope of 1.0.
At 6 months after IMRT, 35.6% of the cases reported $STIC_{M6}$. The mean contralateral submandibular gland dose, the mean sublingual dose and the mean dose to the minor salivary glands located in the soft palate were most predictive for $STIC_{M6}$. For this model, the AUC was 0.70 (95% CI 0.61 – 0.78) and the discrimination slope was 0.12. Calibration was good with a calibration slope of 1.0.

Conclusions

The multivariable NTCP models presented in this paper can be used to predict patient-rated xerostomia and sticky saliva. The dose volume parameters included in the models can be used to further optimize IMRT treatment.

Introduction

One of the most frequently reported side effects of radiotherapy in the head and neck region is hyposalivation and subsequent xerostomia, resulting from irradiation of at least some parts of the salivary glands (1-8).

The current study, including head and neck cancer (HNC) patients treated with curatively intended radiotherapy (RT) or chemoradiation (CHRT), was part of the ALLEGRO project (EArLy and Late hEalth risks to normal/healthy tissues from the use of existing and emerGing techniques for RadiatiOn therapy), funded by the European Union (9). One of the objectives of this project was to develop multivariable Normal Tissue Complication Probability (NTCP) models for patients treated with 3D conformal radiotherapy (3D-CRT) and to investigate if these models were sufficiently valid when used among patients treated with new and emerging radiation techniques, such as with intensity modulated radiotherapy (IMRT).

Recently, we reported on the results of a prospective study, which was conducted to develop multivariable NTCP models for patient-rated moderate-to-severe xerostomia and sticky saliva among head and neck cancer (HNC) patients treated with 3D-CRT (10). In a subsequent analysis, we tested the validity of these 3D-CRT based NTCP-models among patients treated with IMRT (11). The results of that study showed that the 3D-CRT based NTCP models performed worse among patients treated with IMRT, suggesting that major changes in dose distributions in relevant organs at risk (OAR), in particular in the salivary glands, may hamper the performance of 3D-CRT based NTCP-models.

This raises the question if multivariable models initially developed among patients treated with IMRT will indeed be different from the 3D-CRT based models and, ultimately, will do better in terms of predictive power and model performance.

Therefore, the first objective of the current study was to develop multivariable NTCP models for patient-rated xerostomia and sticky saliva among patients treated with IMRT. The second objective was to test if these models indeed

performed better than the 3D-CRT based multivariable NTCP models as reported in earlier studies.

Methods and Materials

Patients

To be included in the analysis, patients had to fulfil the following eligibility criteria: 1) HNC originating in the oral cavity, oropharynx, larynx, hypopharynx, nasopharynx, paranasal sinuses or cervical lymph node metastases from unknown primary tumours; 2) treated with definitive IMRT either alone or in combination with chemotherapy or cetuximab; 3) no previous surgery, radiotherapy and/or chemotherapy ((CH)RT); 4) no previous malignancies; 5) no distant metastases, and: 6) health related quality of life (HRQOL) assessments available prior to and at 6 months after completion of RT or CHRT. The study was conducted according to the regular procedures of the local ethical committee of the University Medical Centre Groningen and VU University Medical Centre, Amsterdam.

The standardised follow up program

All patients included in this analysis were subjected to a standard follow-up program as previously described (10,12). In summary this program includes a prospective evaluation of toxicity and quality of life on a routine base, prior to, during and at regular intervals, weekly during treatment, 6 weeks and every 6 months up to 60 months after curative RT or CHRT.

Endpoints

For the evaluation of patient-rated xerostomia and sticky saliva, the EORTC QLQ-H&N35 questionnaire was used prior to and 6 months after treatment. For all questions, including those regarding xerostomia and sticky saliva, a 4-

point Likert scale was used ranging from none, a bit, quite a bit, to a lot. For the purpose of this study, the primary endpoint was defined as moderate-to-severe xerostomia at 6 months (XER_{M6}) and sticky saliva ($STIC_{M6}$) after completion of radiotherapy, which corresponds with the two highest scores on the 4-point scale. Patients with moderate-to-severe xerostomia or sticky saliva at baseline, respectively, were excluded from the analysis. This was done, as we were primarily interested in xerostomia and sticky saliva induced by radiation treatment itself.

Treatment

In all patients, a planning CT-scan with contrast-enhancement was performed in treatment position. Radiotherapy was delivered using a 6 MV linear accelerator. The target volumes for the initial fields and boosts were similar as reported in earlier studies (10). In summary, the clinical target volume of the initial field (CTV1) was composed of the primary tumour and pathological lymph nodes plus a 1.0 cm margin, and the elective nodal areas on both sides of the neck, selected according to the guidelines reported by Gregoire, et al. (13). The CTV for the boost irradiation (CTV2) consisted of the primary tumour and pathological lymph nodes with a 0.5 cm margin. In all cases, a 0.5 cm margin was applied for the planning target volumes (PTV1 and PTV2). The mean dose to both parotid glands was reduced as much as possible without compromising the required dose to the target volumes.
Patients were treated with dynamic IMRT with a sliding window technique, as well as with step-and-shoot IMRT. In general, a seven-field equidistant, non-opposing beam configuration was used. Step-and-shoot IMRT treatment planning was performed on the Pinnacle Treatment Planning System (TPS) (version 8.0 h, Philips Radiation Oncology Systems, Fitchburg, WI). Dynamic IMRT treatment planning was performed on Eclipse (version 7.1.31, Varian Medical Systems Inc., USA). All patients were treated with a simultaneous integrated boost (SIB) technique. PTV1 was treated with 35 fractions of 1.55 Gy up to a total dose of 54.25 Gy. The PTV2 was treated with 35 fractions of 2 Gy up to a total dose of 70 Gy.

Contouring of organs at risk

OARs potentially involved in salivary function related symptoms were delineated according to the guidelines as described by Van de Water et al. (14). These included the parotid, submandibular and sublingual glands, as well as the minor salivary glands located in the soft palate, the inner surface of the lower and upper lip and the minor salivary glands in the inner surface of the cheeks. All OARs were delineated by an expert in head and neck radiation oncology.

Statistics

NTCP models for moderate-to-severe patient-rated xerostomia and sticky saliva were developed using a multivariable logistic regression analysis with an extended bootstrapping technique and forward variable selection as previously described (10). The model with the highest average likelihood was selected as the best predictive model.

Before carrying out the regression analysis, a correlation matrix was produced to check for high correlations between candidate prognostic determinants, in particular between dose volume histogram (DVH) parameters. In case of Pearson correlation coefficients ≥ 0.75 between candidate prognostic determinants, these variables were combined into a single variable to avoid the problem of multicollinearity which may negatively affect the generalisability of the model. Finally, all DVH data were connected to all other potential pre-treatment prognostic factors for each individual patient.

After reducing the number of variables based on the correlation coefficient analysis, a multivariable logistic regression analysis with forward selection and an extended bootstrapping technique was carried out. We used 2000 bootstraps for each analysis. For every model order, the average likelihood of predictions was calculated and the combination of variables with the highest average likelihood was selected for the definite NTCP model for moderate-to-severe patient-rated xerostomia and sticky saliva.

After selecting the combination of variables with the highest performance, adjusted Odd's ratios (OR) and 95% confidence intervals (95% CI) were calculated for the selected variables in the model. For each patient, predictive values were calculated for each set of prognostic variables based on the regression coefficients according to the formula:

$$NTCP = \left(1 + e^{-S}\right)^{-1}, \text{ where}$$

$$S = \beta_0 + \sum_{i=1}^{n} \beta_i \cdot x_i$$

Model performance was described using different validation tools (15,16). The overall performance was expressed by Nagelkerke's R^2, which quantifies the amount of explained variation by the model (17). In addition, model performance was evaluated using measures for discriminative ability, including the Area Under the receiver operating Curve (AUC) (18,19) and by calculating the discrimination slope, defined as the absolute difference between the mean predicted NTCP-values of patients with the primary endpoint and those without. Model performance was further quantified in terms of calibration, i.e. the agreement between predicted and observed outcome in the dataset, while the Hosmer-Lemeshow "goodness-of-fit" test (20) was used to test the agreement between the expected and observed outcomes.

Results

The majority of patients were male (71%) and the median age of the study population was 61.0 years, ranging from 32 to 85 years for patients included in both the xerostomia and sticky saliva analysis. One third of the patients were treated with IMRT in combination with chemotherapy (33%). The demographic and tumour characteristics of the study population are listed in Table 1.

Table 1 Demographic and disease-related characteristics for the patients included in the xerostomia (161) and sticky saliva analysis (n=149).

Characteristics	Xerostomia (n=161)	%	Sticky saliva (n=149)	%
Sex				
Male	114	71	106	71
Female	47	29	43	29
Age				
≤65	113	70	102	69
≥65	48	30	47	31
Chemotherapy				
Yes	53	33	49	33
No	108	67	100	67
Cetuximab				
Yes	10	6	8	5
No	151	94	141	95
Tumour classification				
T0	6	4	6	4
T1	13	8	13	9
T2	50	31	47	31
T3	51	32	46	31
T4	41	25	37	25
Node classification				
positive	99	61	83	56
negative	62	39	65	44
Site				
Oral cavity	57	35	50	34
Oropharynx	12	7	11	7
Larynx	59	37	55	37
Hypopharynx	20	12	20	13
Nasopharynx	1	1	1	1
Sinuses	8	5	8	5
Unknown primary	4	3	4	3
Bilateral neck irradation				
yes	139	86	129	87
no	22	14	20	13

From the 178 patients treated with IMRT, 17 already suffered from moderate-to-severe xerostomia at baseline and were excluded from further analysis,

leaving 161 patients to be analysed. Twenty-three patients suffered from moderate-to-severe sticky saliva and were excluded from the analysis for $STIC_{m6}$. Out of the remaining 156 patients for the analysis of sticky saliva, 149 (96%) completed the EORTC QLQ-HN35 at 6 months after treatment and were included in the analysis.

Table 2 Univariate logistic regression analysis for all possible predictors for patient-rated xerostomia and sticky saliva 6 months after treatment.

Variable	Xerostomia				Sticky saliva			
	β	*OR*	*95% CI*	*p-value*	*β*	*OR*	*95% CI*	*p-value*
Mean dose ipsilateral parotid gland (Gy)	0.03	1.03	1.01 - 1.05	0.01	0.02	1.02	0.99 - 1.04	NS
Mean dose contralateral parotid gland (Gy)	0.05	1.05	1.02 - 1.08	<0,01	0.04	1.04	1.01 - 1.07	0.01
Mean dose ipsilateral submandibular gland (Gy)	0.04	1.04	1.01 - 1.07	0.02	0.03	1.03	1.00 - 1.06	NS
Mean dose contralateral submandibular gland (Gy)	0.04	1.04	1.01 - 1.07	<0.01	0.05	1.05	1.02 - 1.08	<0.01
Mean dose sublingual glands (Gy)	0.02	1.02	1.00 - 1.04	NS	0.01	1.01	0.99 - 1.03	NS
Mean dose cheeks (gy)	0.01	1.01	1.00 - 1.03	NS	0.01	1.01	0.99 - 1.04	NS
Mean dose soft palate (Gy)	0.02	1.02	1.00 - 1.03	0.03	0.01	1.01	1.00 - 1.03	NS
Mean dose lips (Gy)	0.00	1.00	0.98 - 1.02	NS	0.01	1.00	0.98 - 1.03	NS
Sex	0.46	1.58	0.79 - 3.15	NS	0.10	1.11	0.53 - 2.31	NS
Age	0.01	1.01	0.98 - 1.04	NS	0.02	1.02	0.99 - 1.06	NS
Chemotherapy	0.77	2.16	1.10 - 4.24	0.03	-0.19	0.83	0.40 - 1.70	NS
Cetuximab	0.84	2.30	0.57 -9.24	NS	0.63	1.88	0.45 - 7.84	NS
Accelerated radiotherapy	-0.21	0.81	0.43 - 1.51	NS	0.16	1.16	0.59 - 2.28	NS
Baseline xerostomia/sticky saliva score (none vs a bit)	0.81	2.25	1.12 - 4.52	0.02	0.01	1.01	0.48 - 2.13	NS
Bilateral neck irradiation (unilateral vs bilateral)	0.95	2.59	0.99 - 6.73	NS	0.90	2.45	0.77 -7.75	NS

To reduce the number of variables eventually included in the analysis a correlation matrix was produced. For all OARs, high correlations were found between all DVH-parameters and the mean dose of that OAR. Therefore, we excluded the V_X values which were highly correlated with each other from the analysis. High correlations were also found between the mean dose to the upper and lower lips, the mean dose to the left and right cheek and the mean dose to the sublingual glands and, therefore, we decided to include the mean doses of these paired glands as one single variable each in the analysis. Eventually, 8 DVH parameters were included in the analysis (Table 2).

Six months after treatment, 83 patients (51.6 %) suffered from XER_{m6}. In the univariate analysis, the mean dose in the ipsilateral and contralateral parotid gland, the mean dose in the ipsilateral and contralateral submandibular gland, the mean dose in the soft palate, chemotherapy and baseline xerostomia score

(none vs. a bit) were significantly associated with XER_{M6} after treatment (Table 2).

The average likelihood of bootstrap predictions in the multivariable logistic regression analysis was optimal with a model consisting of two variables, including the mean dose in the contralateral parotid gland and baseline xerostomia (none vs. a bit). The final results of the multivariable logistic regression analysis are listed in Table 2. The NTCP-curves for the mean contralateral parotid dose stratified by baseline xerostomia (none vs. a bit) are depicted in Figure 1A. The NTCP-value for each individual patient can be calculated by the following logistic regression formula:

$$NTCP = \left(1 + e^{-S}\right)^{-1}, \text{ where}$$

S = -1.443 + (*mean dose contralateral parotid gland* * *0.047*) + (*baseline xerostomia score* * 0.720)

Overall model performance and calibration was satisfactory (Table 4). The AUC was 0.68 (95% CI 0.60 – 0.76) and the discrimination slope was 0.10 respectively (Table 3). The calibration slope of 1.0 (Figure 2), indicating a good agreement between observed and predicted NTCP-values.

Fifty three patients (35.6%) reported STICM6 after completion of treatment. In the univariate analysis, the mean dose to the contralateral parotid gland and in the contralateral submandibular gland were significantly associated with STICM6 after treatment (Table 2).

Table 3 Logistic regression coefficients and Odds ratios for the NTCP models for patient-rated xerostomia and for patient-rated sticky saliva 6 months after treatment. The constant refers to the constant of the logistic regression formula.

NTCP model	Variable	*β*	*p-value*	Odds ratio	95%CI
Patient-rated xerostomia	Mean dose contralateral parotid gland (Gy)	0.047	<0.01	1.05	1.02 - 1.08
	Baseline xerostomia score (none vs a bit)	0.720	0.05	2.05	1.00 - 4.23
	Constant	-1.443	<0.01		
Patient-rated sticky saliva	Mean dose contralateral submandibular gland (Gy)	0.075	<0.01	1.08	1.03 - 1.13
	Mean dose sublingual glands (Gy)	-0.060	0.01	0.94	0.90 - 0.98
	Mean dose soft palate (Gy)	0.026	0.04	1.03	1.00 - 1.05
	Constant	-3.243	<0.01		

Average likelihood of bootstrap predictions in the multivariate logistic regression analysis was optimal with a model consisting of three variables, including the mean dose in the contralateral submandibular gland, the mean dose in the sublingual glands, and the mean dose in the soft palate (Table 2).

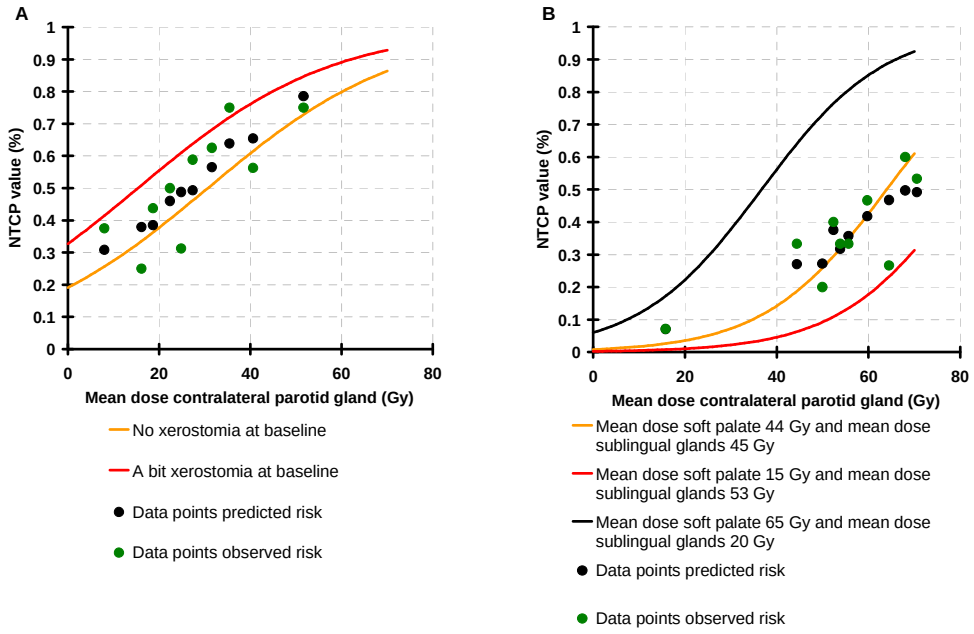

Figure 1: The NTCP curves for patient-rated xerostomia 6 months after treatment with primary RT or CHRT (A). The lines represent the NTCP curves for patients with no xerostomia at baseline (red line) and patients with minor xerostomia at baseline (orange line).
Figure B shows the NTCP curves for patient-rated sticky saliva 6 months after treatment. The orange curve represents the situation when the mean dose to the soft palate and sublingual glands equals the mean dose of the study population. The black and red NTCP curves represent the most extreme values to the soft palate and sublingual glands as observed in the study population. The green dots represent the mean observed risk of groups of patients. The black dots represent the same group of patients as the green dots, but represent the calculated predicted risk based on the NTCP models.

Of notice is that a negative regression coefficient was found for the mean dose to the sublingual glands indicating an inverse relationship between the mean dose to the sublingual glands and the probability on STICM6. The NTCP-curves for STICM6 as a function of the mean contralateral submandibular dose stratified by different mean doses in the sublingual glands and soft palate are depicted in Figure 1B.

The NTCP-value for each individual patient can be calculated by the following logistic regression formula:

$$NTCP = \left(1 + e^{-S}\right)^{-1}, \text{ where}$$

S= -3.243 + (*mean dose contralateral submandibular gland * 0.075*) + (*mean dose sublingual glands* * -0.060) + (*mean dose soft palate* * 0.026)

Table 4: Model performance and internal validation for the NTCP models for patient-rated xerostomia and sticky saliva.

Performance measure		Xerostomia	Sticky Saliva
Overall	Brier (scaled)	0.10	0.12
	R^2 *Nagelkerke*	0.13	0.17
Discrimination	Area under the curve	0.68	0.70
	Discrimination slope	0.10	0.12
Calibration	Hosmer-Lemeshow test	X^2 = 4.24 (p=0.84)	X^2 = 5.78 (p=0.67)
	Intercept of calibration curve	0.00	0.01
	Slope of calibration curve	1.00	1.00

Overall model performance and calibration was satisfactory (Table 3). The discriminative abilities described with the AUC and the discrimination slope were 0.70 (95% CI 0.61 – 0.78) and 0.12 respectively (Table 3). Calibration, the agreement between predictive risk and the observed outcome was good with a calibration slope of 1.0 (Figure 2).

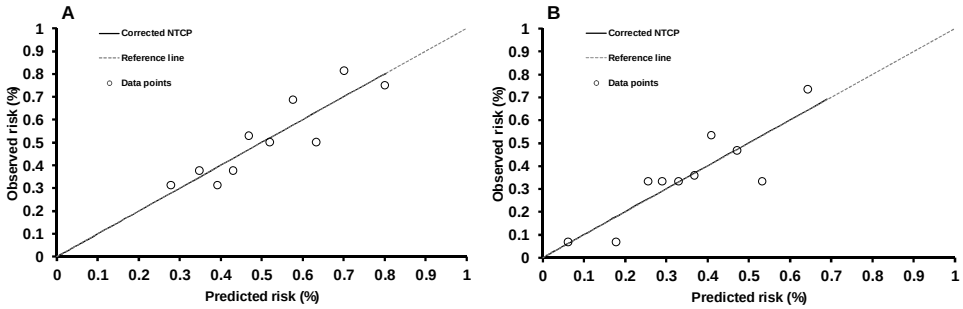

Figure 2 Calibration of the NTCP models for patient-rated xerostomia (A) and calibration (the agreement between predicted and observed outcome) of the NTCP model for patient-rated sticky saliva (B). All plots show the relation between predicted risk and real outcome. The dots represent groups of patients with a specific mean calculated probability. The corrected NTCP is the trendline between the data points compared with the reference line, which indicates a perfect calibration between predicted risk and real outcome.

Discussion

In this study, we developed predictive models for XER_{M6} and $STIC_{M6}$ for HNC patients treated with primary RT or CHRT using IMRT. The analysis showed that the contralateral parotid gland was the most important OAR for XER_{M6}. For $STIC_{m6}$, the contralateral submandibular gland, the sublingual glands and the minor glands in the soft palate turned out to be the most important OARs.

In a previous report, we showed that the performance of 3D-CRT based multivariable predictive models for XER_{M6} and $STIC_{M6}$ were markedly worse when used among patients treated with IMRT (11). In particular, there was a significant discrepancy between predicted and observed outcome values (calibration). Based on these results the current analysis was performed in order to see if we could develop separate multivariable NTCP models for the same endpoints among patients treated with IMRT with better performance than the 3D-CRT based models.

In the current analysis, the two-factor model containing baseline xerostomia and the mean dose to the contralateral gland performed significantly better in that respect. Overall performance as described with the scaled Brier score and explained variance increased respectively from 0.04 to 0.10 and from 0.05 to 0.13. Calibration, the differences between observed and predicted risk, was markedly better (increased from 0.53 to 1.0) and the Hosmer-Lemeshow test did not show a significant disagreement between predicted and observed risk anymore. The question arises as to whether there is a logical explanation for the differences found between the 3D-CRT based NTCP models and the IMRT-based NTCP models.

First, it should be noted that patient-rated xerostomia is a rather complex endpoint, which can be influenced by several factors either related to dose distributions to major and minor salivary glands, or by other factors such as baseline xerostomia, age and medication (10,21-24). Although we tried to take these factors into account as much as possible, given the relatively low values for the explained variance of the model, there will be other prognostics factors that remained unidentified.

Second, significant differences were noted with regard to the dose distributions to particularly the parotid glands. In the 3D-CRT cohort, the average mean dose to the ipsilateral and contralateral parotid glands were highly correlated, while in the IMRT cohort this correlation was much weaker, allowing the ipsilateral and contralateral parotid glands to be entered in the multivariable model as two separate OARs. As the average mean dose to the contralateral parotid glands was significantly lower when treated with IMRT, it is not surprising that the mean dose to the contralateral parotid gland turned out to be more important than the dose to the ipsilateral gland. Indeed, some investigators showed that the contralateral parotid flow increased after unilateral irradiation (25-27). These investigators showed that when patients were treated with unilateral irradiation, the stimulated and unstimulated salivary production was taken over by the spared contralateral parotid gland and that physician-rated toxicity was particularly correlated with the radiation dose to these spared parotid glands (25,27).

In the current analysis, the three-factor model for $STIC_{M6}$ performed with regard to overall performance and calibration significantly better than the four factor 3D-CRT model which contains the submandibular, sublingual glands, baseline sticky saliva and age (10).

The submandibular glands and sublingual glands play a pivotal role in the development of sticky saliva, for patients treated with IMRT as well for those treated with 3D-CRT. A remarkable finding was the inverse relationship between the mean dose to the sublingual glands and patient-rated sticky saliva. Irradiation of the submandibular glands and parotid glands reduce the production of serous salivary. Sparing of the sublingual glands, which are responsible for more mucous secretion of saliva, will change the ratio between mucous and serous saliva, resulting in a higher viscosity of the produced saliva (28). Irradiation to the sublingual glands will reduce the mucous saliva production resulting in a more balanced ratio between mucous and serous saliva production.

Given that the risk on the endpoints discussed depend on more than one factor, it is not possible to define clear dose constraints as the threshold dose for the DVH parameters which were identified will be different in the various subsets. E.g. for patient-rated xerostomia, the dose response curves for patients with and without baseline xerostomia will be different. For sticky saliva, this will be even more difficult as the risk on patient-rated sticky saliva depend on even more factors.

In the current analysis, the mean dose to the soft palate had a minor though significant effect on the development of $STIC_{M6}$. Such relationship was not found in the 3D-CRT cohort. IMRT primarily aiming at sparing the parotid glands, will inevitably result in additional different dose distributions to other regions, such as the oral cavity, which may result in different dose distributions to the minor salivary glands, such as those located in the soft palate. Indeed, in our study populations, in patients treated with IMRT, the average mean dose to the soft palate was 15 Gy higher as compared to that in patients treated with 3D-CRT (data not shown). Possibly, these higher doses exceed the threshold dose of the minor salivary glands located in the soft palate, which may explain the increasing importance of the mean dose to the soft palate.

Also other authors found that the minor salivary glands are important for symptoms related to salivary function as reported by patients. Little et al. showed a shifting importance of dose distributions to the minor salivary glands located in the oral cavity when the parotid and submandibular glands were spared with IMRT with regard to patient-rated xerostomia (29).

In conclusion we developed predictive models which are valid for patients treated with IMRT. These models are useful to further optimize current IMRT treatment with regard to patient rated xerostomia and sticky saliva and are more reliably to predict these endpoints when patients will be treated with IMRT and indicate which organs at risk are the most important to spare as much as possible, to optimize current treatment with IMRT.

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CHAPTER 5

The QUANTEC criteria for parotid gland dose and their efficacy to prevent moderate to severe patient-rated xerostomia

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Abstract

Background

Recently, the Quantitative Analysis of Normal Tissue Effect in the Clinic (QUANTEC) Group defined dose-volume constraints for the parotid glands to avoid severe xerostomia. The aim of this study was to determine if application of these QUANTEC criteria also protected against moderate-to-severe patient-rated xerostomia.

Material and methods

The study population consisted of 307 head and neck cancer patients treated with primary (chemo)radiotherapy, either with 3D-CRT (56%) or with IMRT (44%). All patients participated in a standard follow-up program in which radiation-induced toxicity and quality of life were prospectively assessed. Patients who met the QUANTEC criteria were classified as low risk and otherwise as high risk.

Results

In total, 41% of the patients (treated with 3D-CRT and IMRT) were classified as low risk patients. In the group treated with 3D-CRT and IMRT, it was possible to meet the QUANTEC criteria in 47% and 32% of the patients, respectively. Sparing the parotid glands with IMRT was considerably more difficult in patients with lymph node metastases and in patients with nasopharyngeal and oropharyngeal tumours. Low risk patients reported significantly less moderate-to-severe xerostomia than high risk patients. However, the predicted risk of elderly patients and patients with pre-existing minor patient-rated xerostomia at baseline was >20%, even when the QUANTEC criteria were met.

Conclusions

Significantly lower rates of radiation-induced patient-rated xerostomia were found among low risk patients treated according to the QUANTEC criteria, but these criteria do not completely protect against xerostomia. Particularly in elderly patients and patients already suffering from minor xerostomia at baseline, the QUANTEC criteria do not sufficiently protect against persistent, moderate-to-severe patient-rated xerostomia.

Introduction

Radiotherapy is a commonly used treatment modality in the management of head and neck cancer (HNC) patients. When treating patients with radiotherapy, co-irradiation of normal tissues is generally unavoidable.

Based on the results of a number of randomised controlled trials (1,2) showing that salivary dysfunction can be prevented by using intensity modulated radiotherapy (IMRT) instead of conventional radiation techniques, IMRT has become the standard of care for patients with HNC who are treated with radiotherapy. Nevertheless, parts of the salivary glands still receive considerable radiation doses even when IMRT is used, resulting in hyposalivation and subsequent xerostomia (3).

Recently, the QUANTEC (Quantitative Analyses of Normal Tissue Effects in the Clinic) Group suggested practical guidelines to reduce the toxicity risk based on dose constraints to be used in IMRT treatment planning (4). More specifically, the QUANTEC Group concluded that severe xerostomia, defined as long-term stimulated salivary flow <25% of baseline, can be reduced if at least one parotid gland is spared with a mean dose of less than 20 Gy or if both glands are spared with a mean dose of less than <25 Gy (5).

Recently, Moiseenko et al. (6) reported the results of a prospective study which was performed to validate these QUANTEC recommendations with regard to salivary flow. When the QUANTEC criteria were met, the rate of grade 4 xerostomia, defined as 25% reduction of pretreatment salivary flow measured at 3 months was >40% but indeed improved to less than 20% at 12 months. The authors therefore concluded that the QUANTEC recommendations were sufficiently valid to be used in clinical practice.

However, the QUANTEC criteria are only based on the dose to the parotid glands. Although parotid gland dysfunction plays an important role in the development of patient-rated xerostomia (7), it is not the only prognostic factor. We recently showed that age and baseline xerostomia were independent prognostic factors for patient-rated xerostomia, in addition to the mean dose to the parotid glands (7). As previous studies have shown that the correlation between salivary flow and patient-rated xerostomia is relatively

weak (2,8), it is important to investigate the value of the QUANTEC criteria for patient-rated xerostomia as well.
Therefore, the purpose of the current study was twofold: 1) to test the hypothesis that the application of the QUANTEC criteria is sufficient to prevent patient-rated moderate-to-severe xerostomia, and 2) to determine the extent to which this effect depends on age and the presence of baseline patient-rated xerostomia.

Material and methods

Patients

The study population of the current analysis was composed of 307 patients, including 171 patients treated with 3D-CRT and 136 patients treated with IMRT. All patients met the following eligibility criteria: 1) HNC originating in the oral cavity, oropharynx, larynx, hypopharynx, nasopharynx, paranasal sinuses or cervical lymph node metastases from unknown primary tumours; 2) treated with curative radiotherapy (RT), either alone or in combination with chemotherapy (CHRT) or cetuximab; 3) no previous surgery, radiotherapy and/or chemotherapy; 4) no previous malignancies; 5) no distant metastases; 6) health-related quality of life (HRQOL) assessments available prior to, 6 weeks after treatment and at 6 months after completion of RT or CHRT, and 7) no moderate-to-severe xerostomia at baseline. Patients with moderate-to-severe complaints at baseline were excluded from the analysis as we were primarily interested in xerostomia induced by the radiation treatment itself. The demographic and tumour characteristics are listed in Table 1. The majority of patients were male (74%) and the mean age of the study population was 62 years. The range was 32 to 92 years.
The study was performed according to the regulations of the local ethical committees.

Treatment

In all patients, a planning CT-scan with contrast-enhancement was performed in treatment position. Radiotherapy was delivered using a 6 MV linear accelerator. The target volumes for the initial fields and boosts were similar, as previously described (7). In summary, the clinical target volume of the initial field (CTV1) was composed of the primary tumour and pathological lymph nodes plus a 1.0 cm margin, and the elective nodal areas on both sides of the neck. The CTV for the boost irradiation (CTV2) consisted of the primary tumour and pathological lymph nodes with a 0.5 cm margin. In all cases, a 0.5 cm margin was applied for the planning target volumes (PTV1 and PTV2).

The parotid glands were contoured according to the guidelines described by Van de Water et al. (9). All parotid glands were contoured by an expert in head and neck radiation oncology.

When treated with 3D-CRT, no attempts were made to spare the salivary glands. Patients with early laryngeal carcinoma were treated with a fraction dose of 2.5 Gy (5 times/week) up to a total dose of 60 Gy in 5 weeks or with a fraction dose of 2.0 Gy (5 or 6 times/week) up to a total dose of 66 Gy. In these patients, only the primary site was irradiated.

Patients treated with concomitant CHRT were treated with conventional fractionation (2.0 Gy per fraction, 5 times per week, up to 70 Gy in 7 weeks). In case of primary radiotherapy of the more advanced cases, which were considered ineligible for CHRT, an accelerated schedule with concomitant boost technique was used, alone or combined with cetuximab. These patients were generally treated with 6 fractions per week, with a second fraction on Friday afternoon and with a minimum interval of 6 hours, up to a total dose of 70 Gy in 6 weeks. Most patients received bilateral elective irradiation of the neck nodes to a total dose of 46 Gy, and a boost to the primary tumour and pathological lymph nodes to a total dose of 70 Gy. In some cases, radiotherapy with only conventional fractionation was used.

When treated with IMRT, the mean dose to both parotid glands was reduced as much as possible without compromising the required dose to the target volumes. Patients were treated with both a sliding window technique and

step-and-shoot IMRT. A seven-field equidistant, non-opposing beam configuration was used. All patients were treated with a simultaneous integrated boost (SIB) technique. PTV1 was treated with 35 fractions of 1.55 Gy up to a total dose of 54.25 Gy. The PTV2 was treated with 35 fractions of 2 Gy up to a total dose of 70 Gy. All treatment plans were produced by Pinnacle version 9.0 (Philips, Madeson) using a collapsed cone algorithm taking into account dose inhomogeneities.

The standardised follow up programme

Since 1997, all patients referred for radiotherapy for HNC to the department of Radiation Oncology of the VU University Medical Center, Amsterdam, the Netherlands (VU*mc*), were included in a standardised follow up program (SFP). Since March 2007, a similar SFP was established at the department of Radiation Oncology of the University Medical Center Groningen, Groningen, the Netherlands (UMCG). Essentially, the SFP includes prospective evaluation of toxicity and HRQOL on a routine base, prior to, during and at regular intervals after curative RT or CHRT (7). HRQOL was assessed using the head and neck cancer module EORTC QLQ-H&N35 (10). For this study, we used only the xerostomia item.

Endpoints

Patient-rated xerostomia was assessed at baseline, weekly during treatment, 6 weeks after treatment and every 6 months up to 24 months after treatment. A 4-point Likert scale was used (none, a bit, quite a bit, a lot). Patients with quite a bit to a lot of xerostomia were classified as having moderate-to-severe complaints.

Statistics

The patients included in this analysis were divided into two groups (high risk and low risk) based on the criteria described by the QUANTEC Group (5): patients with at least one parotid gland receiving less than 20 Gy and/or both parotids glands receiving less than 25 Gy were classified as low risk patients. All other patients were classified as high risk patients.

Differences in proportions between groups were compared using a chi-square test. Changes over time were calculated for each group and were tested for statistical significance using the McNemar test. P-values below 0.05 were considered statistically significant.

An additional multivariate logistic regression analysis was performed on the group of patients with a complete follow-up of 24 months. This was done because we were also interested in the influence of age and minor xerostomia symptoms at baseline in the development of patient-rated xerostomia over time. In a previous study we showed that patients' age and minor xerostomia at baseline are both independent risk factors in the development of patient-rated xerostomia at 6 months after treatment (7). This separate analysis therefore enabled us to test if the QUANTEC criteria were sufficient to protect against moderate-to-severe patient-rated xerostomia among patients with and without baseline symptoms and how this depended on age. A predicted risk below 20% for an individual patient was considered successful for the QUANTEC criteria.

In addition to the analysis on the value of the QUANTEC criteria to prevent patient-rated xerostomia, we performed an additional analysis on the proportion of patients in which the QUANTEC criteria could be met when treated with IMRT.

All analyses were performed with SPSS for Windows (version 16.0; SPSS, Chicago, Il).

Results

Proportion of patients meeting the QUANTEC criteria

In total, 41% of the patients (treated with 3D-CRT and IMRT) were classified as low risk patients. In the group treated with 3D-CRT and IMRT, it was possible to meet the QUANTEC criteria in 47% and 32% of the patients, respectively.

Table 1: Patient characteristics.

Patiënt characteristics		Number	%
Sex			
	Male	227	74
	Female	80	26
Age			
	≤65	204	66
	≥65	103	34
Chemotherapy			
	Radiotherapy alone	207	67
	Concomitant chemoradiotherapy	89	29
	Concomitant Cetuximab	11	4
Tumour classification			
	T0	9	3
	T1	40	13
	T2	129	42
	T3	70	23
	T4	59	19
Node classification			
	positive	142	46
	negative	165	54
Site			
	Oropharynx/oral cavity	107	35
	Larynx	150	49
	Hypopharynx	28	9
	Nasopharynx/paranasal sinuses	14	5
	Miscellaneous	8	2
Treatment technique			
	3D-CRT	171	56
	IMRT	136	44

Patient-rated xerostomia (EORTC QLQ-HN35)

Figure 1 shows patient-rated xerostomia over time stratified by risk group. From week 4 during radiation up to 24 months after treatment, patients in the high risk group reported significantly more xerostomia compared to those in the low risk group. Between 6 and 24 months after treatment, significant recovery was observed in the low risk as well as in the high risk patients. Ultimately, in the low risk group, the prevalence of moderate-to-severe patient-rated xerostomia after 12 months of follow up was less than 20%.

Proportion of patients meeting the QUANTEC criteria when using IMRT

In the group of patients treated with IMRT (136 patients), the average mean dose to the ipsilateral and contralateral parotid glands was 34.1 Gy (SD ± 14.8 Gy) and 28.0 (SD ± 11.8) Gy, respectively. Ultimately, the QUANTEC criteria were met in 44 patients (32%), including 35 patients (26%) who received a mean dose below 20 Gy to both parotid glands. Of the 44 low risk patients, 35 patients (74%) received a dose of less than 20 Gy to one of the parotid glands, while all 44 low risk patients received less than 25 Gy to both parotid glands.
Patients in the high risk group had significantly more positive lymph nodes, had significantly more tumours located in the oropharynx and nasopharynx and were treated significantly more frequently with bilateral irradiation. Significantly fewer laryngeal tumours and unknown primary tumours were observed in the high risk group (Table 2).

Patient-rated xerostomia and the role of age and minor xerostomia at baseline

In the multivariate logistic regression analysis of patients with a complete follow-up up to 24 months after completion of treatment (n=132; Table 3), the significant predictors for patient-rated xerostomia at 6 months, 12 months and

24 months after treatment were the QUANTEC criteria, increasing age and baseline xerostomia.

Table 2 Differences in baseline characteristics of the IMRT treated patients classified as low risk versus IMRT treated patients classified as high risk.

Characteristics		LOW RISK		HIGH RISK		P-value	DF
		n	%	n	%		
T-classification	T0-T2	25	44%	32	56%	p=0.029	1
	T3-T4	19	24%	60	76%		
N-classification	N0	27	57%	20	43%	p<0.001	1
	N-plus	17	19%	72	81%		
Tumour location	Oropharynx / oral cavity	11	18%	49	82%	p=0.002	4
	Larynx	24	50%	24	50%		
	Hypopharynx	6	35%	11	65%		
	Nasopharynx / paranasal sinus	0	0%	8	100%		
	Miscelaneous	3	100%	0	0%		
Bilateral neck iradiation	No	6	100%	0	0%	p<0.001	1
	Yes	38	29%	92	70%		

Table 3 Odds ratios (OR) for potential risk factors in the development of patient-rated xerostomia for patients completed a follow up of 24 months after treatment.

Risk factor	6 months after treatment			12 months after treatment			18 months after treatment			24 months after treatment		
	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
Quantec criteria (met vs. not met)	6.82	(2.82 - 16.48)	<0.01	7.31	(2.80 - 19.09)	<0.01	6.79	(2.59 - 17.76)	<0.01	7.31	(2.87 - 18.62)	<0.01
Age (years)	1.05	(1.01 - 1.09)	0.02	1.07	(1.02 - 1.12)	<0.01	1.04	(1.00 - 1.08)	0.08	1.05	(1.01 - 1.10)	0.01
Baseline xerostomia score (none *vs.* a bit)	4.16	(1.68 - 10.31)	<0.01	2.85	(1.17 - 6.94)	0.02	2.98	(1.26 - 7.06)	0.01	3.14	(1.34 - 7.32)	0.01

For patients without any xerostomia prior to treatment and in which the QUANTEC criteria were met, the risk of persistent moderate-to-severe xerostomia beyond 6 months of follow up was less than 20%, except for the very old patients, over 70 years of age (Figure 2A). However, in patients with minor xerostomia symptoms before treatment, the risk threshold of 20% or less for moderate-to-severe xerostomia was only attained among patients under 55 years of age (Figure 2B). When the QUANTEC criteria were not met,

the risk of moderate-to-severe xerostomia was below 20% in only the very young patients (<40 years) without baseline complaints (Figure 2C and D).
Younger patients without baseline complaints who also met the QUANTEC criteria showed a higher percentage of recovery than elderly patients (Figure 3).

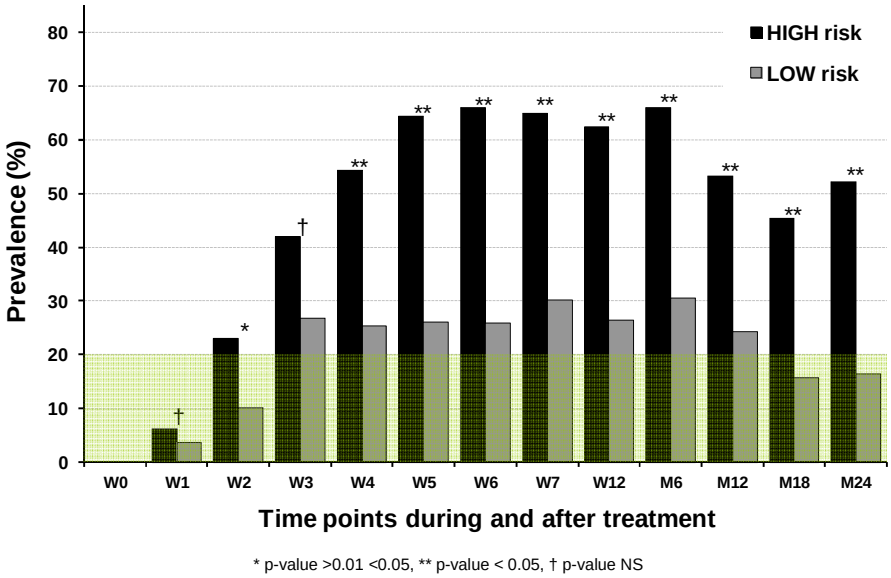

Figure 1 Patient-rated moderate-to-severe xerostomia stratified by risk group (EORTC QLQ-HN35). The p-values refer to the chi-square test, to test for significant differences between high and low risk patients.

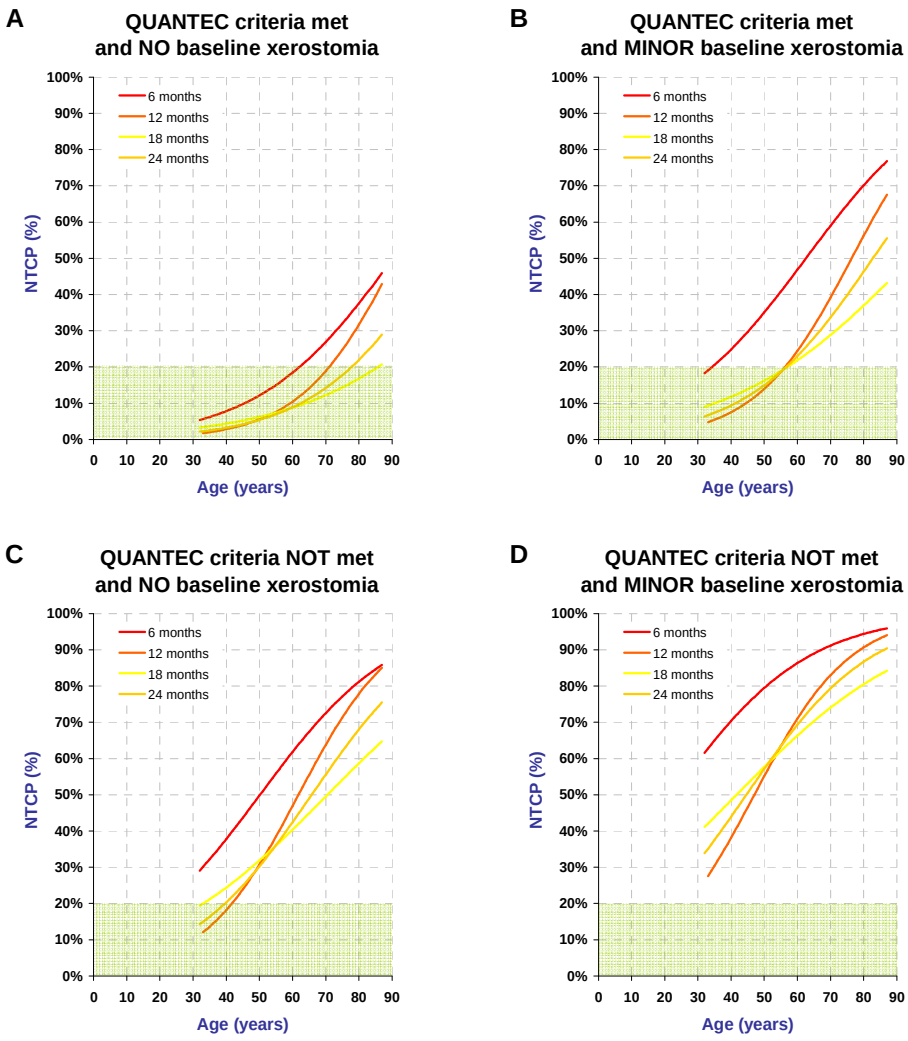

Figure 2 Predicted risk for patient-rated moderate-to-severe xerostomia (EORTC QLQ-HN35) at 6, 12, 18 and 24 months after for different categories; QUANTEC criteria (met vs not met) and baseline xerostomia (none vs minor) as function of increasing age. All curves are based on a multivariate logistic regression analysis for 132 patients with a complete follow up of 24 months.

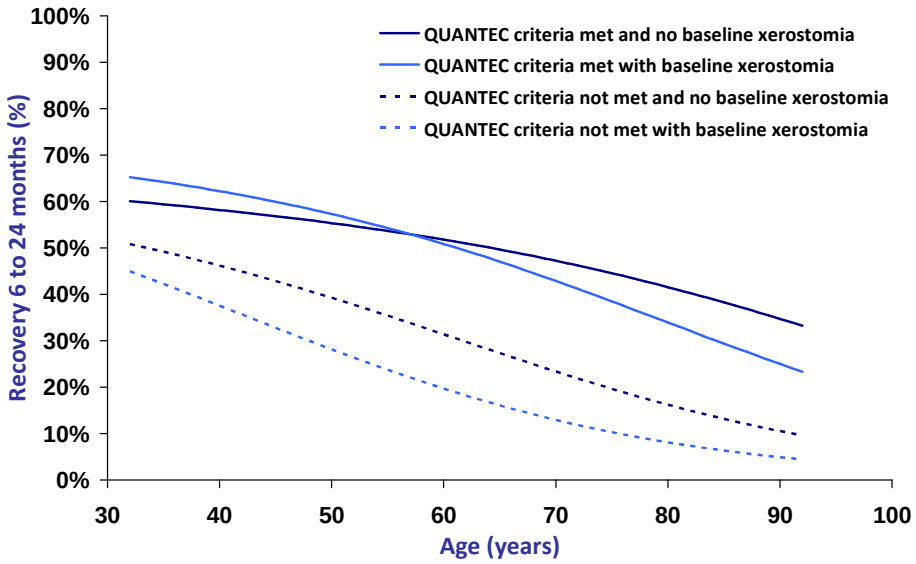

Figure 3 Percentage of recovery of moderate-to-severe xerostomia as a function of age, stratified by the 4 risk group categories shown in Figure 1. The results are based on multivariate logistic regression analysis using the data of 132 patients with a complete dataset at all time points. The curves indicate the estimated percentages of patients with moderate to severe xerostomia 6 months after completion of treatment that will have been recovered at 24 months. Younger patients show higher percentages of recovery than elderly patients. Patients in whom the QUANTEC criteria were met show higher percentages of recovery than in whom they were not met.

Discussion

The purpose of this study was 1) to test the hypothesis that the application of the QUANTEC criteria are useful to prevent patient-rated moderate-to-severe xerostomia, and 2) to determine the extent to which this effect depends on age and the presence of baseline patient-rated xerostomia. The current study indeed showed that patients who met the QUANTEC criteria had significantly lower rates of patient-rated moderate-to-severe xerostomia. These results are in line with those previously reported by Lee et al. where patients treated

according to the QUANTEC guidelines reported less patient-rated xerostomia 12 months after treatment (11).

Main difference between our study and the study of Moiseenko et al. is that the current study focused on patient-rated xerostomia instead of stimulated parotid flow as a result of irradiation of the parotid glands (6). Based on the findings of that study it was stated that the QUANTEC criteria are valid as a guideline to reduce the incidence of grade 4 xerostomia in terms of stimulated parotid flow.

In a previous paper we reported on the influence of increasing age and minor patient-rated xerostomia at baseline on moderate-to-severe patient-rated xerostomia at 6 months after completion of treatment (7). In the current study, we confirmed that these factors were also predictive for moderate-to-severe patient-rated xerostomia at later time points. In addition, we found that the QUANTEC criteria were significantly associated with this endpoint at later time points, but that these criteria were not sufficient to protect against moderate-to-severe xerostomia in many patients who meet the QUANTEC criteria.

This applies especially to elderly patients and those with pre-existing minor complaints of xerostomia. A possible explanation for these findings is that elderly patients generally have more co-morbidity and thus use more medication, both of which may reduce saliva production (12). Moreover, the capacity to recover from radiation-induced damage to the normal tissues may be reduced in elderly patients, which is supported by the shape of the curves in Figures 2 and 3. These curves clearly show that a much higher percentage younger patients reported less severe xerostomia than elderly patients. Figure 3 also showed that patients with "QUANTEC criteria met and no baseline xerostomia" had less recovery than "QUANTEC criteria met with baseline xerostomia" patients in the young age group and over 57 years of age recovery crossover. This illustrates that the influence of age (<57 years) on recovery of xerostomia after treatment is greater than the influence of minor complaints of xerostomia at baseline. These findings are in line with those reported by Ghezzi et al., who showed that the secretory reserve capacity of the major salivary glands decreases with age. Elderly patients are therefore more

vulnerable to xerostomia due to their reduced secretory reserve (13). The probable cause is that radiation-induced salivary dysfunction results from the loss of parotid gland stem cells and that the number of stem cells decreases with age (14).

Moreover, despite the use of IMRT it was possible to meet the QUANTEC criteria in only 32% of the patients. In the present study, we identified some subsets of patients in which it was more difficult to spare the parotid glands with IMRT, in particular patients being treated for oropharyngeal and nasopharyngeal carcinoma, those being treated with bilateral irradiation and patients with lymph node metastases. This is mainly due to major overlap of the PTV with larger parts of the parotid glands. Conversely, the parotid glands could be adequately spared in a much higher proportion of patients with laryngeal carcinoma, unilateral irradiation, N0 disease and lymph node metastases from unknown primary tumours.

A possible explanation for these findings is that the quality of IMRT given at our departments was poor and could be further improved. However, we have been using similar dose constraints for the parotid glands in the patients included in this analysis. Moreover, the results in our series are quite similar to those reported elsewhere (1,2). For instance, Nutting et al. (1) recently published the results of a prospective randomised study, in which 47 patients were treated with IMRT. In that study, the average mean doses to the ipsilateral and contralateral parotid glands were of 47.6 Gy and 25.4 Gy, respectively. These doses are more or less similar to those observed in the IMRT treated patients (35.2 Gy and 28.0 Gy to the ipsilateral and contralateral parotid gland, respectively), but it has to be emphasized that in our study patients received a higher total dose to PTV2 than the patients in the cohort of Nutting et al.(1). In our study, patients were treated with 35 fractions and 54.25 Gy to PTV1 and 70 Gy to PTV2, compared to 54 Gy and 65 Gy in 30 fractions when treated with primary IMRT as reported by Nutting et al. For post-operative therapy, the total dose to PTV2 was even lower than 60 Gy, which might explain the differences between our study and that of Nutting et al. In another study, in which patients with nasopharyngeal carcinoma were treated with IMRT (2), the average mean dose to the parotid glands was 32.2

Gy. In our population, these average dose levels were much higher in the subset of nasopharyngeal cancer patients: 56.0 Gy and 44.7 Gy to the ipsilateral and contralateral gland, respectively. However, Kam et al. only included patients with T1 and T2 tumours and with unilateral disease (N1). In our study, 6 of the 7 patients treated for nasopharyngeal tumours had stage N2 or N3 neck disease and all had advanced T-stages, which might explain the higher average mean dose to the parotid glands in nasopharyngeal cancer patients.

Due to the above findings, the question arises as to whether other radiation delivery techniques are more effective at sparing the parotid glands without compromising the dose to the PTV. Van de Water et al. (15) recently showed that the dose to the parotid glands could be reduced even further in approximately 70% of oropharyngeal cancer patients by using spot scanning protons. The possible benefits of using protons instead of photons was described for swallowing disorders after radiotherapy treatment for head and neck cancer (16). In line with swallowing disorders patients could also benefit from protons in the protection of patient-rated xerostomia. The use of protons instead of photons is subject of further research, in particular in the subsets of patients in which the QUANTEC criteria cannot be met.

Based on the findings of the present study, it appears that with IMRT it is more difficult to spare the parotid glands than with 3D-CRT, which is actually not true. The 3D-CRT cohort also included patients who were locally irradiated for early laryngeal cancer, while the patients treated with IMRT had more extensive disease and were treated more often with bilateral neck irradiation. This affected the parotid glands move severely.

In conclusion, the dose constraints recommended by the QUANTEC group have prognostic value with regard to patient-rated moderate-to-severe xerostomia. When these criteria can be met, the risk of this side effect drops below 20%, except in elderly patients and patients with pre-existing, although minor, complaints of xerostomia prior to treatment. Unfortunately, the QUANTEC criteria in this study could only be met in a minority of patients. New radiation delivery techniques to further reduce the dose to the relevant salivary glands are therefore required, which we suggest as a topic for future research.

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CHAPTER

6

The Groningen Radiotherapy-induced xerostomia questionnaire; development and validation of a new questionnaire

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Abstract

Purpose

The purpose of this study was to develop and validate a questionnaire (Groningen Radiotherapy Induced Xerostomia Questionnaire (GRIX)) that has the ability to distinguish between patient rated xerostomia during day and night and can be used to evaluate the impact of emerging radiation delivery techniques aiming at prevention of xerostomia in more detail.

Methods and Materials

All questions in the GRIX were generated from an exhaustive list of relevant questions according to xerostomia as reported in the literature and reported by patients and health care providers. Finally the GRIX was reduced from 56 questions to a 14 item questionnaire, with four subscales; xerostomia during day and night and sticky saliva during day and night. 315 patients filled out 2936 questionnaires and the GRIX was evaluated by calculating Crohnbach α's for all subscales. Criterion validity was evaluated to compare the GRIX with patient rated xerostomia scored with the EORTC QLQ-HN35 and physician-rated xerostomia, test-retest analysis and responsiveness was also tested.

Results

Crohnbach α's varied for all subscales between 0.88 and 0.94. The GRIX scored well for criterion related validity on all subscales with high correlations with the EORTC QLQ-HN35 xerostomia and sticky saliva scale as well with physician-rated toxicity scoring. No significant differences were found between test and retest score and the GRIX showed good responsiveness with different time points for all subscales.

Conclusion

The GRIX is a validated questionnaire which can be used in future research focusing on patient rated xerostomia and sticky saliva during day and night in relation with the impact of emerging radiation delivery techniques aiming at reduction of xerostomia.

Introduction

In patients with head and neck squamous cell carcinoma (HNSCC), radiotherapy either as primary or postoperative modality, generally includes irradiation of at least some parts of the salivary glands. Irradiation of the salivary glands may result in salivary dysfunction and subsequent xerostomia, which is one of the most frequently reported side effects of radiation treatment in the head and neck area (1-6). In addition, salivary dysfunction may lead to a sensation of dry mouth, altered taste, swallowing problems and speech problems and has a significant impact on the more general dimensions of health-related quality of life (HRQOL) (1,7-11). From this point of view, xerostomia as reported by patients may provide important additional information in the assessment of radiation-induced salivary gland dysfunction.
The EORTC QLQ-C30 and the EORTC QLQ-H&N35 are the most commonly used validated questionnaires to determine HRQOL after irradiation of head and neck cancer in clinical trials (12-14). The EORTC QLQ-H&N35 contains 35 questions concerning treatment-related symptoms and symptoms frequently present in head and neck cancer patients. This questionnaire is organised into seven multi item scales and eleven single item scales, including one xerostomia and one sticky saliva scale. All scales are rated on a four-point Likert-scale. As the EORTC QLQ-H&N35 only contains one question about xerostomia and one question about sticky saliva, the question arises as to whether this questionnaire is sufficiently sensitive to score more discrete changes of patient-rated xerostomia. In addition, this questionnaire does not allow for the assessment of different aspects of xerostomia at different time points. Some patients mainly suffer from xerostomia at night while others have complaints predominantly during the day (15). Content and production of saliva may differ among different salivary glands and show a circadian rhythm (16,17), which may have various impacts on different aspects of symptoms related to salivary dysfunction.
Therefore, the purpose of the current study was to develop and validate a questionnaire that enables scoring of different aspects of patient-rated

xerostomia which can be used to evaluate the impact of emerging radiation delivery techniques aiming at prevention of xerostomia in more detail.

Methods and Materials

Patients

Since March 2007, a prospective consecutive cohort of patients with HNSCC referred for radiotherapy was established at the department of Radiation Oncology of the University Medical Centre Groningen. This prospective cohort was composed of 315 patients, who had to have head and neck cancer originating in the oral cavity, oropharynx, larynx, hypopharynx, or nasopharynx. All patients were treated with radiotherapy either alone or in combination with surgery, chemotherapy and/or cetuximab. Understanding of the Dutch language was required to fill out the questionnaire. The study was approved by the ethical committee of the University Medical Centre Groningen.

The demographic and pre-treatment tumour characteristics of all patients who filled out the questionnaire are listed in Table 1. The majority of patients were male (69%). The mean age of the study population was 62 years, ranging from 19 to 90 years. The 315 patients filled out a total of 2936 questionnaires with a maximum of two years follow-up and a mean and median follow up of 12 months.

Assessment of radiation-induced toxicity

In April 2007, a standard follow-up program (SFP) was started at the department of Radiation Oncology for all patients with head and neck cancer, who were treated with primary and/or postoperative (chemo) radiation. Acute and late radiation-induced side effects were assessed according to the Common Terminology Criteria of Adverse Events v3.0 (CTCAE v3.0). Baseline and acute side effects were assessed by the physician on a weekly base during

radiation treatment, while late side effects were assessed at 6 weeks after completion of treatment and every 6 months after treatment.

Assessment of patient rated QoL

For the evaluation of the different aspects of patient-rated xerostomia, a new questionnaire was developed referred to as the Groningen Radiation-Induced Xerostomia questionnaire (GRIX).
In the first phase, we composed an initial list of relevant questions related to xerostomia as reported in earlier studies (15,18-23) and as reported by patients and health care providers experienced in treating patients with head and neck cancer. This initial phase resulted in a questionnaire that contained 56 questions.
This initial list of 56 questions was reviewed by the investigators to delete questions that were closely related or in fact posed the same question in another way. In this phase, the questions were reconstructed in order to obtain the same response format as used in the aforementioned EORTC questionnaires, i.e., not at all, a little, quite a bit, and very much. This adjusted questionnaire was presented to three different health care providers and one patient. These observers were asked to indicate: 1) for each question if this was considered relevant (varying from very much to not at all) and 2) for each question if the formulation was clear. Eventually, this resulted in a first version of the questionnaire that contained 16 questions, which after a first evaluation, was reduced to a 14-item questionnaire (see appendix).
The GRIX version 1.0 was conceptualised as containing four subscales xerostomia and sticky saliva during day and night. This four subscales were chosen based on the physiological differences in content and production of saliva during day and during night (16,17). Patients filled out the GRIX and the EORTC QLQ-H&N35 at baseline, weekly during radiation treatment, six weeks after treatment and every 6 months after completion of treatment until 24 months after treatment. All scores were linearly converted to a 0-100 scale, in which higher scores represent more xerostomia

Statistics

The reliability of the scale of the GRIX was evaluated by examining the internal consistency of the scale by using Crohnbach α's, which refers to the extent to which the items within a scale are interrelated. Crohnbach α's were calculated for all questionnaires together and for each individual time point. Stability of the GRIX was evaluated by correlating test-retest scores using Pearson's correlation coefficients between pre-test, on the day of the first visit to the outpatient clinic and retest on the first day of radiation treatment. In general, the interval between these two time points was approximately 2 weeks and not any treatment was given during this period. For this test-retest analysis, patients referred for postoperative radiotherapy were excluded, to exclude any influence due to recovery of surgery on test- retest scores (n=149).

Criterion validity of the GRIX was evaluated by comparing the questionnaire's score with the score on the two questions about xerostomia and sticky saliva in the EORTC QLQ-HN35 questionnaire and the physician-rated CTCAEv3.0 toxicity scoring system for xerostomia and salivary gland changes using Pearson's correlation coefficients. Criterion validity was also tested for all filled out questionnaires together as well for four different time points, baseline, 6 weeks after start radiotherapy treatment and 6 months and one year after completion of treatment.

Responsiveness of the GRIX, which refers to the ability of a questionnaire to detect important changes over time, was evaluating by testing the scores of different subscales as a function of time during radiation treatment, which in fact corresponds to the delivered dose to the salivary glands during treatment.

All analyses were performed with SPSS for windows (version 16.0; SPSS, Chigaco, Il).

Table 1: Demographic and disease-related characteristics (n=315).

Characteristics		Patients (n=315)	%
Sex			
	Male	218	69
	Female	97	31
Age			
	≤65	189	60
	≥65	126	40
Treatment modalities			
	Radiotherapy alone	182	58
	Postoperative radiotherapy	133	42
Tumour classification			
	T0	22	7
	T1	58	18
	T2	101	32
	T3	45	14
	T4	88	28
	Tis	1	0
Node classification			
	N0	136	432
	N1	41	13
	N2a	10	3
	N2b	49	16
	N2c	67	21
	N3	12	4
Site			
	Oropharynx	125	40
	Sinuses and nasopharynx	16	5
	Hypopharynx	19	6
	Larynx	92	29
	Salivary glands	22	7
	Other	41	13

Results

Compliance

From the 3411 possible questionnaires during follow up, 2936 questionnaire (86.1%) were filled out by the 315 patients. The compliance of physician-rated toxicity was 88.6 percent (6041 out of 6822 required assessments).

Internal consistency

Internal consistency was established by calculating Crohnbach α's for the four subscales of all questionnaires together. For the subscale xerostomia during the day and night and sticky saliva during the day and night, the Crohnbach α's were 0.94, 0.88, 0.89 and 0.88 respectively. Crohnbach α's for each individual time point were also calculated and varied between 0.82 and 0.94.

Test-retest reliability

Test-retest reliability was calculated by Pearson's correlation coefficients between pre-test during the first visit of the outpatient clinic and the retest on the first day of radiation treatment. One-hundred-forty-nine patients treated with radiotherapy alone filled out the questionnaire at baseline and on the first day of treatment. Pearson's correlation coefficients for each subscale were moderate and were 0.63, 0.69, 0.67 and 0.64 respectively. All correlation coefficients between test and re-test were statistically significant ($p<0.05$).

Criterion validity

Criterion related validity was investigated by evaluating the Pearson's correlation between each subscale of the GRIX with the two single-item questions assessed by the EORTC QLQ-HN35 questionnaire, i.e., xerostomia and sticky saliva subscales (Table 2). For each subscale and for the combined

subscales for xerostomia and sticky saliva correlations were high (between 0.68 and 0.85) and were all statistically significant. At the different time points (i.e. baseline, 6 weeks after start treatment, 6 months, 12 months), Pearson's correlations varied between 0.56 and 0.87 and were statistically significant for all subscales (Table 2). Physician-rated xerostomia and sticky saliva were also significantly correlated with the four subscales of the GRIX at all time points (Table 2) and varied between 0.34 and 0.65.

Table 2 criterion validity; Pearson's correlations for each individual subscale and the combined scales of xerostomia and sticky saliva, for all questionnaires, baseline, 6 weeks after start treatment, 6 months and one year after treatment.

2a: Comparison with EORTC QLQ-HN35*

Subscale GRIX	Total (n=2936)	Baseline (n=294)	6 weeks (n=278)	6 months (n=205)	1 year (n=134)
Xerostomia during day	0.839	0.775	0.866	0.789	0.789
Xerostomia during night	0.692	0.657	0.654	0.661	0.673
Sticky saliva during day	0.747	0.647	0.782	0.658	0.614
Sticky saliva during night	0.677	0.578	0.686	0627	0.559
Xerostomia total score	0.845	0.657	0.854	0.804	0835
Sticky saliva total score	0.760	0.620	0.785	0.691	0.654

2b: Comparison with CTCAE v3.0*

Subscale GRIX	Total (n=2936)	Baseline (n=294)	6 weeks (n=278)	6 months (n=205)	1 year (n=134)
Xerostomia during day	0.655	0.465	0.605	0.650	0.631
Xerostomia during night	0.493	0.340	0.455	0.510	0.514
Sticky saliva during day	0.565	0.352	0.522	0.407	0.518
Sticky saliva during night	0.511	0.326	0.417	0.365	0.372
Xerostomia total score	0.644	0.360	0.593	0.652	0.658
Sticky saliva total score	0.574	0.454	0.504	0.419	0.519

****all coefficients were significantly correlated ($p<0.05$)***

Responsiveness

The GRIX had the ability to detect changes over time, for the four different subscales. An increase in patient-rated xerostomia and sticky saliva was observed with increasing dose delivered to the tumour and salivary glands (Figure 1).

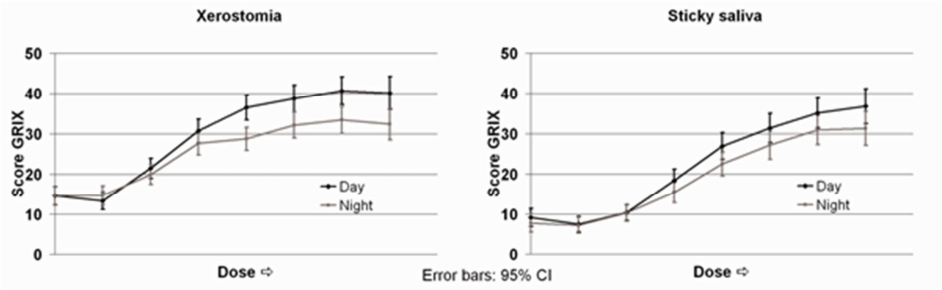

Figure 1 changes on mean score for the four different subscales of the GRIX, according to increased dose to salivary glands on the course of treatment.

Discussion

This study was undertaken to test the reliability and validity of the Groningen Radiation-Induced Xerostomia (GRIX) questionnaire. The GRIX showed good reliability and criterion validity in scoring different aspects of xerostomia and sticky saliva in head and neck cancer patients treated with radiotherapy either as single modality or combined with surgery, chemotherapy and/or cetuximab. The GRIX showed moderate responsiveness and enabled scoring of different aspects of salivary gland dysfunction during the day and during the night.

The GRIX showed a significant correlation with physician-rated xerostomia and sticky saliva, although these correlations were weaker as compared to those with the corresponding scales as assessed by the EORTC QLQ-H&N35. In a previous study, Jensen et al. showed that physicians tend to underestimate xerostomia as rated by patients (24), which may explain the lower criterion validity as observed between physician-rated and patient-rated xerostomia and sticky saliva.

Content and production of saliva may differ among different salivary glands and different time points (16,17). The parotid and submandibular glands are responsible for the main stimulated saliva production and the production of saliva at rest, while during sleep, the saliva is predominantly produced by the sublingual glands and the minor salivary glands lining the oral cavity. In contrast, during sleep the saliva production by the parotid gland is almost zero and can be negligible in relation to the total saliva production during the night (25). Therefore radiation-induced tissue damage in different salivary glands may results in different clinical manifestations. In the GRIX, patient-rated xerostomia and sticky saliva during the day and during the night can be scored separately, in contrast to the most commonly used questionnaire, such as the EORTC QLQ-H&N35. The main shortcoming of the existing and published questionnaires is that they have not been validated (18,23) or did not allow for scoring all relevant aspects of xerostomia, such as day- and night-time complaints (19,21-26). The xerostomia questionnaire used by Eisbruch et al. is the only validated questionnaire that can distinguish between stimulated and unstimulated saliva flow. However, this questionnaire only takes into account xerostomia and does not take into account complaints about sticky saliva as reported by patients. Moreover, this questionnaire, with only one question regarding sleeping disorders due to xerostomia does not allow to differ between day and night time complaints (26).

Recently, Langendijk et al. reported on the relationship between physician-rated late toxicity according to the RTOG Late Radiation Morbidity Scoring System on different aspects of HRQOL (7). A striking finding was the impact of RTOG-xerostomia on fatigue. Additional analysis revealed that RTOG-xerostomia also significantly correlated with sleeping problems (personal communication), indicating that nocturnal salivary dysfunction is of particular importance with respect to its impact on the more general dimensions of HRQOL. These findings may have implications in relation to future direction with regard to optimizing IMRT aiming at reduction of patient-rated xerostomia. Thus the relationship between dose distributions in different salivary glands and various endpoints related to xerostomia (e.g., xerostomia during the day and during the night) might be different. Therefore, to get more

insight in the possibilities of new radiation techniques preventing different aspects of patient-rated xerostomia, the use of an instrument that enables scoring these different aspects of xerostomia is required.

Most investigators analysing the relationship between radiation dose and xerostomia mainly focused on the relationship between parotid gland dose and stimulated and/or unstimulated parotid salivary flow (27,28). However, in some studies, discrepancies between different endpoints related to salivary dysfunction have been found (26,29-31). Kam et al. reported on the results of a phase III study in which patients with nasopharyngeal carcinoma were randomly assigned to receive IMRT or 2-dimensional radiotherapy (2D-RT). In that study, significant differences in stimulated parotid salivary flow, whole saliva flow and physician-rated xerostomia according to the RTOG criteria were found in favour of IMRT. However, no significant difference in patient-rated xerostomia at any time point was found (29). These findings clearly illustrate that patient-rated xerostomia can not only be explained by changes in parotid flow due to radiation of the parotid glands, but that irradiation to other salivary glands are of importance as well. The importance of salivary glands other than the parotid glands is confirmed by the findings of other investigators (26,31). Jellema et al. found that patient-rated xerostomia not only depended on the mean dose in the parotid glands but also on the mean dose in the submandibular glands (31). The findings of Eisbruch et al. also suggested that the radiation dose to the minor salivary glands, such as the sublingual gland and the minor salivary glands lining the oral cavity are important as well with regard to patient-rated xerostomia (26,29-32).

The GRIX was particularly developed for the purpose of clinical studies investigating the relationship between dose distributions in different salivary glands (as described by van de Water et al (32)) and different aspects of patient-rated symptoms related to salivary dysfunction. The analysis of these kind of relationships with one endpoint potentially depending on different dose volume parameters in different organs at risk is very complex and is beyond the scope of the current paper. Currently, we are carrying out a large prospective longitudinal cohort study in which these issues are addressed.

In conclusion, the GRIX is a validated questionnaire which can be used in future research focusing on patient-rated xerostomia and sticky saliva in relation with the impact of emerging radiation delivery techniques aiming at reduction of different aspects of salivary dysfunction.

Appendix

Questionnaire

Question	Not at all	A little	Quite a bit	Very much
Have you had a dry mouth during the day?	◘	◘	◘	◘
Have you had a dry mouth outdoors?	◘	◘	◘	◘
Have you had difficulties with eating due to a dry mouth?	◘	◘	◘	◘
Have you had a dry mouth during activities?	◘	◘	◘	◘
Have you had difficulties with talking due to a dry mouth?	◘	◘	◘	◘
Did you drink more during the day due to a dry mouth?	◘	◘	◘	◘
Have you had a dry mouth during the night?	◘	◘	◘	◘
Have you had difficulties with sleeping due to a dry mouth?	◘	◘	◘	◘
Did you need to drink during the night due to a dry mouth?	◘	◘	◘	◘
Have you had sticky saliva during the day?	◘	◘	◘	◘
Have you had difficulties with eating due to sticky saliva?	◘	◘	◘	◘
Have you had difficulties with talking due to sticky saliva?	◘	◘	◘	◘
Have you had sticky saliva during the night?	◘	◘	◘	◘
Have you had difficulties with sleeping due to sticky saliva?	◘	◘	◘	◘

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CHAPTER 7

Role of minor salivary glands in developing patient-rated xerostomia and sticky saliva during day and night

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Abstract

Purpose

The purpose of this prospective study was to investigate the relationship between xerostomia during the day (XER_{day}) and night (XER_{night}) and sticky saliva during the day ($STIC_{day}$) and night ($STIC_{night}$) and dose distributions in different major and minor salivary glands among head and neck cancer (HNC) patients treated with primary radiotherapy (RT) or chemoradiation (CHRT).

Methods and materials

The study population was composed of 201 consecutive HNC patients treated with intensity modulated radiotherapy (IMRT) or 3-dimensional conformal radiotherapy (3D-CRT). All patients were included in a standard follow up program in which acute and late side effects and quality of life (QoL) were prospectively assessed, prior to, during and after treatment.
The primary endpoints were XER_{day}, XER_{night}, $STIC_{day}$, $STIC_{night}$ as assessed by the Groningen Radiotherapy Induced Xerostomia questionnaire (GRIX) six months after completion of treatment. Organs at risk (OARs) potentially involved in salivary function were delineated on planning-CT, including the parotid, submandibular and sublingual glands and the minor glands in the soft palate, buccal mucosa and lips. Patients with moderate-to-severe xerostomia or moderate-to-severe sticky saliva, respectively, at baseline were excluded.
In order to determine which salivary glands were most important, a multivariate logistic regression analysis with an extended bootstrapping technique was used.

Results

In total, 29% and 19% of the cases suffered from XER_{day} and XER_{night}, respectively. The multivariate analysis showed that baseline xerostomia and the mean parotid gland dose were the most important predictors for XER_{day}

and XER_{night}. At 6 months after (CH)RT, 10% and 12% of the cases reported $STIC_{day}$ and $STIC_{night}$ respectively. We were not able to identify prognostic factors related to dose distributions with regard to $STIC_{day}$. The mean submandibular gland dose was associated with $STIC_{night}$. Baseline xerostomia and sticky saliva scores on the GRIX was associated with XER_{day}, XER_{night}, $STIC_{day}$. Increasing age was correlated with both XER_{night} and $STIC_{night}$.

Conclusions

Organs at risk for XER_{day} and $STIC_{day}$ are similar to organs at risk for XER_{night} and $STIC_{night}$.

Introduction

Radiotherapy is frequently applied to patients with head and neck cancer (HNC) either as single modality or as adjuvant treatment after primary surgery. Head and neck radiotherapy generally includes co-irradiation of the major and minor salivary glands located in the mucosal surfaces of the oral cavity (1). Irradiation of the salivary glands results in salivary dysfunction which may lead to subsequent xerostomia and sticky saliva. Xerostomia is one of the most frequently reported side effects among patients after irradiation for HNC (2-7). Salivary dysfunction may lead to subsequent side effects such as altered taste, swallowing problems, dental problems and speech problems which significantly hamper quality of life (QoL) (8-13).

The severity and aspects of xerostomia as reported by patients may differ among individual patients. Some patients mainly suffer from xerostomia at night while others have complaints predominantly during the day or during specific activities, such as during eating and/or exercise (14). Content and production of saliva may differ between different salivary glands during different time points during the day, which may have various impacts on different aspects of symptoms related to salivary dysfunction (15,16). The major salivary glands, including the parotid and submandibular glands are responsible for the main stimulated saliva production. Parotid flow markedly increases during eating, while the daily production of saliva at rest is mainly produced by the submandibular glands. During sleep, saliva is also produced by the sublingual and minor salivary glands lining the oral cavity. At night, the amount of saliva produced by the parotid glands is negligible (17).

The QUANTEC study group recently reported about the role of irradiation of the parotid glands and the development of xerostomia in general. These study results are widely used as dose constraints to parotid glands in the treatment of head and neck cancer patients with radiotherapy. These QUANTEC guidelines do not take into account the different aspects of xerostomia and sticky saliva as reported by patients at different time points (18,19). In that perspective it would be interesting to investigate what the role of other salivary glands is in these different aspects of xerostomia and sticky saliva.

Recently, Langendijk et al. reported that xerostomia had a significant impact on the more general dimensions of health related quality of life (HRQOL), including on fatigue. In an additional analysis, they found that xerostomia significantly correlated with sleeping problems as well (personal communication), indicating that nocturnal salivary dysfunction is of particular importance for patients (8).
Recently, we developed and validated a new questionnaire, the Groningen Radiotherapy Induced Xerostomia (GRIX) questionnaire, allowing for differentiated assessments of patient-rated xerostomia and sticky saliva, during the day and during the night (20). With this questionnaire it is possible to correlate different aspects of patient-rated xerostomia and sticky saliva to the dose distributions to different major and minor salivary glands. Therefore, the purpose of this study was to test if organs at risk for patient-rated xerostomia during the day differed from organs at risk for patient-rated xerostomia and sticky saliva during the night.

Material and methods

Patients

To be included in the analysis, patients had to fulfil the following eligibility criteria: 1) HNC originating in the oral cavity, oropharynx, larynx, hypopharynx, nasopharynx, paranasal sinuses or cervical lymph node metastases from unknown primary tumours; 2) treated with primary radiotherapy either alone (RT) or in combination with chemotherapy (CHRT) or cetuximab; 3) no previous surgery, radiotherapy and/or chemotherapy; 4) no previous malignancies; 5) no distant metastases, and: 6) QoL assessments available prior to and at 6 months after completion of CHRT or RT.

The standardised follow up program

All patients included in this analysis were subjected to a standard follow-up program (SFP) as previously described (21,22). The SFP includes a prospective evaluation of toxicity and QoL on a routine base, prior to, during and at regular intervals, weekly during treatment, 6 weeks and every 6 months after curative CHRT or RT. For the purpose of this study, only the outcome of the GRIX questionnaire was used. All included patients completed the GRIX questionnaire at the outpatient clinic, just before the consultation with the radiation oncologist.

Endpoints

The endpoints for this study were defined as moderate-to-severe xerostomia during the day ($RespXER_{day}$), moderate-to-severe xerostomia during the night ($RespXER_{night}$), moderate-to-severe sticky saliva during the day ($RespSTIC_{day}$) and moderate-to-severe sticky saliva during the night ($RespSTIC_{night}$) as assessed at 6 months after completion of treatment using the GRIX (20).
The GRIX is organised into four functional multi-item scales (XER_{day}, XER_{night}, $STIC_{day}$, $STIC_{night}$). Each scale is composed of a number of questions using a 4-point Likert scale ranging from none, a bit, quite a bit, to a lot. For each scale the scores on the GRIX were linearly converted to 0-100 score according to the same guidelines as proposed by the EORTC. For the purpose of this study, patients were divided into two groups, i.e. a subgroup with a score from 0-50, corresponding with no-to-minor complaints for each scale, and a subgroup with a score from 51-100 corresponding with moderate-to-severe complaints ($RespXER_{day}$, $RespXER_{night}$, $RespSTIC_{day}$, $RespSTIC_{night}$). Patients with scores ≥ 50 at baseline were excluded from the analysis. This was done, as we were primarily interested in xerostomia and sticky saliva induced by radiation treatment itself.

Treatment

In all patients, a planning CT-scan with contrast-enhancement was performed in treatment position. Radiotherapy was delivered using a 6 MV linear accelerator. The target volumes have been described previously (21). In summary, the prophylactic clinical target volume was composed of the primary tumour and pathological lymph nodes plus a 1.0 cm margin, and the elective nodal areas on both sides of the neck, selected according to the guidelines reported by Gregoire, et al. (23). The therapeutic CTV consisted of the primary tumour and pathological lymph nodes with a 0.5 cm margin. In all cases, an additional 0.5 cm margin was applied for the planning target volumes.

Among patients treated with 3-dimensional conformal radiotherapy (3D-CRT), no attempts were made to spare the salivary glands. Patients with early glottic carcinoma were treated with a fraction dose of 2.5 Gy (5 times/week) up to a total dose of 60 Gy in 5 weeks or with a fraction dose of 2.0 Gy (5 or 6 times/week) up to a total dose of 66 Gy. These patients were only irradiated at the primary site.

Patients treated with concomitant CHRT were treated with conventional fractionation (2.0 Gy per fraction, 5 times per week up to 70 Gy in 7 weeks). In case of primary radiotherapy of the more advanced cases, which were considered not eligible for CHRT, an accelerated schedule with concomitant boost technique was used, either or not combined with cetuximab. These patients were generally treated with 6 fractions per week with a second fraction on Friday afternoon with a minimum interval of 6 hours, up to a total dose of 70 Gy in 6 weeks. Most patients received bilateral elective irradiation of the neck nodes to a total dose of 46 Gy and a boost on the primary tumour and pathological lymph nodes to a total dose of 70 Gy. In some cases, radiotherapy only with conventional fractionation was used.

When treated with intensity modulated radiotherapy (IMRT) the mean dose to both parotid glands was reduced as much as possible without compromising the required dose to the target volumes. Patients were treated with step-and-shoot IMRT. In general, a seven-field equidistant, non-opposing beam

configuration was used. All patients were treated with a simultaneous integrated boost (SIB) technique.

Contouring of organs at risk

Organs at risk (OARs) potentially involved in symptoms related to salivary function were delineated according to the guidelines as described by Van de Water et al. (1), including the parotid, submandibular and sublingual glands, as well as the minor salivary glands located in the soft palate, the inner surface of the lower and upper lip and the minor salivary glands in the inner surface of the cheeks. All OARs were delineated by an expert in head and neck radiation oncology (JL).

Statistics

A multivariate logistic regression analysis with an extended bootstrapping technique was performed as described previously (21). In order to determine the predictive value of a certain model (i.e. a certain combination of variables), 2000 fitting bootstrap data sets were generated with replacement, while the corresponding 2000 test data sets consisted of the non-selected cases. The logistic model was fitted to each fitting bootstrap data set. The regression procedure was stopped in case of a change <10-12 in either the model predictions or the model parameters in subsequent iterations, or if the maximum number of 100 iterations was reached. The total log likelihood was calculated based on the model predictions and measured endpoints for all corresponding test dataset. The average over the 2000 log likelihood values was defined to be the predictive value of the model. Variables were added using the sequential forward selection procedure. In general, the predictive value first increases when the number of variables increases, reaches a maximum value, and then starts to decrease again due to overfitting.

Table 1 Demographic and disease-related characteristics for the patients included in the analysis for each endpoint.

Characteristics	Patient-rated xerostomia day (GRIX)		Patient-rated xerostomia night (GRIX)		Patient-rated sticky saliva day (GRIX)		Patient-rated sticky saliva night (GRIX)	
	Patients (n=189)	%	Patients (n=184)	%	Patients (n=190)	%	Patients (n=187)	%
Sex								
Male	136	72	134	73	138	73	134	72
Female	53	28	50	27	52	27	53	28
Age								
≤ 65	116	61	113	61	117	62	114	61
> 65	73	39	71	39	73	38	73	39
Chemotherapy								
Yes	42	22	42	23	42	22	41	22
No	147	78	142	77	148	78	146	78
Cetuximab								
Yes	12	6	11	6	12	6	11	6
No	177	94	173	94	178	94	176	94
Tumour classification								
T0	6	3	5	3	7	2	6	3
T1	37	20	36	20	37	20	37	20
T2	67	35	64	35	68	36	69	37
T3	38	20	37	20	37	20	34	18
T4	41	22	41	22	41	22	41	22
Node classification								
positive	96	51	92	50	97	51	96	51
negative	93	49	92	50	93	49	91	49
Site								
Oral cavity	12	6	12	7	12	6	12	6
Oropharynx	47	25	48	26	47	25	45	24
Larynx	92	49	89	48	92	48	92	49
Hypopharynx	17	9	16	9	17	9	16	9
Nasopharynx	6	3	6	3	7	4	7	4
Sinuses	8	4	7	4	8	4	8	4
Unknown primary	7	4	6	3	7	4	7	4
Treatment technique								
3D-CRT*	12	6	12	7	12	6	12	6
IMRT*	47	25	48	26	47	25	45	24

* 3E-CRT: three dimensional radiotherapy, IMRT: Intensity modulated radiotherapy

Before carrying out the regression analysis, a correlation matrix was produced to check for high correlations between candidate prognostic determinants, in particular between dose volume histogram (DVH) parameters. In case Pearson correlation coefficients were ≥ 0.75 between potential prognostic DVH parameters, these parameters were combined into a single variable to avoid the problem of multicollinearity which may negatively affect the generalisability of the model. Finally, all DVH data were connected to all other potential pre-treatment prognostic factors for each individual patient.
After selecting the combination of variables with the highest performance, adjusted Odd's ratios (OR) and 95% confidence intervals (95% CI) were calculated for the selected variables.

Results

Patients

Initially, 201 patients fulfilled the eligibility criteria to be included in the analysis. In total, 189, 184, 190 and 187 of the patients were evaluable for XER_{day}, XER_{night}, $STIC_{day}$, $STIC_{night}$, respectively. These numbers differed between the four endpoints because only patients with scores <50 were included in the analysis. The demographic and tumour characteristics of all included patients for each endpoint are listed in Table 1. An overview of the mean doses to the organs at risk are depicted in Table 2.

Variable reduction and dose distribution procedure

In order to reduce the number of variables in the model, we first produced a correlation matrix to identify potential prognostic factors, including the DVH-parameters of all OARs that were highly correlated (i.e., Pearson correlation coefficient ≥ 0.75). Strong correlations were found between the mean dose to all ipsilateral and contralateral corresponding paired salivary glands and the mean doses to the upper and lower lips. Therefore, we decided to enter the

mean doses of each of these paired glands as one single variable in the analysis. The mean dose of these paired glands was calculated using the total volume of both glands together and the radiation dose to this paired volume.

Table 2 Dose distributions in the organs at risk.

Organ at risk	Mean dose (Gy)	Standard deviation	Range (Gy)	
			Minimum	Maximum
Parotid gland ipsilateral	30.6	21.3	0.1	70.8
Parotid gland contralateral	23.4	17.1	0.1	61.2
Submandibular gland ipsilateral	49.1	25.4	0.1	72.5
Submandibular gland contralateral	43.5	25.4	0.0	72.4
Sublingual gland ipsilateral	36.9	25.7	0.3	72.4
Sublingual gland contralateral	34.1	24.5	0.2	72.3
Lower lip	21.8	18.8	0.0	72.0
Upper lip	18.3	17.9	0.0	66.7
Buccal mucosa ipsilatera	28.4	23.1	0.2	70.3
Buccal mucosa contralateral	24.0	19.9	0.2	69.5
Soft palate	27.2	18.1	0.1	65.2

Within the DVH parameters of each organ at risk we found high correlations between multiple Vx values (percentage of volume receiving x Gy, steps of 5 Gy) and the mean dose of those specific organs at risk and therefore these variables were excluded from the analysis. Eventually, 6 DVH parameters were included in the analysis (Table 3).

Table 3 Univariate logistic regression analysis for all possible predictors for xerostomia and sticky saliva.

	Xerostomia day			Xerostomia night			Sticky saliva day			Sticky saliva night		
Variabele	*OR*	*95% CI*	p-val	*RO*	*95% CI*	p-val	*OR*	*95% CI*	p-val	*OR*	*95% CI*	p-val
Mean dose parotid glands (Gy)	1.06	1.03-1.08	<0.01	1.04	1.01-1.06	<0.01	1.03	1.00-1.06	NS	1.02	0.99-1.04	NS
Mean dose submandibular glands (Gy)	1.04	1.02-1.06	<0.01	1.02	1.00-1.04	0.02	1.03	1.00-1.07	0.03	1.02	1.00-1.04	NS
Mean dose sublingual glands (Gy)	1.03	1.01-1.04	<0.01	1.02	1.00-1.04	0.01	1.02	1.00-1.04	NS	1.01	0.99-1.03	NS
Mean dose buccal mucosa (Gy)	1.03	1.01-1.04	<0.01	1.02	1.00-1.04	0.02	1.01	0.99-1.04	NS	1.01	0.99-1.03	NS
Mean dose soft palate (Gy)	1.03	1.01-1.04	<0.01	1.02	1.00-1.03	0.01	1.01	0.99-1.03	NS	1.01	0.99-1.02	NS
Mean dose lips (Gy)	1.02	1.00-1.04	0.03	1.02	1.00-1.04	NS	1.01	0.99-1.04	NS	1.00	0.98-1.03	NS
Sex (male vs female)	1.75	0.89-3.44	NS	1.89	0.86-4.15	NS	0.68	0.22-2.16	NS	0.67	0.24-1.91	NS
Age (years)	1.00	0.79-1.02	NS	1.021	0.99-1.06	NS	0.98	0.96-1.04	NS	1.03	0.99-1.07	NS
Chemotherapy	1.95	0.95-4.00	NS	2.58	1.16-5.76	0.02	4.18	1.15-15.22	0.03	0.99	0.34-2.85	NS
Cetuximab	3.76	1.14-12.42	0.03	1.72	0.43-6.85	NS	8.37	2.35-29.82	<0.01	2.93	0.72-11.94	NS
Accelerated radiotherapy	0.61	0.32-1.16	NS	0.86	0.40-1.85	NS	3.19	0.90-11.38	NS	1.28	0.50-3.30	NS
Baselinexerostomia/sticky saluiva score (none vs a bit)	1.02	0.98-1.04	NS	1.04	1.01-1.07	<0.01	1.05	1.02-1.08	<0.01	1.02	0.98-1.05	NS
Bilateral neck irradiation (unilateral vs bilateral)	4.63	1.94-10.99	<0.01	2.55	0.99-6.55	NS	2.88	0.81-10.29	NS	1.92	0.68-5.44	NS

Patient-rated xerostomia during the day

The mean score for XER_{day} in all patients was 33.6 (SD: 26.6). A total number of 55 out of 184 patients (29.1%) reported $RespXER_{day.}$.
In the univariate analysis, significant associations were found between the mean doses of all salivary glands and $RespXER_{day}$. Significant associations were also found for the addition of cetuximab and bilateral neck irradiation (Table 3).
Average likelihood of bootstrap prediction in the multivariate logistic regression analysis was optimal with a model consisting of two variables, including the the mean dose in the parotid glands and baseline xerostomia (none versus a bit) during the day (Table 4). Increasing the number of variables to three did not further increase the average likelihood of the model compared to the 2-factor model.

Patient-rated xerostomia during the night

The mean score for XER_{night} in all patients was 27.2 (SD: 25.2). A total number of 34 patients (18.5%) reported $RespXER_{night}$.
In the univariate analysis, significant associations were found between the mean doses to the parotid, submandibular, sublingual glands and the salivary glands located in the buccal mucosa and located in the soft palate and XER_{night}.
Significant associations were also found for the addition of chemotherapy and the presence of minor complaints of xerostomia during the night prior to treatment (Table 3).
The multivariate logistic regression analysis showed that the mean dose in both parotid glands, the baseline xerostomia score at night and age were significantly associated with XER_{night} (Table 3).

Patient-rated sticky saliva during the day

The mean score for $STIC_{day}$ in all patients was 17.1 (SD: 24.7). A total number of 19 patients (10.0%) reported $RespSTIC_{day}$.

In the univariate analysis, significant associations were found between the mean doses to submandibular glands and XER_{night}. Significant associations were also found for the addition of chemotherapy, cetuximab and the presence of minor complaints of sticky saliva during the day prior to treatment (Table 3).
In the multivariate logistic regression baseline sticky saliva score on the GRIX turned out to be the most predictive factor for the development of $STIC_{day}$ (Table 4). We were not able to identify prognostic factors related to dose distributions.

Patient-rated sticky saliva during the night

The mean score for $STIC_{night}$ in all patients was 14.7 (SD: 24.1). A total number of 23 patients (12 %) reported $RespSTIC_{night}$. The mean dose to both submandibular glands and age were selected as most important predictive factors for the development of $STIC_{night}$ in the multivariate analysis (Table 4).

Table 4 Odd's ratios and corresponding 95% confidence intervals for the selected variable in the multivariate logistic regression analysis for xerostomia during the day and night and for sticky saliva during the day and night.

Endpoint / Variable	OR	95% CI	P-value
Xerostomia day			
Mean dose parotid glands (Gy)	1.06	1.04-1.09	<0.01
Baseline xerostomia score day (GRIX)	1.02	1.00-1.05	0.09
Xerostomia night			
Mean dose parotid glands (Gy)	1.04	1.02-1.07	<0.01
Baseline xerostomia score night (GRIX)	1.04	1.01-1.07	<0.01
Age	1.04	1.00-1.09	0.03
Sticky saliva day			
Baseline sticky saliva score (GRIX	8.37	2.35 -29.82	<0.01
Sticky saliva night			
Mean dose submandibular glands (Gy)	1.03	1.00-1.06	0.02
Age (years)	1.06	1.01-1.11	0.02

Discussion

The main purpose of this study was to test the hypothesis that due to in the circadian rhythm of salivary production during the day by different salivary glands, organs at risk could be different for xerostomia and sticky saliva during the day and night. The results of this study revealed that dose distributions to the minor salivary glands has limited significance for the development of xerostomia and sticky saliva as reported by patients.

The mean dose to the parotid glands turned out to be most important prognostic factor for patient-rated xerostomia both during the day and during the night. In this regard, the results are in line with the results from our previous studies, in which we also found that the parotid gland was the most important and only OAR for patient-rated xerostomia in general (21). The question arises, why we were not able to find different OARs for xerostomia during the night in particular because under normal physiological circumstances saliva production by the parotid glands during the night and at rest is negligible (17).

A possible explanation for the role of the parotid glands in the development of xerostomia during the night could be the compensatory mechanism of the parotid glands. The majority of patients included in this study were treated with IMRT mainly resulting in decreasing the dose to the parotid glands. In a previous study we showed that by sparing the parotid glands, the dose to other minor salivary glands may increase (24). Increased radiation dose to the minor salivary glands as consequence of sparing the parotid glands may trigger a compensatory production of saliva by these parotid glands (25). Therefore sparing of the parotid glands may still result in a reduction of patient-rated complaints during the night.

In the current study, elderly patients appeared to be more vulnerable for the effects of radiation to the salivary glands with regard to both patient-rated xerostomia and sticky saliva during the night. These findings are in agreement with those reported by Johanson et al., who performed a study among a large number of healthy volunteers showing a dramatic increase in patient-rated xerostomia between the age of 50 and 75 years of age (26). This increase in

self-reported xerostomia was particularly observed in night-time complaints and among women. A possible explanation for these findings is that elderly patients generally use more medication and have more co-morbidity that may influence and reduce the saliva production at rest (27,28). As saliva production during the night is already low, only minor changes in saliva production, such as caused by medication and radiation may already be sufficient to cause hyposalivation and subsequent xerostomia (29,30).

The submandibular glands turned out to be the most important OAR for patient-rated sticky saliva during the night. This was in agreement with previous published data of patient-rated sticky saliva for patients treated with 3D-CRT and IMRT. Jellema et al. also concluded that irradiation of the submandibular glands are responsible for the development of sticky saliva (31).

A remarkable finding was that no salivary glands were selected as predictors for the development of sticky saliva as reported by patients during the day. Only minor complaints of sticky saliva during the day prior to treatment were identified as prognostic factor for sticky saliva during the day. The most likely explanation for not finding any dose distribution parameter could be the relatively low prevalence of moderate-to-severe sticky saliva during the day (10%). From a statistical point of view, it is more difficult to find significant predictors for endpoints with low prevalence's.

In the present study, patients were treated with 3D-CRT (using a sequential boost technique) as well as with IMRT (using a simultaneous integrated boost technique). One of the limitations of this study is that we did not took into account the possible influence of differences in fractionation between the two different treatment techniques. To do this would require a pixel-based analysis after deformable image registration of the dose distribution of the cohort treated with 3D-CRT in order to be able to calculate the biological equivalent dose to the normal tissues, which is currently not available.

Not only the prevalence of sticky saliva during the day was lower than previously reported, but of all other endpoints (21). Xerostomia and sticky saliva as scored with the EORTC QLQ-HN35 only contains one question about xerostomia and sticky saliva. The GRIX contains multiple questions for each subscale and offered patients the possibility to differentiate more clearly

between different kinds of xerostomia and sticky saliva even within one subscale (20). This resulted in lower prevalence's for the endpoints defined with the GRIX, because some patients only scored moderate-to-severe complaints on one or two questions, eventually resulting in an average score below 50%.

In conclusion, the role of the minor salivary glands appears to be limited in the development of patient-rated xerostomia and sticky saliva at different time points during the day. The dose to the parotid glands and submandibular glands are of main importance in development of radiation induced xerostomia and sticky saliva and should be target for improvement of current and emerging radiation techniques (32).

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CHAPTER 8

General discussion

Ivo Beetz

1. Introduction and endpoints

1.1 Introduction

The studies included in this thesis, which were conducted and reported on, all had the main objective of developing multivariable NTCP models for various aspects of patient-rated complaints related to radiation-induced salivary dysfunction. Apart from the dose to the parotid glands, we also included the possible role of dose distributions in other major and minor salivary glands and the role of other candidate prognostic variables, such as treatment modality and age.

As shown in this thesis, a considerable proportion of patients are still at risk for developing xerostomia, despite the introduction of new radiation delivery techniques such as Intensity Modulated Radiotherapy (IMRT) in routine clinical practice. Therefore, it is worthwhile to identify patients at risk for developing clinically relevant xerostomia who may benefit from emerging preventive measures, such as radiotherapy with protons and/or stem cell therapy.

1.2 Endpoints

In this project, we decided to focus on two patient-reported endpoints: moderate-to-severe xerostomia and moderate-to-severe sticky saliva. Recent research has focussed mainly on the relationship between radiation dose to the parotid glands and stimulated and/or unstimulated parotid salivary flow (1-3). Patients' awareness of xerostomia and sticky saliva is caused not only by hyposalivation of the major salivary glands, but may also result from insufficient mucosal wetting for which the minor salivary glands in the oral cavity, soft palate, buccal mucosa and lower and upper lips are mainly responsible (4,5).

The development of prognostic models for these patient-rated endpoints is important for several reasons. First, considerable discrepancies exist between objective measurements of salivary dysfunction, such as parotid flow, and patient-rated xerostomia (6,7). Second, some phase III randomized studies

showed improvement of salivary flow and physician-rated xerostomia using IMRT instead of 2D-RT (8), but showed no difference with regard to patient-rated xerostomia. Third, xerostomia and sticky saliva as experienced by patients is clinically more relevant and has a major impact on quality of life (QoL). Finally, the aetiology of patient-rated xerostomia and sticky saliva is more complex, and the development of prediction models which can be used for radiotherapy treatment optimization requires other and more complex methodological approaches than generally used when analysing the univariate relationship between parotid dose and parotid flow.

2. Management of xerostomia and sticky saliva

2.1 Treatment of xerostomia

Although some head and neck cancer patients recover spontaneously from radiation-induced xerostomia, most patients experience some degree of dry mouth symptoms once the dose to the parotid glands exceeds the threshold dose. Several treatment options are available for patients suffering from xerostomia, including oral administration of pilocarpine and the use of topical agents.

2.1.1 Pilocarpine

Pilocarpine is a cholinergic agonist which stimulates salivary secretion both in individuals with normal salivary gland function and in those with impaired salivary flow (xerostomia or oral dryness). Pilocarpine is inexpensive, easy to administer and relatively safe, with only mild side effects (9). After oral pilocarpine administration, a rapid increase in salivary flow rate can be observed, and peak levels are maintained for at least 1 to 2 hours. Mean salivary flow rates after administration of pilocarpine are significantly higher than after placebo, and no evidence of tolerance to the pharmacological effects of the drug has been observed during prolonged administration for up

to 5 months (10). A systematic review reported on three studies on the efficacy of pilocarpine in the treatment of post-radiotherapy xerostomia (11), which included a total of 298 patients. The data suggest that pilocarpine is more effective than placebo. The response rate was approximately 50%, and the time-to-response was up to 12 weeks. Side effects were frequently observed but were mild, resulting mainly from generalized parasympathomimetic stimulation, such as sweating, headaches, increased urinary frequency and vasodilatation. Other studies showed that pilocarpine may offer some relief in glands responsive to stimuli (12,13). However, when there is no residual function of the salivary gland post treatment, xerostomia is usually therapy resistant.

2.1.2 Topical therapies

Recently, the Cochrane Oral Health Group performed a systematic review on the efficacy of topical therapies, including lozenges, mouth rinses, gels, oils, chewing gum and toothpastes (14). A total number of 36 RCT's were indentified in which 1597 patients were included. Due to the range of interventions, comparisons and outcome measures in the trials, meta-analysis was possible for only a few comparisons. A significant effect was found for the use of oxygenated glycerol triester saliva substitute spray to counteract xerostomia (15,16). Although integrated mouth care systems (toothpaste plus gel plus mouthwash) and oral reservoir devices showed promising results, the evidence was too weak to recommend their use in routine clinical practice (17-19). No evidence was found for the use of chewing gum (20-26).
In one double-blind, placebo-controlled study, xanthan-based saliva substitutes were compared to placebo (27). However, this study also showed no significant effect on dry mouth symptoms, although there was a trend towards fewer problems with speech and senses.

2.1.3 Interim conclusion

Because the results of xerostomia treatment approaches are generally disappointing, the best option is prevention. The following section addresses this approach.

2.2 Prevention of xerostomia and sticky saliva

2.2.1 Systemic preventive measures

Apart from local measures (such as dose reduction to salivary glands), xerostomia can also be prevented by systemic agents, including pilocarpine and radioprotective agents.

2.2.1.A Pilocarpine

At our institution, Burlage et al. performed a double-blind randomized, placebo-controlled trial on the value of pilocarpine which showed neither improvement of parotid flow nor of other endpoints related to salivary function during and after radiotherapy (28). However, subset analysis revealed that patients who received a mean parotid dose of more than 40 Gy tended to have better parotid flow 12 months after completion of radiation. The results of other randomized studies that investigated the role of pilocarpine are conflicting, which may be due to various methodological shortcomings, such as the lack of information on dose distributions in the salivary glands (13,29-35), too few patients (13,29-31,33,34) and a lack of reliable late data on salivary flow. Therefore, the role of pilocarpine administration during radiation to prevent hyposalivation and xerostomia is unclear, but is probably limited.

2.2.1.B Amifostine

Systemic radioprotection can be achieved by administering amifostine, a radical scavenger, during radiation treatment (36-40). Subjectively, it has been shown that amifostine has the potential to reduce xerostomia during and post radiation treatment (36). Randomized studies showed objective data on the sparing effect of amifostine on the post radiation level of salivary secretion (39) and the subjective symptoms of xerostomia (40). However, the high cost of amifostine together with the patient burden caused by daily intravenous administration of the agent during radiotherapy and its side effects, have prevented the standard use of amifostine in clinical practice. Amifostine also became less popular because a negative effect on locoregional tumour control could not be excluded. However, the results of a recently published meta-analysis showed that locoregional control and overall survival were not reduced when amifostine treatment was added to radiotherapy or chemoradiation (41).

2.2.2 Prevention using parotid-sparing IMRT

The most effective way to prevent salivary dysfunction is most likely reducing the dose to the salivary glands. In recent years, a number of randomized controlled trials (RCT) have been published comparing parotid-sparing IMRT with conventional radiation techniques.
In an RCT reported by Pow et al. (42), patients with nasopharyngeal carcinoma were randomly assigned to receive 2D-radiotherapy or parotid-sparing IMRT. In that study, IMRT resulted in significantly higher post-treatment salivary flow rates and QoL than after 2D-radiotherapy. In another study of patients with nasopharyngeal carcinoma, Kam et al. (8) also compared 2D radiotherapy with parotid-sparing IMRT and found similar results in terms of significantly higher salivary flow rates and lower incidences of observer-rated severe xerostomia in the IMRT arm. More recently, Nutting et al. reported on an RCT comparing parotid-sparing IMRT with 3D-conformal radiotherapy (3D-CRT) among patients with oropharyngeal and hypopharyngeal cancer (43). In that study,

IMRT significantly reduced the incidence of physician-rated xerostomia, improved saliva secretion recovery and patient-rated measures associated with xerostomia.
The results of these RCTs showed that the risk of parotid flow reduction and xerostomia as reported by physicians can be reduced by parotid-sparing IMRT. However, in two of these studies, no effect was found on patient-reported complaints. Moreover, although Nutting et al. also found a significant effect on patient-rated xerostomia, the differences between the two techniques were markedly less than the differences with regard to salivary flow and physician-rated xerostomia. Given the relatively poor results of parotid sparing IMRT with regard to prevention of patient-rated xerostomia, it is still unclear which other factors contribute to the development of radiation-induced patient-rated xerostomia. This is illustrated by the results in Chapter 4, showing that after IMRT more than 50% of the cases still suffered from moderate-to-severe xerostomia 6 months after completion of treatment. The first step in preventing patient-rated xerostomia and sticky saliva is therefore the development of multivariate predictive models for these endpoints.

2.3 Normal Tissue Complication Probability (NTCP) modelling

2.3.1 Multivariable NTCP models

Because the risk of radiation-induced side effects after radiotherapy normally depends on the radiation dose and the volume of irradiated tissue (44), attempts should be made to minimize the amount of normal tissue that is co-irradiated. To achieve the most optimal reduction of radiation-induced side effects, information about the most relevant dose/volume parameters is required in order to define dose constraints for radiotherapy treatment optimization. To determine which dose parameters are most important and worthwhile for treatment optimization, multivariate NTCP models are required.
In this thesis we have reported on the development and validation of multivariable logistic regression models for patient-rated xerostomia and sticky

saliva. In contrast, most other published studies on NTCP modelling for xerostomia have described univariate relationships between radiation dose to the parotid glands and stimulated parotid flow (1-3). Several NTCP models have been used to describe this relationship. The Lyman-Kutcher-Burman model is currently the most commonly used NTCP modelling technique (45,46). This model assumes a dose/volume dependent and tolerance dose relationship between a specific organ at risk and a specific endpoint. Other models also use information about dose distributions and fractionation (47,48). El Naqa et al. were the first to publish a methodology for developing NTCP models based not only on dose volume characteristics, but also taking other potential prognostic clinical factors into account (49). As we were interested in the role of dose to the major and minor salivary glands and the role of other treatment-related factors in the development of patient-rated xerostomia and sticky saliva, we decided to use this multivariable methodology to build NTCP models.

The results obtained from patients treated with 3D-CRT as well as those obtained among patients treated with IMRT indeed showed a multifactorial etiology in the development of both patient-rated xerostomia and sticky saliva. Also in a number of other studies performed at our department in which the relationships between radiation dose and other radiation-induced side effects were investigated, the risk of these side effects depended on more than one factor, related either to the dose to various OARs or to other factors.

After 3D-CRT, the mean dose to both parotid glands was indeed found to be the most important prognostic factor for patient-rated xerostomia, together with the presence of baseline xerostomia and increasing age (Chapter 2). After IMRT, the mean dose to the contralateral parotid gland and baseline xerostomia were found to be the most important prognostic factors for patient-rated xerostomia (Chapter 4).

For patient-rated sticky saliva, other prognostic factors were found. After 3D-CRT, the mean dose to both submandibular glands and both sublingual glands as well as baseline sticky saliva were most important. After IMRT, the mean dose to the contralateral submandibular gland, the mean dose to both

sublingual glands and the mean dose to the minor glands in the soft palate were the most important prognostic factors.

These results may have several important implications for future clinical practice. First, for both endpoints the performance of the multivariable models was significantly better relative to the univariate models that use only one dose/volume parameter, such as mean parotid dose. This indicates that more accurate estimates of the risks of patient-rated xerostomia and sticky saliva can be obtained with these multivariable NTCP models as compared to the currently used univariate NTCP models.

Second, multivariable model developed for patients being treated with one technique for a given endpoint may be different when another technique is used. This may have implications for selecting patients for emerging, more expensive and demanding radiation technologies, which will be discussed below.

Third, the fact that the development of side effects depends on more than one dose/volume parameter implies more than one NTCP curve for patient-rated xerostomia and sticky saliva. This will be discussed in the next section.

2.3.2 Implications for defining dose constraints (QUANTEC)

The definition of dose constraints is generally based on the shape of one NTCP curve and the more or less arbitrary decision about an acceptable rate of a certain side effect. For severe hyposalivation, a risk of 20% or less of severe hyposalivation (i.e. post-treatment parotid flow rate of less than 25% compared to baseline (50,51)) is generally considered acceptable, which corresponds with the criteria defined by the Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) Group (i.e. mean parotid dose <25 Gy in both glands or mean parotid dose <20 Gy in at least one gland).

This endpoint was defined differently from that used in our studies that are described in this thesis. We therefore performed an additional analysis of the efficacy of the QUANTEC criteria for moderate-to-severe patient-rated xerostomia and sticky saliva (Chapter 5). This is still clinically relevant and important. Despite the introduction of more advanced radiation delivery

techniques such as Intensity Modulated Radiotherapy (IMRT), xerostomia remains one of the most frequently reported late side-effects of head and neck radiotherapy, with a prevalence of >50% at 6 months after completion of treatment (Chapter 4). In this analysis, we arbitrarily defined a risk for moderate-to-severe xerostomia of 20% or less as acceptable.

In Chapter 5 it is reported how the role of the mean dose to the parotid glands in the development of moderate-to-severe patient-rated xerostomia was confirmed at later time points up to 24 months after completion of treatment. However, this analysis also showed that applying the QUANTEC criteria does not protect all patients against the development of moderate-to-severe patient-rated xerostomia when using 20% or less as an acceptable risk for this side effect.

The consequence of applying multivariable NTCP models in clinical practice means that a single NTCP curve is replaced by multiple curves. This is especially the case when continuous rather than categorical prognostic factors are included in the model. For instance, the risk estimate of moderate-to-severe patient-rated xerostomia after 3D-CRT depends on the mean parotid dose, age and the presence of mild xerostomia at baseline. As a result, a wide variety of NTCP curves can be generated depending on age and the presence of mild xerostomia at baseline. Therefore the NTCP curve of a young patient without mild xerostomia at baseline is completely different from that of an elderly patient with mild xerostomia at baseline. When using the 20% or less NTCP value estimate as an acceptable risk level, the thresholds and subsequent dose constraints will also be completely different for these patients. Moreover, if the patients are treated with IMRT, the risk estimates will be different as well. This is because the multivariable NTCP model then consists of other prognostic factors, including the mean dose to the contralateral gland and the presence of mild xerostomia at baseline.

2.3.3 Implications for selecting radiation techniques

The results presented in Chapter 5 indicate that the QUANTEC criteria can only be met in approximately 30-35% of the patients treated with bilateral IMRT. Moreover, in the corresponding study we showed that these criteria are less effective for preventing patient-rated moderate-to-severe xerostomia, particularly in elderly patients with mild xerostomia at baseline. This is also reflected by the xerostomia prevalence of more than 50% at 6 months after completion of treatment. Even in the era of IMRT, there is apparently still room for improvement. New radiation therapy technologies, including stem cell sparing IMRT and IMPT, may potentially reduce the risk of hyposalivation and patient-rated xerostomia and sticky saliva.

2.3.3.A Stem cell sparing IMRT

Animal studies performed at our radiobiology department revealed that the mean dose to the subvolume in the parotid glands containing the stem cells is a better predictor for parotid gland dysfunction than the mean dose to the whole parotid gland. More specifically, this area is located at the lateral lobe of the parotid glands corresponding with the course of the major duct. This finding was confirmed in a retrospective study in patients with salivary flow as primary endpoint. It has been hypothesized that reducing the dose to this specific area of the parotid glands, which in most cases is relatively easy to achieve when using specific dose constraints for this parotid subvolume, will result in better recovery of salivary flow at approximately one year after completion of radiation treatment. A prospective double-blind phase III study has been initiated in which patients treated with bilateral IMRT will be randomly assigned to receive standard IMRT (reducing the mean dose to the parotid glands) or stem cell sparing IMRT (same treatment + further reduction of the dose to the subvolume that contains stem cells). The results of this study will also be used to externally validate our multivariate IMRT-based NTCP model.

2.3.3.B Proton therapy

Radiotherapy with protons is a promising technology in modern radiation oncology. From a physical point of view, radiotherapy with protons has important advantages compared to the currently used photon therapy due to its unique energy absorption profile. Proton beams are typically manipulated to generate a spread-out Bragg peak to yield a flat dose profile across the target volume, followed by a rapid decrease to nearly zero dose distally from the target. This results in highly conformal dose deposition in the tumour. Based on the physical principles of proton beams, two main applications can be expected to produce a clinical benefit for cancer patients: improvement of local tumour control and prevention of radiation-induced side effects.
Recently, van de Water et al. showed that Intensity Modulated Proton Therapy (IMPT) can reduce the dose to the parotid glands significantly compared to current IMRT (52), which may result in a further reduction of the risk of hyposalivation and subsequent xerostomia. Additional reduction of the dose to the parotid glands could be obtained with reduced spot size IMPT. This technique could reduce the dose to the contralateral submandibular gland even further. Given the importance of the mean dose to the contralateral submandibular gland, this could theoretically result in a further reduction of patient-rated moderate-to-severe sticky saliva.

2.3.4 Implications for the model-based approach

As described in Chapter 1, optimization and validation of new radiation techniques should be based on three consecutive phases: phase 1, aiming at the development and external validation of Normal Tissue Complication Probability (NTCP) models; phase 2, aiming at defining cohorts of patients who may benefit most from these new radiation techniques (e.g. proton therapy or stem cell sparing IMRT) by integrating the results of individual in silico planning comparative studies into these NTCP models; and phase 3, aiming at the clinical validation of new radiation techniques either through RCTs or

prospective observational cohort studies using historical comparisons as a reference, whenever appropriate(53).

One of the prerequisites of the model-based approach is that NTCP models that are developed in patient groups treated with an older technique (e.g. 3D-CRT) will also be valid when used for patient groups treated with a new technique (e.g. IMRT). The results presented in Chapter 3 illustrate one of the possible caveats of this approach, as it is not self-evident that models developed in a population treated with a specific technique can be generalized to patients treated with another technique.

In Chapter 2, the results of a prospective cohort study on the development of NTCP models are presented for head and neck cancer patients treated with 3D-CRT. In this study, the role of the major and minor salivary glands was taken into account as well as patient- related and treatment-related factors. This study showed that in patients treated with 3D-CRT, the mean dose to both parotid glands turned out to be the most important prognostic factor for moderate-to-severe xerostomia as reported by patients at 6 months after completion of radiotherapy. However, the analysis revealed two other important prognostic factors, ultimately resulting in a predictive model consisting of the mean dose to both parotid glands, age and xerostomia prior to radiation.

Although this prediction model performed reasonably well for patients treated with 3D-CRT, model performance was markedly worse when used for patients treated with IMRT (Chapter 3). Performance of the IMRT-based model in the IMRT cohort was better than that of the 3D-CRT-based model. The IMRT-based model is based on the mean dose to the contralateral parotid gland and xerostomia at baseline (Chapter 4).

We showed that differences in case-mix between the two study populations resulted in lower model performance. However, these findings cannot explain completely why models developed in patients treated with 3D-CRT could not be extrapolated to the population treated with IMRT. The case mix refers to the distribution of the predictors that were selected and not selected for the predictive model, where both sets of predictors influence the outcome measure. In general, as illustrated by Vergouwe et al., differences in case mix

between a test cohort and a validation cohort may explain differences in model performance, but larger differences in model performance cannot be explained by differences in case mix alone (54). The main implications from these studies are twofold: 1) NTCP models should always be validated in independent cohorts, and 2) validation should be repeated if a new technique, which is used to reduce the dose/volume parameters resulting from the NTCP-models, leads to clearly different three-dimensional dose distributions. This may be become relevant when head and neck cancer patients are selected for proton therapy in the near future using the model-based approach. Although the differences in dose distribution between IMPT and IMRT are smaller than those between 3D-CRT and IMRT, clinical validation of proton therapy still requires validation of the NTCP model developed in a population of IMRT-treated patients (52,55,56).

For patients treated with IMRT as well for those treated with 3D-CRT, the submandibular glands and sublingual glands play a pivotal role in the development of sticky saliva (Chapter 2 and Chapter 4). A remarkable result was the inverse relationship that we found between the mean dose to the sublingual glands and patient-rated sticky saliva. The multivariate model for sticky saliva for patients treated with 3D-CRT, including the mean dose to the submandibular and sublingual glands, age and baseline sticky saliva, was unable to make valid predictions for patients treated with IMRT (Chapter 3). The development of patient-rated sticky saliva in patients treated with IMRT was predicted more accurately by the mean dose to the contralateral submandibular gland and sublingual glands and the mean dose to the soft palate.

Chapter 3 includes an important message: without external validation, prediction models developed in a population treated with a specific radiation technique cannot be generalized to a population treated with another technique.

2.4 Other factors influencing xerostomia and sticky saliva

2.4.1 The role of day and night

In Chapter 7, the role of the major and minor salivary glands in the development of radiation-induced patient-rated xerostomia and sticky saliva at different time points during the day and night is discussed. We hypothesized that due to daily differences in the salivary production by the various salivary glands, different organs at risk for xerostomia and sticky saliva during the day and during the night could be distinguished. This hypothesis could not be confirmed. The prevalences of patient-rated xerostomia and sticky saliva during the day and during the night as reported in this analysis were markedly lower than those reported in Chapters 2, 4 and 5. The EORTC QLQ-HN35 instrument contains only one question about xerostomia and one question about sticky saliva. The GRIX, however, contains multiple questions for each subscale and gives patients the option of differentiating more clearly between various kinds of xerostomia and sticky saliva, even within one subscale (Chapter 6). This resulted in lower prevalences for the endpoints defined with the GRIX, because some patients only scored moderate-to-severe complaints on one or two questions.

Although we still believe that patient-reported xerostomia and sticky saliva are highly relevant from a clinical perspective, the endpoints used in Chapters 1-5 may not be sufficiently specific to detect subtile changes related to the circadian rhythm of saliva production by the various glands. We have suggested this as a topic for future clinical research.

2.4.2 The role of the minor salivary glands

The composition and production of saliva from the minor salivary glands located in the soft palate, inner surface of the lips and buccal mucosa, and of saliva from the sublingual and submandibular glands, differ from the saliva from the parotid glands (4,57-62). In Chapter 2 and Chapter 4, the role of the submandibular and sublingual glands in the development of patient-rated

sticky saliva is discussed. However, other than the influence of radiation dose to the salivary glands located in the soft palate on the development of sticky saliva in IMRT- treated patients, the role of the minor salivary glands appears limited. A striking finding was the inverse association between the dose to the sublingual glands and the severity of sticky saliva after completion of treatment, which illustrates the sometimes complex relationship between the functional impairment of the various salivary glands and clinical symptoms. The prediction models presented in Chapters 2 and 4 may suggest that increasing the dose to the sublingual gland when the submandibular gland also receives a relatively high dose could prevent moderate-to-severe sticky saliva (due to the persistent production of high-viscosity saliva by these glands in the absence of the watery secretion of the submandibular glands). However, it is unlikely that this strategy will be applied in clinical practice. Other investigators concluded that patient-rated xerostomia in general not only depends on the mean dose to the parotid glands, but also on the mean dose to the submandibular glands (63). Salivary dysfunction of the sublingual glands and the minor salivary glands lining the oral cavity is important as well with regard to patient-rated xerostomia and might explain why dose reduction to the parotid glands is not protective against every aspect of xerostomia and sticky saliva (8,42,63-65).

2.4.3 The role of age

Of particular interest is the finding that elderly patients suffer relatively more from patient-rated xerostomia and sticky saliva (Chapter 2 and Chapter 5) after completion of treatment. These findings confirm that elderly head and neck cancer patients differ from younger patients in this regard. In the past decade new treatment modalities, such as the addition of chemotherapy to radiation (66), altered fractionation schedules (67) and the addition of cetuximab to radiation (68), have led to significant improvements in locoregional tumour control and overall survival. However, the benefits obtained with these new treatment modalities are confined mainly to the younger age groups. A meta-analysis on the value of chemotherapy in combination with radiotherapy

concluded that the addition of concurrent chemotherapy to radiation significantly improves overall survival only in patients younger than 70 (69). A meta-analysis on altered fractionation concluded that the benefits of accelerated and hyperfractionated radiotherapy with regard to locoregional tumour control are also limited to patients younger than 70 (67). Finally, the subset analysis of a phase III randomized study on the addition of cetuximab to radiation suggested that the benefit of cetuximab is limited to patients younger than 65 (68). In this regard, it appears that age is the most important and most persistent predictive factor among patients with HNSCC and that conventional radiotherapy (70 Gy, 2 Gy/fraction, 5 times/week in 7 weeks) can still be considered as the standard for elderly patients (> 70 years). Although age is an important predictive factor, it remains unclear why patients do not benefit from these intensified regimens. One hypothesis is that elderly patients have more competitive risks due to higher rates of pre-existing co-morbidities. Another explanation could be that elderly patients are more susceptible for treatment-related toxicity and that the compliance rates for these intensified regimens are lower. The capacity to recover from radiation-induced damage to the normal tissues is probably reduced in elderly patients. These findings are in line with those reported by Ghezzi et al. who showed that the reserve secretory capacity of the major salivary glands decreases with age (70). This probably means that elderly patients are more susceptible to xerostomia because radiation-induced salivary dysfunction depends on the loss of parotid gland stem cells (71) and the number of stem cells decreases with age (72). Moreover, elderly patients generally have more co-morbidity and thus use more medication, which may also affect saliva production (73,74).

Indeed, the results presented in Chapter 5 show that elderly patients are more vulnerable for developing radiation-induced side-effects, at least with regard to xerostomia and sticky saliva. In another prospective cohort study performed at the UMCG, elderly head and neck cancer patients turned out to be more vulnerable for other acute and late radiation-induced toxicities as well. Moreover, elderly HNC patients with high frailty scores (as assessed with the Groningen Frailty Index) developed significantly more acute and late radiation-induced side effects, and developed more head and neck symptoms (as

assessed by the EORTC QLQ H&N35) than their non-frail counterparts (preliminary work, unpublished data). Moreover, frail elderly patients scored significantly worse on the more general dimensions of quality of life over time.
Elderly patients not only benefit less from more intensified treatment regimens, they are also more susceptible for developing acute and late radiation-induced side effects, in particular xerostomia and sticky saliva. Consequently, the threshold doses for the parotid glands as defined by the QUANTEC group become less suitable with increasing age. To prevent xerostomia in elderly patients, the search for other preventive measures is even more relevant than in younger patients.

3. Future perspectives and Conclusions

3.1 Future perspectives

Despite the use of IMRT, it was possible to spare the parotid glands in only 36% of the cases (Chapter 5), which leaves room for improvement of current radiation treatment techniques and emerging radiation delivery techniques. We were able to identify subsets of patients in which it was more difficult to spare the parotid glands with IMRT, in particular in patients treated for oropharyngeal and nasopharyngeal carcinoma, in those treated with bilateral irradiation and in patients with nodal metastases. This difficulty was mainly due to major overlap of the Planning Target Volume with larger parts of the parotid glands. In contrast, the parotid glands could be adequately spared in a much higher proportion of patients with laryngeal carcinoma, unilateral irradiation, N0 disease and lymph node metastases from unknown primary tumours. The question arises as to whether other radiation delivery techniques are more effective at sparing the parotid glands without compromising the dose in the PTV in these specific patients.
To complete phases 2 and 3 of the 3-phase approach as described in Chapter 1, more insight into the potential effects of new radiation delivery techniques is needed, along with improved knowledge of the physiology of salivary function and other potential factors involved in the development of xerostomia and

sticky saliva. These last two phases are needed to determine the extent to which a reduction in NTCP value can be realized with the introduction of new treatment techniques. Future studies should focus on treatment planning studies based on the NTCP models described in Chapters 2 and 4. The models developed for patients treated with IMRT (Chapter 4) could be useful for optimizing treatment with intensity modulated proton therapy (IMPT) because the dose distributions to the salivary glands are quite similar to the dose distributions of treatment with IMRT (56). On the other hand, it is not self-evident that the NTCP models developed in IMRT treated patients can be generalized to patients treated with IMPT. The results of these treatment planning studies will require clinical validation.

3.2 Conclusions

Despite the introduction of IMRT, hyposalivation, resulting in moderate-to-severe xerostomia and sticky saliva as reported by patients, is still an important and frequently occuring problem after curative radiation for head and neck cancer. The QUANTEC criteria are certainly useful for optimizing radiotherapy treatment planning in head and neck cancer, but they do not protect sufficiently against these side effects, especially in elderly patients and those who suffer from minor xerostomia prior to radiation.

The risk of patient-rated xerostomia and sticky saliva depends on several factors, including factors related to radiation dose to the major salivary glands. These findings offer opportunities to select patients for more advanced radiation delivery techniques, such as proton therapy.

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Summary

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The head and neck region harbours numerous delicate organs that are essential for basic physiological functions such as vision, speech, swallowing and saliva production. Besides the benefits with regard to tumour control and life expectancy, radiation treatment in this area may also result in a wide variety of radiation-induced side effects. One of the most common side effects after curative radiation for head and neck cancer is salivary dysfunction.

The saliva produced in the oral cavity is produced by the major salivary glands (parotid, submandibular and sublingual glands) and by the minor salivary glands located in soft palate, cheeks and lips *(figure 1, chapter 1)*. Current research is mainly focussed on the relation between radiation dose to the parotid glands and salivary flow. However, patients' awareness of xerostomia and sticky saliva is not only caused by hyposalivation of the major salivary glands but may also result from insufficient mucosal wetting for which mainly the minor salivary glands located in the oral cavity, soft palate, buccal mucosa and lower and upper lips are responsible. Therefore, overall aim of this PhD thesis was to investigate which major and minor salivary glands are responsible for radiation induced xerostomia and sticky saliva as reported by patients.

In *chapter 1* we described a new three phase methodology to investigate and clinically validate new radiation techniques aiming at reduction of side effects after radiation treatment. This methodology consists of three consecutive phases: phase 1, aiming at the development and external validation of Normal Tissue Complication Probability (NTCP) models; phase 2, aiming at the definition of cohorts of patients who may benefit most from new radiation techniques (e.g. intensity modulated radiotherapy (IMRT) and proton therapy) using the combination of NTCP-models and in silico planning comparative studies, and: phase 3 aiming at the clinical validation of new radiation techniques of these model-based indications, either through RCT's or prospective observational cohort studies using historical comparisons as a reference, whenever appropriate. Phase 3 is beyond the scope of this thesis. For the purpose of this thesis we decided to initially develop NTCP-models among patients treated with conventional 3D-conformal radiotherapy (3D-

CRT) and, subsequently, to test these NTCP-models among patient populations treated with IMRT *(Chapter 2 and 3)*.

In *Chapter 2* we developed NTCP models in a study population consisting of 167 consecutive head and neck cancer (HNC) patients treated with 3D-CRT without parotid -sparing. The optimum number of variables for the multivariate logistic regression models for patient-rated xerostomia and sticky saliva 6 months after (chemo)radiation treatment was determined using a bootstrapping method. In this chapter we showed that dose distributions in the minor salivary glands in patients receiving 3D-CRT have limited significance with regard to patient-rated symptoms related to salivary dysfunction. Besides the parotid and submandibular glands, only the sublingual glands were significantly associated with sticky saliva. In addition, reliable risk estimations also require information from other factors such as age and baseline subjective scores. When these factors are included in multivariable NTCP models, instead of only dose volume histogram parameters, model performance can be improved significantly.

Next step was to investigate the ability of the 3D-CRT based prediction models for patient-rated xerostomia and sticky saliva at 6 months *(Chapter 2)* to predict outcome in patients treated with IMRT. In *Chapter 3*, a population consisting of 162 patients treated with IMRT was used to test the external validity of these 3D-CRT based models. External validity was described by the explained variation (R^2 Nagelkerke) and the Brier score. The discriminative abilities of the models were calculated using the area under the Receiver Operating Curve (AUC) and calibration (i.e. the agreement between predicted and observed outcome) was assessed with the Hosmer-Lemeshow "goodness-of-fit" test. Overall model performance in terms of Brier score and R^2 Nagelkerke among patients treated with IMRT was significantly worse for as well the multivariable NTCP-model for xerostomia as for the model for sticky saliva. The Hosmer Lemeshow test showed a significant disagreement for both models between predicted risk and observed outcome. From chapter 3 we can conclude that 3D-CRT based models for patient-rated xerostomia and sticky saliva among head and neck cancer patients treated with primary radiotherapy or chemoradiation turned out to be less valid for patients treated with IMRT.

The main message from these findings is that models developed in a population treated with a specific technique cannot be generalized and extrapolated to a population treated with another technique without external validation.

In order to develop multivariable logistic regression models for patient-rated xerostomia and sticky saliva which can be used to further optimize treatment with IMRT for HNC patients, the study as described in *chapter 4* was performed. The optimum number of variables for the multivariate NTCP models for patient-rated xerostomia and sticky saliva six months after (chemo)radiation treatment with IMRT was determined using the same analysis method as performed in *chapter 2*. The multivariate analysis showed the mean contralateral parotid gland dose and baseline xerostomia (none versus a bit) to be the most important predictors for xerostomia 6 months after treatment. For sticky saliva, the mean contralateral submandibular gland dose, the mean sublingual dose and the mean dose to the minor salivary glands located in the soft palate were most predictive for sticky saliva. The model performance with internal validation of these models was good, which makes these models useful in optimizing current IMRT treatment.

The studies as performed in *Chapter 2, 3 and 4* described the development of multivariable NTCP-models to optimize current treatment with 3D-CRT and IMRT, aiming to reduce patient-rated xerostomia and sticky saliva after treatment with primary (chemo)radiotherapy. Current dose constraints are generally based on the shape of one NTCP-curve instead. Recently, the QUANTEC (Quantitative Analyses of Normal Tissue Effects in the Clinic) Group suggested practical guidelines to reduce the toxicity risk based on dose constraints to be used in IMRT treatment planning. Therefore the aim of *chapter 5* was to determine if the application of the QUANTEC criteria also protected against moderate-to-severe patient-rated xerostomia. In a study cohort of 307 HNC patients, we found significantly lower rates of radiation-induced patient-rated xerostomia among low risk patients treated according to the QUANTEC criteria, but these criteria do not completely protect against xerostomia. Particularly in elderly patients and patients already suffering from

minor xerostomia at baseline, the QUANTEC criteria do not sufficiently protect against persistent, moderate-to-severe patient-rated xerostomia.

As described in *chapter 1* content and production of saliva varies among different salivary glands and at different time points during the day, which may have various impacts on different aspects of symptoms related to salivary dysfunction. Therefore the purpose of *chapter 6* was to develop and validate a questionnaire: The Groningen Radiotherapy Induced Xerostomia Questionnaire (GRIX), that enables scoring of different aspects of patient-rated xerostomia. All questions in the GRIX were generated from an exhaustive list of relevant questions according to xerostomia as reported in the literature and reported by patients and health care providers. Finally the GRIX was reduced from 56 questions to a 14 item questionnaire. The GRIX was evaluated by calculating Crohnbach α's for all subscales and criterion validity was evaluated to compare the GRIX with patient rated xerostomia scored with the EORTC QLQ-HN35 and physician-rated xerostomia, test-retest analysis and responsiveness was also tested. The GRIX scored well for criterion related validity on all subscales with high correlations with the EORTC QLQ-HN35 xerostomia and sticky saliva scale as well with physician-rated toxicity scoring. No significant differences were found between test and retest scores and the GRIX showed good responsiveness with different time points for all subscales. We concluded that the GRIX is a useful and valid tool which can be used in future research on patient-rated xerostomia, providing more accurate information on different aspects of this endpoints.

With the GRIX we were able to investigate the relationship between xerostomia and sticky saliva during the day and night and dose distributions in different salivary glands *(Chapter 7)*. In a multivariate logistic regression analysis with an extending bootstrap technique in a study cohort of 201 consecutive patients HNC patients treated with IMRT or 3D-CRT, we found similar organs at risk responsible for radiation induced xerostomia and sticky saliva during the day and night.

From this thesis we can conclude *(Chapter 8)* that despite the introduction of IMRT, hyposalivation, resulting in moderate-to-severe xerostomia and sticky saliva as reported by patients, is still an important and frequently occuring

problem after curative radiation for head and neck cancer. The QUANTEC criteria are certainly useful for optimizing radiotherapy treatment planning in head and neck cancer, but they do not protect sufficiently against these side effects, especially in elderly patients and those who suffer from minor xerostomia prior to radiation.

The risk of patient-rated xerostomia and sticky saliva depends on several factors, including factors related to radiation dose to the major salivary glands. These findings offer opportunities to select patients for more advanced radiation delivery techniques, such as proton therapy.

Samenvatting

Nederlandse Samenvatting

Het hoofdhalsgebied bevat verschillende vitale organen die van belang zijn voor het uitvoeren van verscheidene fysiologische functies zoals zicht, spraak, slikken en de speekselproductie. Behoudens de voordelen van radiotherapie met betrekking tot tumorcontrole en levensverwachting, heeft de behandeling met radiotherapie vele bijwerkingen. Een van de meest voorkomende bijwerkingen na curatieve bestraling voor hoofdhalstumoren is de verminderde productie van speeksel door de speekselklieren.

De grote speekselklieren in de mondholte (parotis, submandibularis en sublingualis) en de kleine speekselklieren in het palatum molle, lippen en wangen zijn verantwoordelijk voor de totale speekselproductie (*figuur 1, hoofdstuk 1*). Het huidige onderzoek is voornamelijk gericht op de relatie tussen radiatiedosis op de glandula parotis en speekselvloed. Echter hoe droogheid (xerostomie) en plakkerig speeksel worden ervaren door patiënten is niet alleen toe te schrijven aan verminderde speekselproductie door de grote speekselklieren, maar insufficiënte bevochtiging van de mucosa in de mondholte door de kleinere speekselklieren in het palatum molle, lippen en wangen lijken ook een rol te spelen. Het doel van dit proefschrift was om uit te zoeken welke grote en welke kleinere speekselklieren verantwoordelijk zijn voor optreden van klachten van een droge mond en plakkerig speeksel zoals gerapporteerd wordt door patiënten.

In *Hoofdstuk 1* werd een nieuwe 3-fasemethodologie beschreven om het effect in reductie op bijwerkingen van nieuwe bestralingstechnieken te evalueren en klinisch te valideren. Deze methode bestaat uit drie opeenvolgende fasen. Fase 1, heeft tot doel om “normal tissue complication” (NTCP) modellen te ontwikkelen en extern te valideren. In fase 2 wordt onderzocht of op basis van de ontwikkelde modellen in fase 1 en vergelijkende planningsonderzoeken er onderscheid gemaakt kan worden tussen patiëntgroepen die in meer of mindere mate baat zouden kunnen hebben bij een nieuwe bestralingstechniek (b.v. protonen). Fase 3 bestaat uit de klinische validatie van de model-gebaseerde indicaties voor behandeling met nieuwe bestralingstechnieken door middel van gerandomiseerde onderzoeken of prospectieve cohort-

onderzoeken met een historische vergelijking. Fase 2 en 3 zijn in dit proefschrift buiten beschouwing gelaten. In dit proefschrift zijn we begonnen met de ontwikkeling van predictieve modellen voor patiënt-gerapporteerde xerostomie en klachten omtrent plakkerig speeksel bij patiënten die behandeld zijn met 3D-conformal radiotherapie (3D-CRT) en vervolgens is getest of deze modellen ook bruikbaar zijn voor patiënten die behandeld zijn met intensity modulated radiotherapy (IMRT) *(hoofdstuk 2 en 3)*.

In *hoofdstuk 2* ontwikkelden we NTCP-modellen in een onderzoekspopulatie bestaande uit 167 patiënten met hoofdhalstumoren die behandeld zijn met 3D-CRT. In een multivariate analyse van logistische regressie met uitgebreide boostrap-methodologie werd het optimale aantal variabelen bepaald voor de NTCP-modellen voor xerostomie en plakkerig speeksel 6 maanden na (chemo)radiatie. In dit hoofdstuk lieten we zien dat de rol van radiatiedosis op de kleine speekselklieren van beperkte omvang was. Naast de parotiden en de submandibulaire speekselklieren, speelden alleen de sublinguale speekselklieren een rol in de ontwikkeling van plakkerig speeksel. Om een goede risico-inschatting te maken voor het optreden van drogemondklachten en plakkerig speeksel 6 maanden na (chemo)radiatie is ook informatie met betrekking tot leeftijd en de aanwezigheid van minimale klachten vóór behandeling van belang. Wanneer al deze factoren worden toegevoegd aan de NTCP-modellen kan er een betere risico-inschatting gemaakt worden.

De volgende stap was om te onderzoeken of de modellen zoals die ontwikkeld zijn in *hoofdstuk 2* voor patiënten die behandeld waren met 3D-CRT ook een valide voorspelling konden maken wanneer patiënten werden behandeld met IMRT. In *hoofdstuk 3* werd in een groep van 162 patiënten die behandeld waren met IMRT, de validiteit van de op 3D-CRT gebaseerde modellen onderzocht. Deze externe validiteit werd beschreven door middel van de verklaarde variantie (R^2 Nagelkerke) en de Brier-score. Het onderscheidend vermogen werd berekend door gebruik te maken van het oppervlak onder de receiver-curve (AUC) en calibratie (de overeenkomst tussen voorspelde en gemeten waarde) werd beschreven met de Hosmer-Lemeshow-test. Algehele modelprestaties die beschreven waren met de Brier-score en R^2 Nagelkerke bij met IMRT behandelde patiënten waren beduidend slechter voor zowel het

multivariate NTCP-model voor xerostomia als voor het model voor plakkerig speeksel. De Hosmer-Lemeshow-test toonde een discrepantie voor beide modellen tussen voorspeld risico en waargenomen uitkomst. Uit *hoofdstuk 3* kan geconcludeerd worden dat predictieve modellen die ontwikkeld zijn in een met 3D-CRT behandelde patiëntengroep voor patiënt-gescoorde xerostomie-klachten en plakkerig speeksel 6 maanden na behandeling met (chemo)-radiatie, geen valide voorspellingen kunnen maken in met IMRT behandelde patiënten. De belangrijkste boodschap uit dit hoofdstuk is dat modellen die ontwikkeld zijn in een met een specifieke radiatietechniek behandelde populatie niet gegeneraliseerd en geëxtrapoleerd kunnen worden naar een met een andere techniek behandelde populatie zonder externe validatie.
Voor de ontwikkeling van multivariate modellen van logistische regressie voor patiëntgescoorde xerostomie en plakkerig speeksel die gebruikt kunnen worden om behandeling met IMRT van patiënten met hoofdhalstumoren verder te optimaliseren, werd de studie zoals beschreven is in hoofdstuk 4 uitgevoerd. Het optimaal aantal variabelen voor de multivariate NTCP-modellen voor patiëntgescoorde xerostomia en plakkerig speeksel zes maanden na (chemo)radiatie met IMRT werd bepaald met dezelfde analyse-techniek als beschreven is in *hoofdstuk 2*. De multivariate analyse toonde de gemiddelde contralaterale parotisdosis en de aanwezigheid van minimale xerostomieklachten voor aanvang van de behandeling (geen versus een beetje) als de meest belangrijke voorspellers van xerostomie 6 maanden na behandeling. Voor plakkerig speeksel waren de gemiddelde contralaterale submandibulairedosis, de gemiddelde sublingualedosis en de gemiddelde dosis van de kleine speekselklieren die zich in het palatum molle bevinden, de meest geschikte voorspellers. Interne validatie van deze modellen was goed, wat maakt dat deze modellen bruikbaar zijn voor het optimaliseren van huidige IMRT behandelingen.
De studies zoals in *hoofdstuk 2, 3 en 4* uitgevoerd zijn, beschrijven de ontwikkeling van multivariate NTCP-modellen om de huidige behandeling met 3D-CRT en IMRT verder te optimaliseren, ten einde bijwerkingen met betrekking tot patiëntgescoorde xerostomie en plakkerig speeksel te verminderen na behandeling met (chemo)radiotherapie. Huidige dosislimieten

worden in hoofdzaak op basis van de vorm van één NTCP-curve bepaald. De QUANTEC (Quantitative Analyses of Normal Tissue Effects in the Clinic) onderzoeksgroep presenteerde praktische richtlijnen om de toxiciteit van radiotherapie met behulp van dosislimieten te beperken wanneer patiënten met IMRT worden behandeld. Het doel van *hoofdstuk 5* was om te onderzoeken of de opgestelde dosislimieten door de QUANTEC-onderzoeks-groep ook een beschermend effect zouden hebben op patiënt-gescoorde xerostomie. In een onderzoekspopulatie van 307 hoofdhals-patiënten, werden significant minder xerostomieklachten geobserveerd bij patiënten met een laag risico die volgens de QUANTEC-criteria werden behandeld. In *hoofdstuk* 5 lieten we ook zien dat de QUANTEC-criteria niet volledig beschermen tegen xerostomieklachten zoals door patiënten beschreven zijn. Met name bij oudere patiënten en patiënten met minimale klachten van xerostomia bij aanvang van de behandeling, bleken QUANTEC-criteria niet afdoende te beschermen tegen het ontstaan van xerostomie.

Zoals beschreven is in *hoofdstuk 1* varieert de samenstelling en productie van speeksel over de dag, deze variatie in dagelijkse productie zou van invloed kunnen zijn op verschillende aspecten van patiëntgescoorde xerostomie en plakkerig speeksel. In *hoofdstuk 6* hebben we daarom een vragenlijst ontwikkeld en gevalideerd: De Groningen Radiotherapy Induced Xerostomia Questionnaire (GRIX), die de verschillende aspecten van patiëntgescoorde xerostomie kan scoren. De uiteindelijke vragen in de GRIX werden gegenereerd uit een uitgebreide lijst van relevante vragen zoals die in de literatuur en door patiënten vermeld worden. De GRIX werd uiteindelijk van 56 vragen gereduceerd tot een vragenlijst met 14 vragen. De GRIX werd gevalideerd door het berekenen van de Crohnbach α's voor alle subschalen en criteriumvalditeit werd geëvalueerd door het vergelijken van de GRIX met patiëntgescoorde xerostomie volgens EORTC QLQ-HN35 en artsgescoorde xerostomie. Test-hertestanalyse en responsiviteit werden ook getest. De GRIX scoorde goed voor criteriumvaliditeit op alle subschalen met hoge correlaties met de EORTC QLQ-HN35 evenzo met de artsgescoorde toxiciteit. Er werden geen belangrijke verschillen gevonden tussen test- en hertestscores. De GRIX toonde goede responsiviteit op verschillende tijdmomenten voor alle subschalen. Uit de

resultaten van *hoofdstuk 6* kunnen we concluderen dat de GRIX een bruikbaar en geldig hulpmiddel is dat in de toekomst gebruikt kan worden om meer gedetailleerd onderzoek te doen naar de verschillende aspecten van op patiëntgescoorde xerostomie.
Met behulp van de GRIX waren wij in staat te onderzoeken wat de relatie is tussen xerostomie en plakkerig speeksel gedurende de dag en de nacht en dosisverdelingen in verschillende speekselklieren *(hoofdstuk 7)*. In een multivariate analyse van logistische regressie met een uitgebreide bootstrap-methode werden in een groep van 201 opeenvolgende patiënten die behandeld werden met IMRT of 3D-CRT voor hoofd-halstumoren, vergelijkbare risico-organen gevonden die verantwoordelijk zijn voor door radiotherapie geïnduceerde xerostomie en plakkerig speeksel zowel tijdens de dag als tijdens de nacht.
Uit dit proefschrift kunnen we concluderen *(hoofdstuk 8)* dat ondanks de introductie van IMRT, verminderde speekselproductie, resulterende in matig tot ernstige patiëntgescoorde xerostomie en plakkerig speeksel, nog een frequent voorkomende bijwerking is bij patiënten die curatief behandeld zijn met (chemo)radiatie voor hoofd-halskanker. De QUANTEC-criteria zijn bruikbaar voor het optimaliseren van radiotherapie, maar ze zijn niet volledig beschermend tegen deze bijwerkingen, met name oudere patiënten en patiënten met minimale klachten van xerostomie voor aanvang van therapie hebben een vergrote kans op klachten van xerostomie en plakkerig speeksel.
Het risico op klachten van patiëntgescoorde xerostomie en plakkerig speeksel hangt van verschillende factoren af. De bevindingen in dit proefschrift bieden mogelijke aanknopingspunten om groepen patiënten te selecteren die voordeel zouden kunnen hebben van behandelingen met nieuwe bestralingstechnieken, zoals een behandeling met protonen.

Curriculum Vitae

Curriculum Vitae

Ivo Beetz werd geboren op 11 juni 1982 en groeide op in Oss, Noord Brabant. In 2000 behaalde hij zijn VWO-diploma aan het Titus Brandsma Lyceum in Oss. Na het behalen van het VWO-diploma startte hij met de opleiding Geneeskunde aan de Universiteit van Leiden. In 2005 startte hij met zijn co-schappen, waar zijn interesse voor hoofd-hals- en algemene chirurgie werd gewekt. Na het artsexamen in december 2006 was hij werkzaam als arts-assistent-niet-in-opleiding bij de afdeling chirurgie in het HagaZiekenhuis te Den Haag. In 2008 begon hij met zijn promotieonderzoek naar patiënt-gerapporteerde klachten van drogemond na behandeling met radiotherapie voor patiënten met hoofdhalstumoren. De resultaten van dit promotie-onderzoek worden in dit proefschrift besproken. Vanaf januari 2012 is Ivo in opleiding tot medisch specialist op de afdeling chirurgie in het HagaZiekenhuis te Den Haag.

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Dankwoord

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