Summary

In chapter 1, the general introduction, an overview is presented of radiation-induced dry mouth, its relation with radiotherapy parameters, the methods to assess xerostomia, the relation with QoL and research on therapy and prevention. Despite many efforts, xerostomia is still a very common, troublesome and usually therapy-resistant side effect for head and neck cancer patients treated with radiotherapy.

Quality of life

Saliva plays an important role in many aspects of daily life. Therefore, it is often assumed that a reduced salivary flow may have an impact on QoL. In chapter 2, the results are presented of a prospective study in which we investigated the impact of xerostomia on QoL. In this study we used the RTOG late toxicity score system as a measure to assess xerostomia. The results of this prospective study are the first that showed a significant impact of radiation-induced xerostomia on QoL and on xerostomia-related dimensions. With increasing xerostomia grade a decrease in functioning scales is seen as well as an increase in the symptoms of insomnia and fatigue. This effect is more pronounced in female and younger patients. Furthermore, though the incidence of xerostomia decreases with time, the impact of a dry mouth on QoL increases.

Radiation parameters

Studies on radiation-induced xerostomia have primarily focused on the role of the parotid gland. However, saliva is also produced by other salivary glands. Irradiation of these glands may affect the risk of development of radiation-induced xerostomia as well. In chapter 3, the relation between the mean dose of the parotid glands, the submandibular glands and the minor salivary glands lining the oral cavity and the risk of developing radiation-induced patient-rated xerostomia and sticky saliva is described. We showed that the mean dose of the parotid glands as well as the mean dose of the submandibular glands influences the risk of developing subjective complaints of moderate or severe xerostomia. This risk as a function of the mean parotid dose is influenced by the mean dose to the submandibular gland, i.e. with increasing mean submandibular dose a lower dose to the parotid gland is needed to cause the same degree of xerostomia. No significant effect of the mean dose of the oral cavity was seen. Patient-rated sticky saliva mainly depends on the dose in the submandibular glands and shows some recovery over time. Most studies concerning radiation and xerostomia involve patients treated with bilateral irradiation. However, in some patients, e.g. in those with T1 or T2 tonsillar carcinoma, radiation can be limited to the ipsilateral neck, without compromising loco-regional control. In chapter 4, the relationship between the mean dose in the salivary glands and xerostomia among patients treated with unilateral irradiation as compared to patients treated with bilateral irradiation is described. The risk of developing patient-rated moderate or severe xerostomia and sticky saliva is significantly worse after bilateral compared to unilateral irradiation. After unilateral irradiation, patient-rated xerostomia and sticky saliva recovered to the baseline level. The probability on moderate or severe xerostomia is not only determined by the mean parotid dose, but also on the technique used. When focussing on the individual glands, the mean
dose of the contralateral parotid gland is the only factor relevant for the risk of developing patient-rated moderate or severe xerostomia. No significant role of the mean dose of the oral cavity or the mean dose of the submandibular glands was observed, neither for the risk of patient-rated xerostomia nor for the risk of patient-rated sticky saliva.

**Combined modality**

In chapter 5, the effect of combined modality, in casu chemotherapy and radiotherapy, on the risk of developing radiation-induced patient-rated xerostomia is described. For this study 148 patients were eligible, 93 treated with radiotherapy and 55 treated with chemotherapy and radiotherapy. In this study, the addition of chemotherapy does not significantly further increase the risk of developing xerostomia in patients treated with radiotherapy. Only the mean dose in the parotid gland plays a significant role. Though, the univariate analysis according to treatment arm suggests that chemotherapy may be of some importance as patients in the combined modality group have a higher odds ratio, i.e. a higher risk per 1 Gy increase in mean dose of the parotid gland, this is not reflected in the multivariate analysis.

**Amifostine**

Amifostine has been investigated in order to prevent side effects of chemotherapy and radiotherapy. Most studies on Amifostine in head and neck cancer patients treated with radiotherapy used a daily scheme. However, this scheme is labour intensive, expensive and troubles patients 5 times a week. In chapter 6, the results of a prospective randomised trial are described in which Amifostine in two different administration schedules (three times and 5 times a week) is compared to no Amifostine in head and neck cancer patients treated with radiotherapy. In this study 91 patients were included, 31 were treated with radiotherapy alone, 30 in combination with Amifostine 3 times a week and 30 in combination with Amifostine 5 times a week. Patients treated with Amifostine 5 times a week had a reduced risk of xerostomia as measured with the RTOG late toxicity score system at 6 months after radiotherapy, but not thereafter. Amifostine 3 times a week proved to be less effective. However, considering patient-rated xerostomia as an endpoint, less deterioration was seen with Amifostine, with no difference between the two administration schedules. No benefit was observed of Amifostine on acute toxicity as measured with the RTOG acute toxicity score system. Also no effect was seen on patient-rated sticky saliva.

An important problem encountered in this study was the reduced compliance due to toxicity of Amifostine, in particular nausea and vomiting. A total of 24 patients (28%) discontinued Amifostine before the end of radiotherapy. Though toxicity scores were in the lower range and were considered mild, for many patients nausea and vomiting complaints were a serious burden, even after adjustment of the anti-emetic regimen. Oral correction of hydration status did not reduce nausea sufficiently in all patients. Less frequent observed reasons for discontinuation were allergic skin reactions and non-Amifostine realted hypotension.

**Xialine®**

In chapter 7, the results of a pilot study with Xialine®, a saliva substitute on a xanthan base, are described. In this prospective, placebo-controlled
double-blinded trial with a cross over design 30 head and neck cancer patients with xerostomia were included. They were at least 3 months after radiotherapy and it was estimated that at least 75% of their parotid glands had received 50 Gy or more. Though Xialine® appears to improve problems with speech and ‘taste and smell’, the global QoL in patients with xerostomia resulting from radiation therapy for head and neck cancer was decreased to almost the same level with Xialine® as with placebo.

Chapter 8 contains the general discussion and conclusion of this thesis.