

Summary

This thesis addresses optimization of radiotherapy of the neck in patients with head and neck squamous cell carcinoma (HNSCC) in terms of reducing morbidity and improving regional control.

The introduction of intensity modulated radiotherapy (IMRT) created markedly more opportunities to optimize radiation dose distribution with steeper dose gradients around the target volumes resulting in less dose to surrounding healthy tissues. IMRT has been widely adopted for the treatment of head and neck cancer, although at that time, comparative studies on patient reported xerostomia and health related quality of life were still scarce. We tested the hypothesis that reducing the dose to the parotid glands results in less patient-rated xerostomia. For this purpose we compared patients treated with IMRT and 3D-CRT with regard to radiation-induced xerostomia and quality of life (**Chapter 2**). The results demonstrated a significant reduction of the mean parotid gland dose when using IMRT. This ultimately resulted in a significant reduction of both patient-rated and observer-rated xerostomia. In addition, significantly lower scores were also found for other head and neck symptoms. Consequently, the reduction of radiation-induced side effects translated into better scores of the more general dimensions of health related quality of life.

Patients treated with ipsilateral neck irradiation experience less xerostomia than those treated with bilateral neck irradiation. Therefore, omitting the contralateral neck from the radiation portals will decrease xerostomia rates. In **Chapter 3**, we investigated prognostic factors for the risk of contralateral regional recurrence in HNSCC patients treated with ipsilateral neck irradiation in the postoperative setting, to identify patients in whom the contralateral neck can be safely omitted from the target volume. We showed that in lateralized oral or oropharyngeal carcinomas with a contralateral cN0 neck, postoperative radiotherapy of the neck can be limited to the ipsilateral side. In these patients, the risk of contralateral nodal metastases is very low (6%) and in case of a contralateral regional failure, the majority of patients can be successfully salvaged. Risk factors for contralateral nodal failure were the number of positive nodes in the ipsilateral neck and the presence of extranodal spread (borderline significance). The main advantage of omitting contralateral elective irradiation is the reduction of late radiation-induced morbidity,

especially xerostomia, which ultimately decreased to approximately 5%. However, in case of multiple ipsilateral lymph node metastases, particularly in the presence of extranodal spread, patients are at risk of occult contralateral metastases and should be treated bilaterally.

Chapter 4 investigates outcome and prognostic factors for regional recurrence in elective irradiation of the cN0 and pN0 neck, aiming at a better selection of subgroups of patients who might be safely treated with ipsilateral neck irradiation alone. We showed that in all electively irradiated N0 necks, regional control is indeed excellent. In 785 cN0 and pN0 necks, regional control at 3 years was 94% in the cN0 (non-dissected) neck compared with 97% in the pN0 (dissected) neck. Prognostic factors associated with a higher rate of neck failure are the ipsilateral neck side (compared to contralateral) and positive surgical margins, probably due to tumor spill during the surgical procedure. Therefore, in case of positive surgical margins of the primary tumor, elective nodal irradiation should be applied, even in case of a pN0 neck. Additionally, one could argue to withhold elective irradiation to the contralateral pN0 neck in case of an ipsilateral pN0 neck.

In **Chapter 5**, we described pre-treatment prognostic factors for regional recurrence in the N+ neck in a cohort of 3D-CRT treated patients, in order to identify patients at risk of regional failure. We showed that nodal volume and the addition of chemotherapy are the most important prognostic factors for regional control. Individual nodal control was significantly worse in case of larger nodal volumes, no chemotherapy and the presence of extranodal spread or central necrosis. Individual nodal control in smaller nodes was generally very high, although larger nodes (> 3cm) treated with radiotherapy, with or without the addition of chemotherapy showed much lower regional control rates. In case of treatment with radiotherapy alone, a minimal dose < 95% of the prescribed dose was associated with worse control. In case of combined modality treatment, the minimal radiation dose was of less importance.

With 3D-CRT it is sometimes difficult to obtain adequate dose coverage of target volumes located in proximity of critical normal structures. Intensity modulated radiotherapy treatment plans can obtain adequate dose coverage of target volumes without compromising the tolerance dose to critical structures. Therefore, we tested the hypothesis that dose coverage of nodal metastases and subsequent nodal control was better in IMRT compared to historical 3D-CRT controls (**Chapter 6**). An important finding was the

difference in regional and nodal control among patients treated with 3D-CRT compared to IMRT. Nodal and regional control was very high and significantly better when IMRT was used, most likely due to improved coverage of the nodal gross tumor volume (GTV) in IMRT plans. Nodal volume, minimal nodal dose, central necrosis and chemotherapy were identified as independent prognostic variables for nodal control. Based on these results, a multivariable prediction model for tumor control probability for lymph node metastases was developed. This model showed that small (<1.5 cm) and intermediate (1.5 – 3.0 cm) sized nodes without central necrosis have excellent control with RT alone. Larger nodal volumes, the presence of central necrosis and inadequate coverage of the nodal GTV are associated with lower nodal control rates in RT alone. The addition of chemotherapy could compensate for these adverse prognostic factors.