

# CHAPTER 7

## **GENERAL DISCUSSION AND FUTURE PERSPECTIVES**

## General discussion

This thesis addresses optimization of radiotherapy of the neck in patients with head and neck squamous cell carcinoma (HNSCC) in terms of improving regional control and reducing morbidity. In spite of improvements in radiotherapy, irradiation of the neck is still associated with substantial toxicity. Patients may suffer from permanent side effects, such as difficulties with chewing and swallowing, xerostomia and pain, due to irradiation of salivary glands, swallowing muscles and bone (1–3).

The relationship between dose metrics and radiation-induced side effects is generally described by Normal Tissue Complication Probability (NTCP) models. NTCP-curves show that the function of salivary glands is highly dose dependent. Consequently, reduction of radiation dose to these structures may lead to preservation of function and therefore improve quality of life (4–6).

Reduction of dose dependent toxicity can be achieved in different ways:

- reduction of dose to organs at risk by the use of advanced radiotherapy techniques such as IMRT or VMAT;
- reduction of the size of irradiated volumes (e.g., omitting parts of the prophylactic target volumes in the neck);
- reduction of the prescribed dose (e.g., prophylactic dose to the elective neck).

### Radiotherapy techniques

The introduction of 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 introduced predominantly to enable a significant reduction of the radiation dose to salivary glands without compromising the dose distribution to the target volumes. It is generally accepted that salivary flow rates reduce with increasing mean parotid gland doses and accordingly, IMRT treated patients show improved preservation of salivary flow rates compared to patients treated with conventional radiotherapy (7,8). Due to the expected effects on xerostomia, IMRT has been widely adopted by radiation oncologists 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.

In Chapter 2, we tested the hypothesis that reducing the dose to the parotid glands results in less patient-rated xerostomia and for this purpose we compared patients treated with IMRT with those treated with 3D-CRT with regard to radiation-induced patient-reported xerostomia and quality of life. The results of this non-randomized comparison demonstrated a significant reduction of the mean parotid gland dose. This ultimately resulted in a significant reduction of patient-rated and observer-rated xerostomia. In addition to dry mouth, significantly lower scores were found for other symptoms, including sticky saliva, opening mouth, head and neck pain, swallowing problems, problems with social eating, sexuality problems, problems with teeth and feeling ill. Consequently, the reduction of radiation-induced side effects translated into better scores in more general dimensions of health related quality of life. Patients treated with IMRT scored significantly better with regard to global quality of life, role functioning, cognitive functioning and social functioning. Unexpectedly, IMRT treated patients suffered more fatigue, insomnia and appetite loss compared to 3D-CRT patients. (Chapter 2).

The PARSPORT trial, a prospective randomized controlled trial published in 2011, confirmed the hypothesis that parotid sparing IMRT reduces the incidence of severe xerostomia and improves quality of life. Additionally, the authors showed that IMRT treated patients experience improved recovery of salivary flow and quality of life compared with conventional radiotherapy. Another outcome of the PARSPORT trial was that IMRT treated patients also suffered more acute fatigue compared to the conventionally treated patients. Further analysis of treatment plans showed higher mean doses to the posterior fossa in the IMRT group which could account for the higher fatigue scores (8).

Radiation-induced xerostomia is considered the most frequently reported side effect after definitive radiotherapy or chemoradiation for head and neck cancer, with a major impact on several dimensions of quality of life. However, more recent studies indicate that several other radiation-induced side effects may also have an important impact on quality of life. Langendijk et al. showed that the effect of xerostomia on quality of life was less pronounced than that

observed for swallowing disorders, especially in the first 18 months after treatment (3). This implies that sparing of anatomical structures involved in swallowing, might lead to a reduction of swallowing disorders and further improvement of quality of life after radiotherapy (2).

In Chapter 2, no difference in ipsilateral submandibular gland dose was observed between IMRT and 3D-CRT with only a small difference in the contralateral submandibular gland dose. In this study, no attempts were made to spare the submandibular glands. More recent studies demonstrated that sparing the contralateral submandibular gland is feasible without compromising the dose to the target volumes (9). Prospective data demonstrated that parotid glands, submandibular glands and to a lesser extent the oral cavity (containing the minor salivary glands) are all predictors for patient-rated and observer-rated xerostomia and that sparing of the submandibular glands and oral cavity in addition to sparing the parotid glands improves post-treatment xerostomia scores (10,11).

### **Reduction of radiation volumes**

Previous studies in 3D-CRT treated patients showed that omitting the (contralateral) neck from the radiation portals reduces the incidence of patient-rated xerostomia compared to bilateral neck irradiation. Patients treated with unilateral neck irradiation showed lower xerostomia scores and increased recovery of salivary function back to baseline level at 24 months after treatment (12,13). Additionally, a compensatory overproduction of saliva in contralateral salivary glands was observed in patients treated with unilateral irradiation, suggesting that the spared salivary gland compensates for the loss of function of the irradiated gland (13,14). Therefore, omitting the contralateral elective neck from the radiation fields will reduce dose dependent toxicity. Several studies have questioned the need to treat the contralateral neck in well-selected and well-lateralized oropharyngeal and oral carcinomas, because the risk of contralateral failure and is very low and survival rates are equal to those with bilateral treatment. (15–17). It should be noted that these studies mainly included patients treated with primary radiotherapy. The need to treat the contralateral neck in the postoperative setting after surgery of the primary site and the ipsilateral neck should be considered even more controversial, as

ipsilateral pathologic status is a strong prognostic factor for the incidence of occult contralateral neck metastases or recurrence (15,18,19).

Chapter 3 was the first study that investigated prognostic factors for the risk of contralateral regional recurrence in the postoperative setting. We showed that in selected patients with well lateralized oral or oropharyngeal cancer and  $\leq 1$  ipsilateral metastases without extranodal spread (ENS), postoperative radiotherapy of the neck can be limited to the ipsilateral side, with a very low risk (6%) of contralateral recurrence and a high probability of successful salvage in case of contralateral failure. With this approach, long-term radiation induced morbidity is very low, and considerably lower than observed after bilateral irradiation.

Recent work from Koo et al. (20) showed similar results and found no contralateral neck failures in 20 patients with well-lateralized tonsillar cancer treated with definitive postoperative ipsilateral irradiation. Late RTOG grade 2 xerostomia was found in only one of the 20 patients. Additionally, Cerezo et al. treated 20 patients with well-lateralized tumors of the oral cavity and oropharynx with ipsilateral irradiation, without any contralateral nodal recurrences (CLNR) (21). No grade 3 xerostomia was seen in these patients and 12% suffered from grade 2 xerostomia. Gonzalez-Garcia et al. investigated CLNR after surgical resection of primary SCC of the oral cavity in 315 patients (22) of whom 18 patients developed a CLNR (6%). Prognostic factors for CLNR were TNM tumor stage IV, grade 3 tumor, surgical margins less than 1 cm around the primary tumor, ipsilateral neck dissection (compared to bilateral neck dissection), and perineural tumor involvement. Presence of ipsilateral neck metastasis at the time of diagnosis was associated with an increased incidence of CLNR.

Tumor thickness is also described as a histological prognosticator of cervical nodal metastasis. Bier-Laning et al. (23) found an approximately 5% increased risk of contralateral nodal metastases (CLNM) for every 1-mm increase in tumor thickness, and there were no cases of CLNM when the primary tumor had a thickness  $<3.75$  mm. Others (24,25) also demonstrated that risks of contralateral metastases were higher in cases of tumors with over 6 mm in relation to cases of up to 3 mm thickness and tumor thickness  $>4$  mm were independent factors predicting for late cervical metastases in early-stage oral tongue cancer.

Therefore, in selected well-lateralized oral and oropharyngeal carcinomas, the contralateral neck can be left untreated, with a low risk of CLNR.

However, most head and neck tumors present in midline structures and are at risk of bilateral nodal metastases. General agreement is that so-called elective treatment of the clinically N0 neck is indicated if the risk at occult lymph node metastases exceeds 15 – 20% (26). Surgical studies showed that elective neck dissections of cN0 necks contain occult metastases in approx. 25% of the cases (27). This implies that in the majority of patients the N0 neck will be treated unnecessary. These studies were performed in a period when diagnostic imaging was not as accurate as compared to current techniques. With improved quality of CT, MRI and the introduction of PET, small tumor deposits will be identified more accurately and probably even more N0 necks will be treated unnecessary.

In Chapter 4, we investigated regional control in electively irradiated necks and we showed that in 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 and 97% in the pN0 (dissected) neck. Prognostic factors associated with a higher rate of neck failure are the ipsilateral neck side 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 the series described in Chapter 4, no postoperative chemotherapy was applied, which is now considered gold standard for surgically treated patients with positive margins and/or lymph node metastases with ENS (28–32). Consequently, the addition of postoperative chemotherapy could further reduce the number of regional recurrences in the electively irradiated neck.

Our findings have been confirmed by numerous studies showing excellent regional control rates in the electively irradiated neck of 90% or more (33–35). Lambrecht et al. investigated the incidence of regional recurrences in 368 patients treated with definitive (chemo)radiation and demonstrated that recurrences in the electively treated neck are extremely uncommon (0.5%) (33). Bernier and Bataini investigated 1646 oropharyngeal and pharyngolaryngeal patients and found a nodal control rate of 98% in electively irradiated necks (35).

The very low rates of recurrence in electively irradiated lymph nodes indicate that the treatment of elective volumes may be too aggressive and the question

raises if the elective dose might be de-escalated. The empirical dose levels of 46-50 Gy to sterilize microscopic tumor burden originate from several decades ago (36–38). At that time, assessment of the neck only consisted of physical examination due to the lack of sufficient sensitive diagnostic imaging of lymph nodes. With improved quality of CT, MRI and the introduction of PET, small tumor deposits will be identified more accurately. At present, microscopic tumor load in elective areas will be much less than before and therefore, a lower elective dose may be sufficient to obtain adequate regional control.

### **Reduction of elective dose**

Reduction of radiation induced morbidity can also be achieved by reducing the dose to the elective N0 neck, without compromising regional control.

Nuyts et al. conducted a randomized controlled trial in 200 patients which compared elective doses of 50 Gy and 40 Gy (39). No significant differences were observed in locoregional control, disease free survival or overall survival. The dose to the swallowing structures was significantly reduced and at 3 months significantly less patients in the 40 Gy group suffered from  $\geq$  grade 3 dysphagia (PEG tube dependency). However, median follow up was only 6 months and scoring of toxicity was rather limited, without standardized quality of life questionnaires or more specific toxicity scoring. Additionally, there was heterogeneity in total dose, fractionation schedules, the use of concomitant chemotherapy and in planning and performance of radiotherapy treatment (margins, planning protocol, patient positioning protocol) between participating centers. Salama et al. treated 222 locally advanced head and neck cancer patients with induction chemotherapy and concurrent chemoradiation in 3 cohorts with elective dose levels of 45, 39 and 36 Gy, respectively (40). No significant differences in loco-regional control or overall survival was demonstrated, but no comprehensive assessment on xerostomia, dysphagia and quality of life were performed. Furthermore, as regional control in the electively irradiated neck is generally very high, larger patient numbers are probably needed to demonstrate a (minor) difference in regional control. Therefore, further investigations on reduction of the elective neck dose and the effects on regional control, xerostomia, dysphagia and quality of life are mandatory.

## **Prognostic factors for regional control in the node-positive neck**

In Chapter 5, we described pre-treatment prognostic factors for regional recurrence in the N+ neck 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, patients who did not receive 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 worse regional control. 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.

All patients described in Chapter 5 were treated with 3D-conformal radiotherapy. With this technique, it is sometimes difficult to obtain adequate dose coverage of target volumes located in proximity of critical normal structures. Therefore, suboptimal dosage was occasionally accepted in the target volumes, in order to prevent unacceptable toxicity. The use of IMRT enables us to obtain a highly conformal dose coverage and steep dose gradients. IMRT treatment plans can obtain adequate dose coverage of target volumes without compromising the tolerance dose to critical structures. Therefore, in Chapter 6, we tested the hypothesis that dose coverage of nodal metastases and subsequent nodal control was better in IMRT compared to 3D-CRT.

In this study 208 pathological lymph nodes in 84 IMRT treated patients were compared with a group of 208 pathological nodes in 77 3D-CRT patients, which were also described in Chapter 5. Two patients treated to a total dose of 40 Gy were accidentally included in the analysis of Chapter 5 (n=79) and were excluded in the analysis of Chapter 6 (n=77). Comparison of 3D-CRT and IMRT treatment plans indeed showed better dosimetric coverage in the IMRT plans. Analysis of DVH parameters showed that the dose distribution in nodes treated with 3D-CRT was significantly worse compared to IMRT with a much lower minimal dose (Dmin) among 3D-CRT treated nodes. Additionally, we showed that nodal control was indeed significantly better in IMRT treated patients. Nodal control was obtained in 96% in the IMRT treated lymph nodes,

compared to only 88% of the nodes treated with 3D-CRT. Nodal volume, minimal nodal dose (Dmin), central necrosis (CN) and chemotherapy were identified as independent prognostic variables for nodal control. Based on these pre-treatment prognostic factors, a multivariable prediction model for tumor control probability (TCP) for lymph node metastases was developed. The multivariable TCP-model showed that nodal control in small nodes was excellent after RT alone. Larger nodal volumes, the presence of CN and inadequate coverage of the nodal GTV were associated with lower nodal control rates in RT alone.

Two recent studies confirmed these results and also indicated that IMRT is associated with favorable control rates compared to 3D-CRT (41,42). Clavel et al. demonstrated improved loco-regional control and overall survival rates in IMRT treated oropharyngeal cancer patients compared to 3D-CRT. In this study, the boost volume in IMRT patients was treated with a slightly higher dose per fraction and a shorter overall treatment time compared to 3D-CRT. Additionally, Chen et al. demonstrated improved loco-regional control rates in the postoperative setting in oral cavity carcinoma. Loco-regional control at 3 years was 76% in IMRT patients, compared to 53% in 3D-CRT. Furthermore, they showed that neck failure as first site of recurrence occurred in 15% of the 3D-CRT patients compared to only 3% in IMRT patients. They also showed that neck relapses in 3D-CRT were frequently located in the junction area of the upper opposing and the lower anterior portals and in the posterior electron portals. These areas are at risk of marginal dose due to the limited penetration of the electron beams and due to dose uncertainty in the junction area. Chen et al. and Clavel et al. evaluated regional control in the postoperative setting and in primary irradiated patients with slightly hypofractionated regimens resulting in shorter overall treatment time, which are known to improve outcome (43,44). To our knowledge, our study is the first to demonstrate improved control rates in individual nodes treated with IMRT with conventional 2 Gy per fraction regimens.

In Chapter 5 and 6, several pre-treatment prognostic factors for regional recurrence were described. With the use of the multivariable TCP-model, patients at risk for nodal recurrence can be identified before the start of (chemo-)radiotherapy.

It is generally accepted that complete clinical regression of palpable neck metastases after primary (chemo-)radiation poorly correlates with pathological outcome and planned neck dissections after primary (chemo-) radiation in patients with pathological neck nodes show residual tumor in up to 30% of the cases (45). Due to these findings it was general policy in several institutions to perform a planned neck dissection within 3 months after (chemo-)radiation in patients with advanced nodal disease at presentation. On the other hand, this approach implies that 70% of these patients will undergo unnecessary neck dissections. A salvage neck dissection is associated with substantial complications and morbidity due to delayed wound healing, potential wound break down and extensive fibrosis caused by the (chemo-) radiation treatment (46).

Therefore, pre-treatment selection of patients can be a useful tool to identify patients at risk for regional recurrence and consequently, might reduce the number of unnecessary post (chemo-) radiotherapy neck dissections.

Diagnostic imaging with CT, (diffusion- weighted) MRI and PET may help identifying patients with residual nodal disease and might reduce the number of unnecessary neck dissections. For accurate use of these imaging modalities a high negative predictive value is needed. CT-scans show negative predictive values of 95% for detection of residual or recurrent neck metastases, with high sensitivity, but specificity ranging from 25 -90% (47-49). FDG-PET shows negative predictive values ranging from 15 - 100%, depending on the time interval between the end of treatment and PET imaging (50-54). PET imaging obtained too soon after radiation has been associated with high rates of false positive findings due to post-radiation soft tissue effects and high rates of false negative findings because possible residual viable cancer cells did not have sufficient time to repopulate to a level that can be detected by PET. Therefore, FDG-PET scans are usually performed approximately 3-4 months after the end of (chemo-)radiotherapy (55).

Because IMRT is usually associated with steep dose gradients outside the target volumes, adequate delineation is of utmost importance as inadequate

definition of target volumes could increase the risk of geographical misses. Additionally, inadequate patient positioning during treatment and anatomical changes during radiotherapy can also affect treatment results (56).

Some concern should be made to the reported occurrence of regional failures in the region of spared parotids gland, possibly due to the presence of microscopic tumor deposits in periparotid lymph nodes. Therefore, the occurrence of periparotid nodules in the presence of multilevel or level II nodal metastases should raise suspicion for subclinical disease, and additional evaluation of these nodules might be indicated before proceeding with definitive parotid sparing IMRT (57).

### **Conclusions and future perspectives**

The aim of the studies described in this thesis was to improve radiotherapy of the neck in HNSCC patients with regard to morbidity and regional control. We showed that with the use of IMRT, the dose to the parotid glands can be safely reduced, leading to a reduction of radiation-induced xerostomia. Additionally, treatment with IMRT resulted in a reduction of other head and neck symptoms compared to 3D-CRT, which ultimately resulted in an improvement of several aspect of health-related quality of life. The dosimetric coverage of target volumes was improved in IMRT treatment plans, which resulted in significantly higher nodal control rates compared to 3D-CRT treated patients. In addition, a multivariable TCP-model for N+ necks was developed, which can be used for pre-treatment selection of patients at risk of nodal recurrence. Radiation-induced morbidity can also be reduced by reduction of the electively irradiated volumes. We demonstrated that in selected patients with lateralized oral or oropharyngeal cancers, postoperative radiotherapy can be safely limited to the ipsilateral neck, resulting in a considerable reduction of long-term radiation-induced morbidity. Additionally, we showed that regional control in irradiated cN0 and pN0 necks is excellent and several prognostic factors for regional recurrence in the N0 neck were identified.

In HNSCC, side effects of the aggressive treatment can cause serious morbidity and have the potential to seriously affect function and quality of life (QoL). Emotional distress is also common. At and after the time of diagnosis, head and neck cancer patients commonly suffer from emotional distress

and anxiety. Although there is a gradual improvement of emotional distress during the first year after treatment, many patients continue to suffer from distress, or develop new symptoms of distress (58). At follow-up visits to the outpatient clinic, approximately 30% of patients suffer from distress due to physical problems, less social contacts and style of coping (59). Many patients who experience high levels of distress are not referred to psychosocial care as heightened distress was not recognized by oncological care professionals (60). Screening for psychological distress at follow-up care can help identify patients with an increased level of distress, so appropriate psychological care can be offered (61). Additionally, eHealth applications can support patients by individually tailored feedback and personalized advice on supportive care services (62).

Smoking accounts for approximately 30% of all cancer deaths (63) and more than 80% of all newly diagnosed head and neck cancer patients are current, recently quit or former smokers (64). There is consistent evidence that continued smoking during and after treatment for head and neck cancer leads to lower survival rates and higher recurrence rates compared to patients who quit smoking (65). Although quit rates and quit attempt rates are high shortly after diagnosis, at the longer term the recidivism rates are also high. Smoking cessation, screening, counseling and prevention of relapse are important opportunities to improve cancer survival rates and reduce treatment complications in cancer (66,67).

The introduction of IMRT had a major impact on the treatment of head and neck cancer patients. Due to the physical properties of photons, the opportunities to further reduce the dose to the organs at risk with new radiation techniques using photons are probably limited. Protons show more favorable physical characteristics compared to photons; the dose depth distribution for proton beam therapy is characterized by a sharp increase in dose deposited at the end of the particle range, a phenomenon known as the Bragg peak. Because proton particles do not deliver any energy immediately after the Bragg peak, they do not deposit any exit dose beyond the target (68). In addition, their heavier mass causes a smaller scattering angle, which leads to a sharper lateral dose distribution compared to photons but this may vary as a function of the energy used. The inherent physical properties of proton energy deposition, make proton therapy a logical alternative to IMRT and several studies show advantage for the use of proton therapy in head and neck

cancer (69–73). Due to the steep dose gradient at the distal edge of the Bragg peak, proton treatment plans are more sensitive to variations in tumor size and normal tissue changes over the course of treatment compared to photon plans. An accurate knowledge of the sources and amounts of the uncertainties affecting the proton range is essential for producing plans which are robust to these uncertainties, in order to avoid geographical miss (74). Although several radiation institutes have the possibility to deliver proton therapy, the capacity is highly limited, in particular in Europe. Fortunately, it is expected that within a few years, proton therapy facilities will be operational in the Netherlands.

The very low rate of recurrence in electively irradiated necks suggests overtreatment of currently used elective volumes and the question arises as to whether the elective dose might be decreased. The empirical dose levels of 46-50 Gy to sterilize microscopic tumor burden originate from several decades ago (36,37), when assessment of the neck only consisted of physical examination due to the lack of sufficient sensitive diagnostic imaging of lymph nodes. With improved quality of CT, MRI and the introduction of PET, small tumor deposits will be identified more accurately. At present, microscopic tumor load in elective areas will be much less than before and therefore, a lower elective dose may be sufficient to obtain adequate regional control. To evaluate this hypothesis, a multicenter, randomized controlled trial will be initiated within the near future to evaluate regional control in patients treated with a controlled reduction of elective dose.

During radiation treatment, head and neck cancer patients show general weight loss and reduction of tumor mass during treatment. Castadot et al. demonstrated that nodal GTV's decreased at a mean rate of 2.2% per treatment day (75). Additionally, volumetric reduction of the parotid glands have been described during RT treatment (75,76). These factors and the influence of positioning errors may affect the dose distribution in irradiated patients. Therefore, the actually delivered dose to the target volumes and organs at risk may differ from the dose calculated in the original treatment plans. Adaptive radiotherapy, which integrates the temporal changes in anatomy during the imaging, planning, and delivery of radiotherapy, has the potential to counteract the effects of anatomical changes and positioning errors (77). To visualize anatomical changes, Cone Beam CT-scans (CBCT) can be made during treatment and if necessary, treatment plans can be re-planned. However, the use of CBCT has some disadvantages. Due to the limited tissue contrast in

CT-scans, soft tissue imaging is limited and tumor regression or reduction of parotid gland tissue can be difficult to visualize. Secondly, additional radiation dose will be delivered, although this will be mainly relevant for children and young adults. Thirdly, real time imaging during treatment is currently not possible. The use of MRI could overcome these problems. The ViewRay MRIdian System can provide MR-guided radiotherapy with the use of a 0.35-Tesla MR-scanner and 3 Cobalt heads. This system can perform irradiation with Cobalt sources and beam-on MRI imaging and is currently clinically in use in 3 centers in the USA (78).

Recently, an automatic interactive optimizer (AIO) was developed in our institution to automate the interactive optimization protocol for volumetric modulated arc therapy head and neck cancer treatment planning using the Eclipse treatment planning system in order to improve plan quality and consistency. AIO gradually positions the optimization objectives of organs at risk at lower values during the optimization process and consequently leads to substantially improved sparing of swallowing muscles and oral cavity at cost of only a small increase of PTV dose inhomogeneity (79,80). With this method increased sparing of organs at risk can be achieved in a less time consuming way.

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