

CHAPTER 1

INTRODUCTION AND OUTLINE OF THE THESIS

Introduction and outline of the thesis

Head and neck squamous cell carcinoma (HNSCC) originates from the mucosal surface of the upper aerodigestive tract (oral cavity, oropharynx, larynx, hypopharynx, nasopharynx, nasal cavity and paranasal sinuses). Worldwide, head and neck cancer is the 5th most common cancer and it affects more than 500.000 patients annually. In the Netherlands, approximately 3.000 new patients are diagnosed with head and neck cancer each year (1). After diagnosis of potentially curable head and neck cancer, 5 year overall survival is 50%, of who nearly 25% die from head and neck cancer. These patients are also at high risk of dying from non-cancer causes (cardiovascular and pulmonary diseases) and from second malignancies (predominantly lung cancer and esophageal cancer) (2).

Approximately 30-40% of patients with HNSCC present with early stage disease (stage I and II) and have a favorable prognosis, with overall survival rates ranging from 70 to 90% at 5 years. The majority of patients present with locally advanced disease (stage III and IVa/b). Despite aggressive loco-regional treatment, local recurrences and distant recurrences remain a substantial problem, causing serious morbidity and mortality in these patients. In locally advanced HNSCC, 5 year overall survival rates range from 30 to 60%.

There is a large geographical variability in incidence and primary tumor sites due to differences in the prevalence of risk factors and genetic and ethnic differences between populations. The main risk factors for HNSCC are smoking, smokeless tobacco use, betelnut chewing and alcohol abuse. The incidence of HNSCC has declined over the last 20 years, due to a decline in smoking habits (3). In contrast to this decline, the incidence of oropharyngeal cancer is rising and reflects an increasing attribution of oncogenic human papillomavirus, in particular type 16 (HPV-16). HPV-related oropharyngeal carcinomas form an epidemiologic and clinically distinct group of head and neck cancers. Where smoking- and alcohol related HNSCC predominantly affects elderly males, HPV-related oropharyngeal carcinoma generally affects young, non-smoking patients, with risk factors related to sexual behavior (4). These HPV-related oropharyngeal carcinomas have a more favorable prognosis compared to tobacco- and alcohol related HNSCC (4–7).

Optimization of radiotherapy

The majority of patients with head and neck cancer are treated with radiotherapy in the primary or postoperative setting, with or without the addition of chemotherapy. Historically, radiotherapy was delivered by a small number of photon beams with custom-made cerrobend blocks. Target volumes were defined on planar radiographs and doses were calculated based on one or more 2-dimensional contours.

The planning and delivery of radiotherapy has dramatically improved by the introduction of 3-dimensional radiotherapy, which uses planning CT scans for delineation and treatment planning. The advantage over 2D-radiotherapy is the ability to delineate target volumes and adjacent normal structures in 3 dimensions. Treatment is delivered using a variable number of beams from various directions. The profile of each radiation beam is shaped to fit the profile of the target volume using a multileaf collimator which results in more conformal dose distributions.

Intensity-modulated radiation therapy (IMRT) further improves the ability to conform the treatment volume to concave tumor shapes, for example when the tumor is wrapped around a vulnerable structure such as the spinal cord. IMRT treatment plans are generated using inverse planning systems, which use computer optimization techniques to help determine the intensity patterns of the beams (8). During treatment planning, the pattern of radiation delivery is determined using highly tailored computer applications to perform optimization and treatment simulation. The radiation dose is consistent with the 3-D shape of the tumor by controlling or modulating the radiation beam's intensity. IMRT treatment plans are highly conformal and correct delineation is crucial. IMRT also enables the use of a simultaneous integrated boost (SIB) technique, where different dose levels within one fraction are delivered, e.g. 155 cGy to the elective planning target volume (PTV_{elective}) and 200 cGy to the boost planning target volume (PTV_{boost}). Although several studies have confirmed that the use of IMRT is safe in experienced hands (9–11), the consequences of a lower elective fraction dose on regional control remain unclear and studies comparing regional control in the electively irradiated neck are lacking.

Since 2007, we use volumetric modulated radiotherapy (VMAT) which delivers radiation dose during arc treatment with continuous changes in dose intensity

during the rotation of the gantry (12). This allows for even better treatment plans, which can be delivered in a shorter time period (13).

In the era of 2-dimensional and 3-dimensional conformal radiotherapy, it was often not possible to treat the target volumes to the prescribed dose, without exceeding the tolerance of adjacent critical structures. In these cases, suboptimal doses in target volumes in proximity of critical structures (e.g. spinal cord) were sometimes accepted, to avoid unacceptable toxicity. Due to highly conformal treatment plans and the ability to create steep dose gradients to critical surrounding structures, IMRT has the ability to improve target volume coverage compared to 3D-CRT plans and, theoretically, the potential to improve tumor control rates.

Radiation-induced toxicity

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). During radiation treatment, patients may suffer from mucositis, dysphagia, dermatitis, sticky saliva, loss of taste and xerostomia, depending on site and extension of the primary tumor and nodal metastases, as well as on the extent of the elective nodal levels included in the radiation portals. Generally, patients recover from these acute symptoms within weeks or months following treatment. However, after (chemo)radiation, the majority of patients suffer from permanent side-effects such as eating and swallowing dysfunction, problems with speech, residual pain, fibrosis and xerostomia. Permanent xerostomia, caused by irradiation of the parotid glands, is one of the most frequent and distressing side effects in patients with bilaterally treated necks. Patients with radiation-induced xerostomia frequently complain of oral discomfort and pain and have difficulties with chewing, swallowing and speech. Reduced salivary flow also predisposes to oral infections and caries. As a consequence, xerostomia significantly impairs health-related quality of life in potentially cured patients. (14–18).

It is generally accepted that the mean dose of the parotid gland is the best predictor for parotid gland dysfunction. In order to quantify the probability of radiation induced salivary gland dysfunction (19), models were developed by the use of the Kutcher-Lyman NTCP model (20,21). These models quantify

the radiation dose versus the volume of the parotid gland irradiated and the probability of salivary dysfunction. NTCP models for parotid gland function have been developed by two separate groups from Utrecht and Michigan, in which the NTCP curves showed some differences (22,23). The group from Michigan showed a threshold dose under which substantial preservation of salivary function could be achieved. Data from Utrecht showed a large volume dependency with a more gradual dose response curve. Additionally, the tolerance dose for 50% probability of a complication for irradiation of the whole organ (TD50) at 1 year differed between both groups, in which a complication is defined as a measured stimulated parotid salivary flow rate $\leq 25\%$ of the pre-irradiated flow rate at 12 months. Both groups showed the ability of partial recovery of salivary gland function over time. More recent work from Dijkema et al. (24) combined the work of both groups and investigated 384 parotid glands. The resulting NTCP-curve also demonstrated a more gradual dose response curve and found a TD50 around 40 Gy.

With the use of IMRT, it is possible to reduce the dose to the parotid glands without compromising the dose to the PTV's (25). It is generally accepted that measured salivary flow is reduced when the dose to the parotid glands is increased (22). A linear relation between salivary flow and patient reported xerostomia rates has never been shown (26) and until recently it was unknown if IMRT could indeed improve patient rated xerostomia rates.

Radiotherapy of the node positive neck

HNSCC predominantly metastasizes along the lymphatic system to the regional lymph nodes of the neck. The incidence and patterns of lymphatic spread depend on the location and extension of the primary tumor. The status of the neck nodes is a major determinant of outcome in patients with HNSCC. Patients with positive neck nodes show decreased survival rates and experience more regional failures compared to node negative patients. In case of a regional recurrence, salvage surgery in a previously irradiated neck is not always possible, and is associated with significant morbidity and decreased survival (27,28). Therefore, some clinicians perform a planned neck dissection in patients with advanced nodal stages after primary (chemo)radiation. However, in only 30% of these planned neck dissections, residual lymph node

metastases were found (29). Therefore, the identification of prognostic factors for regional recurrence in node positive patients treated with (chemo)radiation could reduce the number of patients undergoing unnecessary planned neck dissections and might give directions for improvement of regional control rates.

Radiotherapy of the node negative neck

Management of the clinically negative neck may place the treating physician in a complex situation. The risk of occult disease must be balanced against morbidity of treatment, which can include either radiation or surgery. General agreement is that so-called elective treatment of the neck is indicated if the risk at occult lymph node metastases exceeds 15 – 20% (30). Furthermore, occult metastases are found in only 25% of elective neck dissections (31). Therefore, elective treatment of the neck will imply overtreatment in the majority of patients, with consequential morbidity. Identifying prognostic factors for regional recurrence and determining regional recurrence rates of the N0 neck in the primary and postoperative setting could tailor the indications of elective radiotherapy of the neck and consequently reduce unnecessary toxicity. In these situations, unilateral or even local irradiation should be considered.

Previous studies showed that radiation-induced troublesome dryness of the mouth (xerostomia) and sticky saliva were significantly worse in patients treated with bilateral neck irradiation compared to unilateral irradiation (32). Possibly, in carefully selected patients the contralateral neck might be omitted from the radiation fields resulting in decreased morbidity with optimal contralateral regional control.

Outline of the thesis

This thesis addresses optimization in radiotherapy of the neck with respect to toxicity and nodal control. The use of IMRT enables us to reduce radiation dose to organs at risk (e.g. parotid glands) compared to older techniques such as 3D-CRT. In **Chapter 2** acute and late toxicity in patients treated with IMRT and 3D-CRT are evaluated with regard to quality of life and RTOG-scored toxicity. 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. **Chapter 3** investigates 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. In **Chapter 4** the outcome and prognostic factors for regional recurrence in elective irradiation of the pN0 and cN0 neck are investigated, to select subgroups of patients who might be safely treated with ipsilateral neck irradiation alone. In **Chapter 5**, recurrence rates of individual pathological lymph nodes in primary irradiated necks are evaluated. With the use of IMRT it became possible to create highly conformal treatment plans with improved coverage of target volumes, **Chapter 6** investigates the outcomes of improved coverage of nodal target volumes in IMRT compared to 3D-CRT and evaluates the effect of suboptimal dose coverage of nodal target volumes.

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