Parotid gland sparing radiotherapy

Pètra Braam

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Parotid gland sparing radiotherapy

Oorspeekselklier sparende radiotherapie

(met een samenvatting in het Nederlands)

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Chapter 1

Introduction and outline

Introduction

Head-and-neck malignancies are relatively rare with approximately 2400 newly diagnosed patients per year in the Netherlands. The incidence of head-and-neck cancer counts for around 4% of the total newly diagnosed malignancies each year (1). Radiotherapy is often part of the treatment as a single therapy or combined with surgery and/or chemotherapy. Depending on the diagnosis and pre-radiotherapy treatment, the primary tumor or postoperative bed, and the lymph nodes in the neck have to be irradiated. The goal of radiotherapy is to eradicate malignant tumor cells, without causing significant damage to the healthy tissue. In head and neck cancer, when the primary tumor and/or lymph nodes are in close proximity to the parotid glands, irradiation of part of the parotid glands is unavoidable. This can cause salivary dysfunction, which results in reduced salivary flow (hyposalivation) (2;3). This is the most prominent side effect of irradiation of head-and-neck malignancies. Patients treated for head-and-neck cancer often complain about a dry mouth (xerostomia), but parotid gland dysfunction also can give alterations in speech and taste, difficulties in mastication and deglutition that can result in secondary nutritional deficiencies (4-7). It also opens the field for fissures and ulcerations, dental caries, infections, and may contribute to a higher risk of osteonecrosis of the mandible, and to oesophageal injury by decreased acid clearance by salivary bicarbonate (8;9).

Salivary gland function measurements

There are two ways of measuring the salivary gland function, subjective and objective. For subjective measurement several head-and-neck cancer specific quality of life (QOL) questionnaires have been conducted and validated (10;11). The European Organization for Research and Treatment of Cancer (EORTC)-C30(+3) questionnaire and the EORTC-H&N35 questionnaire are both well validated and widely used (12-14). The EORTC-C30(+3) is developed for cancer patients participating in clinical trials for reporting broad QOL issues and health related QOL. The EORTC-H&N35 is a supplementary questionnaire module for providing more detailed information relevant for the evaluation of QOL in head-and-neck cancer patients.

The most common methods for objective measurement are sialometry and scintigraphy (15-18). Quantification of the salivary gland function by measuring the saliva drainage is

called sialometry. Objective salivary gland function can be measured by collecting whole salivary flow or collecting flow from individual glands. Whole salivary flow is defined as the product of the major and minor salivary glands. Several methods for whole saliva sialometry are known including draining, spitting and swabbing (19). Whole saliva might include nonsalivary components such as food debris, bacterial products, serum elements and desquamated cells and is therefore not necessarily the sum of individual gland secretions (20). Selective measurement of the major salivary glands can also be performed. Saliva from the parotid gland can be collected by placing a suction cup over the orifice of the Stensons' duct or by intra oral cannulation. For submandibular saliva collection a silicone rubber device that fits into the floor of the mouth has been described (21). A disadvantage of this device is that the sublingual saliva is measured at the same time. Both sublingual and submandibular saliva can also be collected by pipette while collecting parotid saliva using the suction cups (15). The collection itself can be performed while stimulating the glands or unstimulated. Stimulation is defined as promoting secretion by mechanical, gustatory or pharmacological means (22). Stimulation can be obtained by chewing paraffin or by application of citric acid on the subjects' tongue on regular intervals of 30-60 seconds (19). Both stimulated and unstimulated collection can be performed, but unstimulated collection is quite time consuming because the saliva production rate is rather low especially after radiotherapy.

Salivary gland scintigraphy uses ^{99m}Tc-pertechnetate for quantitative imaging. The uptake of ^{99m}Tc-pertechnetate in salivary glands reflects intact salivary gland parenchyma. In this way both the parenchymal function and the excretion function can be quantified simultaneously. Following intravenous injection of ^{99m}Tc-pertechnetate views of the salivary glands are obtained using a gamma camera with high-resolution collimators.

Single photon emission computerized tomography (SPECT), ^{11}C-methionine positron emission tomography (PET), and magnetic resonance imaging (MRI) have also been used to measure salivary function after radiotherapy (23-27) .

The best parameter to assess the parotid gland function after radiotherapy was found to be stimulated flow measurement, when comparing stimulated parotid flow measurement, scintigraphy, and quality of life questionnaire (28). The best definition of objective parotid gland function impairment is a reduction of the stimulated parotid salivary flow <25% of the pre-radiotherapy flow (complication) (28;29). Consequently we used stimulated

parotid flow measurements and the above defined complication for parotid gland function evaluation.

Dose-response relationship

The degree of reduction in parotid salivary flow is directly related to the radiation dose and the parotid gland volume irradiated and is partially reversible (30;31). Dose-volume-response relationships between the parotid salivary flow and the dose received by the parotid glands have been determined using a variety of methods (24;32). Two dose-response curves are available, obtained from relatively large patient groups. Both studies conclude that the mean dose to the parotid gland best predicts its function after radiotherapy (31;33). The model used is proposed by Lyman-Kutcher (34;35). This model establishes quantitatively the effects of both the radiation dose and the volume of the irradiated gland on the probability of radiation-induced dysfunction. Using this model, a steep sigmoid dose-response curve and a dose resulting in 50% probability of a complication for uniform irradiation of the whole organ (TD_{50}) of 28.4Gy at 1-year after treatment was found by Eisbruch et al, and a less steep dose-response curve and a TD_{50} of 39Gy was found by Roesink et al (10;31). Including the corresponding curves at different time points (6 weeks, and 6 months after radiotherapy), a tendency toward recovery of the parotid gland function in time was seen. Improvement in time of salivary flow after radiotherapy has also been shown in other reports with a maximum follow-up of 2 years (10;30;36;37). However, further long-term prospective data on parotid gland function after radiotherapy are lacking. Some studies report a saliva flow reduction even at low dose levels (10;38-40), while others found a threshold dose above which the salivary flow was significantly decreased (33;41). Because of the incongruence of the reports, the mean dose to the parotid gland should be as low as possible.

Target volume delineation

As the parotid glands are in most cases in close proximity to the primary tumor or the lymph nodes, reducing the dose to the parotid glands is difficult. Depending on the diagnosis, pathology result and pre-radiotherapy treatment the lymph nodes in the neck might be part of the target volume. The traditionally used guidelines for nodal irradiation are based on surgical limitations and anatomical boundaries. According to these

experiences the lymph nodes in the neck are defined into different regions (42). Increasing use of 3D treatment planning in head-and-neck radiation created the need for adapted guidelines and much attention has been paid to the development of guidelines not only based on surgical experience but also imaging based (43-50). In 2003 a consensus guideline for delineation of the node levels in the negative neck was launched, relating to anatomic landmarks visible on CT data (45). The question remained whether an anatomic or imaging based guideline is best to use for clinical treatment.

When using three-dimensional conformal radiotherapy or intensity-modulated radiotherapy, more selective irradiation is possible compared with conventional treatment and accurate volume delineation is of great importance. Different target delineation leads undoubtedly to changes in treatment planning and therewith into dose differences. The dose to the parotid gland depends on the extent of the cranial border of the lymph node target volume. Lowering this border consequently results in a reduction of the dose to the parotid glands. In case of elective irradiation, it is still unclear whether the guideline boundaries of the lymph node levels are related to clinical microscopic spread of malignant cells. Investigating the pattern of macroscopic lymph node spread can reveal possible pathways for microscopic spread. Using this knowledge and the possibility of selective irradiation, the elective target volumes might be adjusted, which can result in a reduction of complications like xerostomia.

Radiotherapy treatment planning and delivery

Despite much research, there is still no effective treatment for radiation-induced salivary dysfunction. The best way to improve impaired parotid function is preventing damage caused by irradiation. Two possible strategies to achieve a dose reduction in the parotid gland are improvement in radiotherapy treatment planning and delivery, and refinements in target volume delineation. With the advances in computer technology, radiation treatment planning and delivery have changed extensively in the last decades. Increased conformity of the radiation dose around the tumor and improved normal tissue sparing became within reach.

Conventional radiotherapy (CRT)

CRT depends on two-dimensional (2D) contour information and the calculated doses are based on 2D dose models. Planar radiographs are made for treatment volume prescription, and rectangular fields are used for treatment planning. Additional blocks can be placed to reduce irradiation of normal tissue. Disadvantages using this method are the lack of a 3-dimensional anatomical image of the patient and the lack of possibility to shape the radiation treatment dose. In head-and-neck cancer treatment, for conventional irradiation mostly two opposing lateral fields are used to cover the target volume. The spinal cord is shielded at 40-46Gy after which electron beams are used to irradiate the posterior neck region. Supraclavicular regions can be treated with an anterior field using independent collimators with half-beam blocking (51;52). While using lateral fields depending on the tumor and/or lymph node involvement, only very limited sparing of the parotid gland can be achieved.

Three-dimensional conformal radiotherapy (3D-CRT)

3D-CRT is an advanced form of external beam radiotherapy in which the high-dose treated volume is planned to encompass the 3D target volume, at the same time minimizing the dose to the surrounding organs at risk (53). This technique requires 3D treatment planning and the advances in computer hardware have made the progress of radiation techniques possible. The radiation delivery is accomplished by fixed beams, which are shaped using the projection of the target volume. The radiation beams have a uniform intensity across the field and wedges or compensating filters modify the intensity.

Intensity-modulated radiotherapy (IMRT)

The Intensity Modulated Radiation Therapy Collaborative Working group defined IMRT in 2001 as “an advanced form of 3D-CRT that uses non-uniform radiation beam intensities incident on the patient that have been determined using various computer-based optimization techniques” (53). The main difference with 3D-CRT is that IMRT uses non-uniform intensities; it is more complex than conventional radiotherapy. It has the potential to selectively irradiate concave and irregular target volumes and offers better normal tissue sparing than other techniques, especially for volumes with irregular shapes

(43;54-56). An IMRT delivery system uses conventional multi leave collimators (MLC) with which the beam intensity is modulated either by superimposing a number of static uniform intensity segments (static step and shoot delivery) (57;58), or by a shaped sliding window that passes across the field during the treatment (dynamic delivery) (53;59;60).

Different IMRT delivery techniques can be used (53). Conventional MLC IMRT uses a series of multiple segment fields and each field consists of a series of MLC shapes delivered from the same gantry angle. The multiple segment fields are set up at selected gantry orientations and is computer controlled. There is only radiation when the MLC leaves have stopped. This method is called step-and-shoot. This type of IMRT is also called segmental MLC or SMLC.

Head and neck IMRT is work intensive and lengthens treatment time. Some criteria can be given when IMRT might be superior: irregular target volume; narrow margins around the volume of interest for critical structure protection; previous irradiation; or when other techniques are insufficient to produce an acceptable dose distribution (30;61). In case of head-and-neck cancer irradiation, many of the criteria may be present, especially in case of oropharyngeal cancer. As in oropharyngeal cancer theoretically most parotid gland sparing can be achieved, these tumors were selected in our institute when implementing IMRT for head-and-neck cancer irradiation. The clinical use of IMRT has only been implemented in a few centres around the world when starting this thesis, and was in its beginning phase although rapidly evolving. Planning studies showed a theoretical advantage for IMRT in case of parotid sparing radiotherapy in oropharyngeal cancer, and only a few clinical studies involving IMRT have been published so far with a limited number of patients (33;62-65). No comparative data concerning objective improvement of the salivary function have been reported.

Outline of the thesis

Irradiation of the parotid glands causes salivary dysfunction resulting in reduced salivary flow. Improvement of the parotid salivary function after radiotherapy can be seen in time, however long-term prospective data are lacking. In **chapter 2** we present the results of long-term analysis of the parotid salivary function. The long-term changes in time of quality of life and the relation with parotid salivary function are described in **chapter 3**.

The degree of parotid salivary flow reduction is directly related to the dose to the parotid gland. As the parotid glands are in close proximity of the cervical lymph nodes, irradiation of (part of) the parotid gland cannot be avoided. Lowering the cranial border of the nodal target volume might reduce the dose to the parotid gland and therewith diminish the complication rate. In **chapter 4** we investigated the position of the most cranial cervical metastatic lymph node in oropharyngeal and hypopharyngeal cancer. This was done to specify the cranial border of the nodal target volume. The question remained whether there is a difference in location of the most cranial metastatic lymph node between different tumor-sites. The consensus guideline for nodal target volume delineation is not tumor-site specific and adjustment might be needed. In **chapter 5** we present the results of the position of the most cranial metastatic lymph node in laryngeal cancer and implications for field optimization are given.

IMRT offers theoretical advantages for reducing the dose to the parotid gland. As IMRT is just recently implemented in clinical setting, clinical data regarding parotid gland-sparing treatment are scarce. No comparative clinical data describing improved objective parotid salivary output have been reported. The value of IMRT for parotid salivary output preservation compared with conventional radiotherapy is presented in **chapter 6**. The question whether preserved salivary output using IMRT results in improved subjective xerostomia is addressed in **chapter 7**.

A general discussion is provided in **chapter 8**.

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Chapter 2

Long-term parotid gland function after radiotherapy

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Abstract

Purpose: Irradiation of the parotid glands causes salivary dysfunction, resulting in reduced salivary flow. Recovery can be seen with time; however, long-term prospective data are lacking. The objective of this study was to analyze the long-term parotid gland function after irradiation for head-and-neck cancer.

Methods and materials: A total of 52 patients with head-and-neck cancer and treated with radiotherapy (RT) were prospectively evaluated. Stimulated bilateral parotid salivary flow rates were measured before RT and 6 weeks, 6 months, 12 months, and at least 3.5 years after RT completion. A complication was defined as a stimulated parotid flow rate of <25% of the pre-RT flow rate. The normal tissue complication probability model proposed by Lyman was fit to the data. Multilevel techniques were used to model the patterns of flow rates with time.

Results: The mean stimulated flow rate of the parotid glands before RT was 0.31 mL/min (standard deviation (SD), 0.21). This was reduced to 0.14 mL/min (SD, 0.15) at 6 weeks after RT and recovered to 0.20 mL/min (SD, 0.22) at 6 months and 0.19 mL/min (SD, 0.21) at 12 months after RT. The mean stimulated flow rate was 0.25 mL/min (SD, 0.28) 5 years after RT. The mean dose to the parotid gland resulting in a 50% complication probability increased from 34 Gy at 6 weeks to 40 Gy at 6 months, 42 Gy at 12 months, to 46 Gy at 5 years after RT. Multilevel modelling indicated that both dose and time were significantly associated with the flow ratio.

Conclusions: Salivary output can still recover many years after RT. At 5 years after RT, we found an increase of the salivary flow rate of approximately 32% compared with at 12 months after RT.

Introduction

Radiotherapy (RT) for head-and-neck cancer can cause salivary dysfunction, which results in reduced salivary flow and diminished quality of life. The degree of reduction in the salivary flow is directly related to the radiation dose to the parotid glands and is partially reversible. We previously showed a correlation between the post-RT flow ratio and the dose to the parotid gland (1).

Little is known about the changes of parotid gland function with time. Most of the long-term survivors of head-and-neck malignancies who were treated with RT have a moderate or severe degree of xerostomia (2). Improvement in salivary production with time after parotid-sparing RT has been shown, with a maximal follow-up of 2 years (3, 4). The results of a larger group of patients accrued during the first 12 months of this study have been previously reported (1). Recovery of parotid gland function was shown at 6 months and 1 year after RT. In this article, we report the long-term results. To our knowledge, this represents the only prospective study of long-term parotid gland function in patients treated with RT for head-and-neck cancer.

Methods and materials

Patients and RT planning

A total of 108 patients with various malignancies of the head and neck were treated with primary or postoperative RT and were eligible for the study. None had previously received RT or chemotherapy, had other malignancies or diseases of the parotid gland, or had used medication that was known to affect the parotid glands. Patients with evidence of bilateral neck lymph node involvement or distant metastatic disease were not included, nor were patients with a World Health Organization status >1. At a minimal follow-up of 3.5 years, 27 patients had died, 6 were too ill to participate, 7 refused participation, 7 had had only one measurement taken, and 9 patients had been lost to follow-up. Thus, the study included 52 patients who had survived, called the survivors. The 27 patients eligible for the study who had died were called the nonsurvivors. This distinction between the above-defined survivors and nonsurvivors was made for analysis**.**The mean follow-up time was 57 months (range, 44-72 months). Patient and tumor characteristics are provided in Table 1.

All patients had been treated at the Department of Radiotherapy of the University Medical Center of Utrecht. Opposing lateral fields were used for target volume coverage, and an anterior field was used for the supraclavicular regions. Electron beams were used to boost the posterior neck region after shielding the spinal cord at 40-46 Gy. The radiation dose varied with the diagnosis, according to generally accepted treatment strategies. The median dose delivered to the primary targets was 66 Gy (range, 40.0 – 70.0). Fourteen patients received accelerated RT. During treatment, patients were positioned supine in customized facial immobilization masks. Contrast-enhanced CT imaging was performed in treatment position with the patient immobilized with the mask. Both the parotid glands were outlined on multiple axial CT slices from each patient. Most of the treatment fields were set up using radiographs. Reconstruction of the treatment fields was done on the CT slices. The other treatment fields were designed using CT data. Three-dimensional treatment planning was performed using PLATO RTS (Nucletron, Veenendaal, The Netherlands), and dose distributions were calculated. This information was condensed into dose-volume histograms (DVHs). Separate DVHs were generated for the right and left parotid glands. The mean dose to the left parotid gland and the mean dose to the right parotid gland were analyzed separately. All patients gave written informed consent before entering the study.

Saliva collection

The parotid salivary flow rates were measured before the start of RT and 6 weeks, 6 months, 12 months, and at least 3.5 years after RT completion. Stimulated parotid saliva was collected for 10 min separately from the left and right parotid glands using Lashley cups, which were placed over the orifice of the parotid duct. Applying three drops of a 5% acid solution to the mobile part of the tongue every 30 s stimulated salivary flow. After finishing the collection, the amount of the saliva was measured in the tubes by weight. It was assumed that the density of the parotid saliva was 1.0 g/mL. The flow rate was expressed for each gland in milliliters per minute. Patients were not allowed to eat or drink for a minimum of 60 min before saliva collection. Because of practical limitations, the saliva flow could not always be measured at the same time during the day, but most of the measurements were taken around 12 PM.

Table 1. Patient and tumor characteristics (*n* = 52)

Gender (*n*)	
Male	40
Female	12
Age (y)	
Mean	56
Range	24-78
Follow-up time (mo)	
Mean	57
Range	44-72
Tumor site (*n*)	
Larynx	24
Floor of mouth/oral cavity	7
Oropharynx	6
Nose (nasal cavity)	4
Hypopharynx	1
Nasopharynx	1
Other	9
Preradiotherapy surgery (*n*)	
Local	8
Local + regional	11
No	33
T stage* (*n*)	
T1	9
T2	19
T3	8
T4	6
Not applicable	10
N stage* (*n*)	
N0	36
N1	5
N2b	1
Not applicable	10

* TNM staging system, 1997.

Normal tissue complication probability model

The flow data were fit to the normal tissue complication probability (NTCP) model proposed by Lyman. The method has been previously described in more detail (1, 5-7). It establishes quantitatively the effects of both the radiation dose and the volume of the irradiated gland on the probability of radiation-induced parotid gland dysfunction. The NCTP parameter TD_{50} represents the dose to the whole organ resulting in a complication probability of 50%. A complication was defined as stimulated parotid flow rate < 25% of the pre-RT flow rate, according to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer Late Effects Consensus Conference (8). The value of the volume-dependent parameter n was fixed at 1 to represent the effective parotid gland dose by the mean dose. Because of the small

number of patients, we added 100 artificial zero-dose DVHs to each series of flow measurements. This was the lowest number for which the resulting NTCP at 5 years after RT was smaller than an arbitrary level of 5% for zero dose (6). The TD_{50} values using the data without artificial zero-dose DVHs are also given.

Statistical analysis

To control for interpatient differences in parotid flow rates, the parotid flow measurements at each visit were converted into the percentage of baseline flow rates. The measurements from the left and right parotid gland were analyzed separately. We first analyzed the relation between the flow ratio and the mean parotid dose for each individual gland. A decrease of both the flow ratio and the scatter of data were seen with increasing doses. The data were logarithmically transformed to create stabilization in the scatter. Regression analysis was performed for comparison between the long-term survivors and the nonsurvivors. Multilevel techniques, including both fixed and random effects, were used to model the patterns of flow rates with time (9). Multilevel analysis of repeated measures data is, in particular, very useful when data are not gathered at exactly the same points and when data points are missing. It does not make specific requirements for the time points to be equally spaced. By introducing random effects, each individual could have their own slope and intercept when regressing the flow rates on time. For both time and dose, first and second order terms were included in the model. The statistical significance of each parameter was tested with a Wald test. A criterion of $p<0.05$ was accepted for significance in all statistical tests.

Results

Pattern of flow with time

The mean stimulated flow rate of the parotid glands before RT was 0.31 mL/min (standard deviation [SD], 0.21). Six weeks after RT completion, the mean stimulated parotid flow rate was 0.14 mL/min (SD, 0.15) and increased with time to 0.19 mL/min (SD, 0.21) at 12 months. With a mean follow-up of 57 months (range, 44 – 72 months), the 5-year mean stimulated flow rate was 0.25 mL/min (SD, 0.28). Figure 1 shows the parotid flow rates expressed as the percentage of the pre-RT flow rates (flow ratio) as a function of the mean parotid gland dose. Six weeks after RT completion, the median flow

ratio was 43% of baseline. The median flow ratio showed an increase with time and was 77% of baseline at 5 years after RT completion (Table 2). This suggests functional recovery of parotid saliva production with time. Examination of the relationship between the flow ratio and time through multilevel modeling indicated that both dose and time were significantly associated with the flow ratio (Table 3). Figure 2 shows the predicted curves for each patient. Approximately two-thirds of the patients showed an increase of the flow ratio with time.

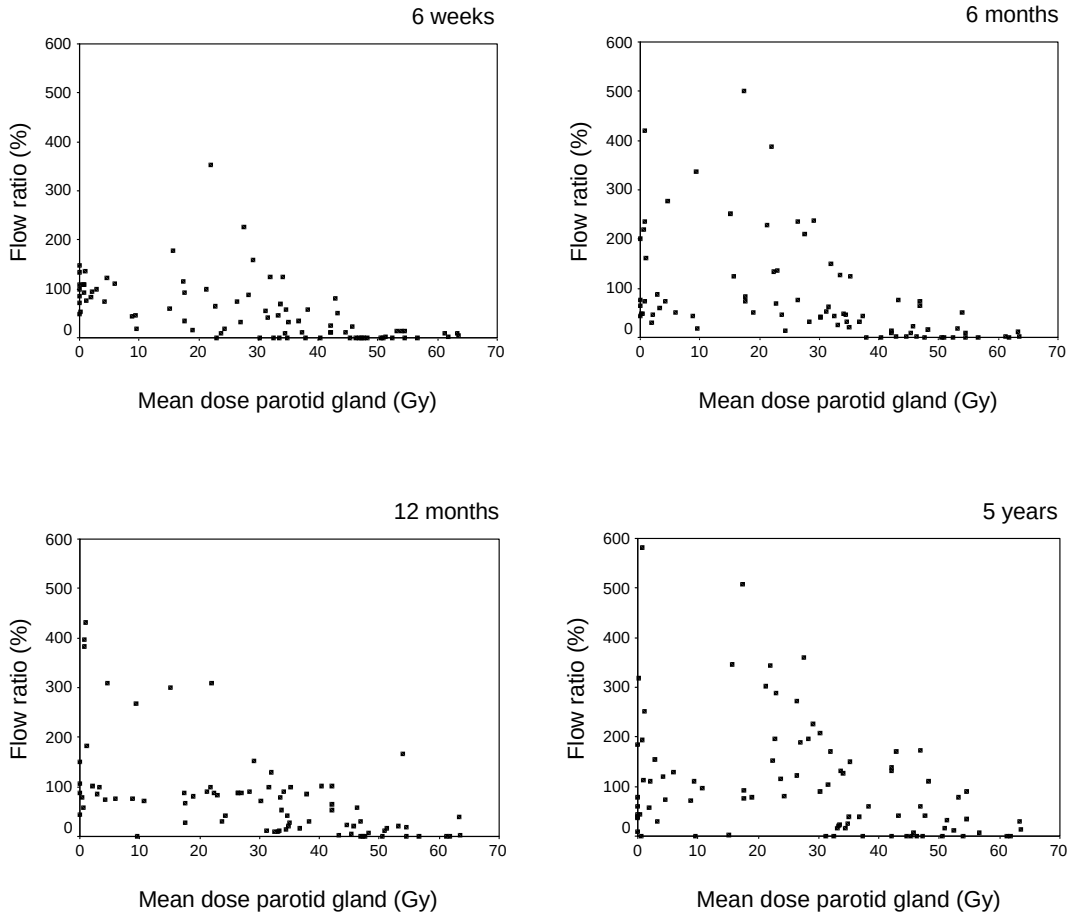

Figure 1. Stimulated parotid flow rates as a function of mean parotid gland dose at varying points after radiotherapy (RT) completion. Flow rates expressed as percentage of pre-RT flow rates for each parotid gland.

Table 2. Median (25th and 75th percentiles) stimulated salivary flow rates expressed as percentage of preradiotherapy flow rate at 6 weeks, 6 months, 12 months, and 5 years after radiotherapy (n = 52)

Time	Median	25^{th} percentile	75^{th} percentile	Glands (n)
6 wk	43	6	92	83
6 mo	48	14	115	79
12 mo	67	15	95	80
5 y	77	16	155	88

Table 3. Flow ratio modeled on dose and time [$\ln(R) = \beta_0 + \beta_1 D + \beta_2 D^2 + \beta_3 T + \beta_4 T^2$]

	Parameter	Estimate	Standard error	p
Mean	β_0	4.3	0.2	<0.005
	β_1	$0.4 \cdot 10^{-6}$	$1.7 \cdot 10^{-6}$	0.79
	β_2	$-1.0 \cdot 10^{-7}$	$1.0 \cdot 10^{-8}$	<0.005
	β_3	$1.2 \cdot 10^{-2}$	$0.4 \cdot 10^{-2}$	<0.005
	β_4	$-4.1 \cdot 10^{-5}$	$1.5 \cdot 10^{-5}$	<0.005
Variance	β_0	0.7	0.17	<0.005
	β_3	$2.6 \cdot 10^{-5}$	$0.77 \cdot 10^{-5}$	<0.005

Abbreviations: R = flow rate expressed as percentage of preradiotherapy flow rate; D = mean dose to the parotid gland (in Gray); T = time after finishing radiotherapy (in weeks)

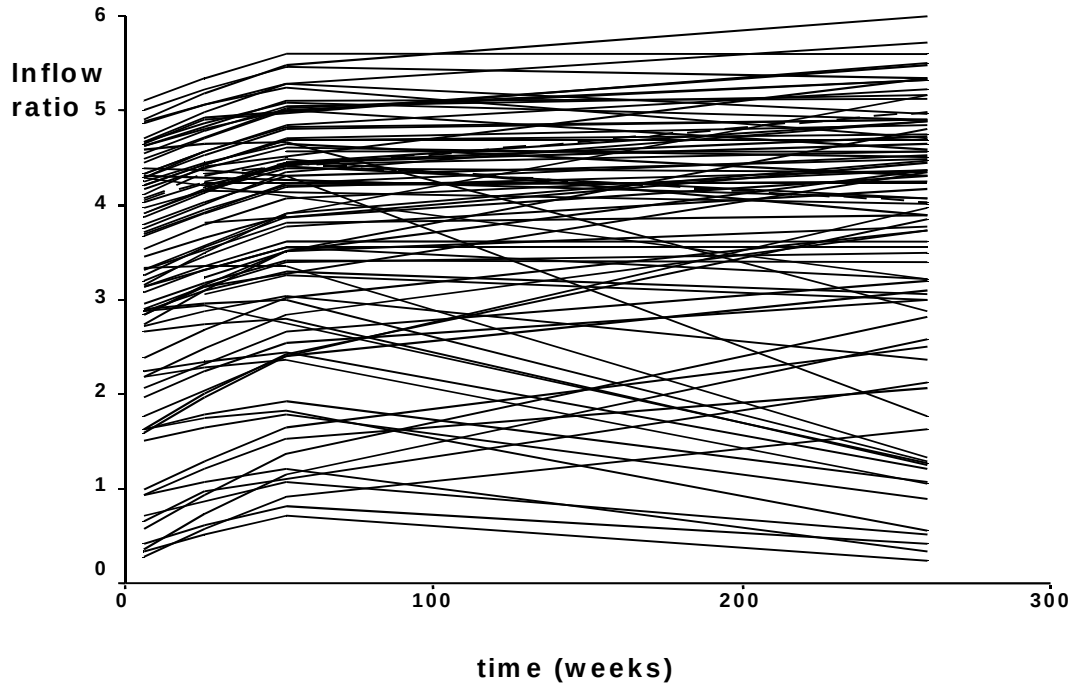

Figure 2. Predicted curves of stimulated parotid flow rates after radiotherapy (RT) completion. Flow rates expressed as percentage of pre-RT flow rates, logarithmically transformed and shown for each individual patient.

Table 4. Parameters estimated from dose distribution and parotid flow data at different points after the completion of radiotherapy

Time	TD_{50} (Gy)	95%CI	m	95%CI
6 weeks	34	30-40	0.37	0.28-0.50
6 months	40	35-46	0.33	0.25-0.46
12 months	42	37-50	0.37	0.28-0.51
5 years	46	39-60	0.53	0.44-0.69

Abbreviations: TD_{50} = dose resulting in 50% probability of complication for uniform irradiation of the whole organ; 95%CI = 95% confidence interval; *m* = slope of dose-response curve.

Survivors vs. nonsurvivors

The study population consisted of 52 survivors derived from a larger group of patients. By making this selection in patient population, we might have introduced a bias. It is possible that the nonsurvivors had had less favorable tumor characteristics and/or a less favorable prognosis than the survivors. Contrary to our expectations, only small differences in patient characteristics, tumor site, T stage, or N stage were found, and these were not statistically significant. It should be noted that the number of patients in each group was small (52 vs. 27) with a broad range in characteristics. The median dose delivered to the primary target was 66 Gy and 60 Gy to the survivors and the nonsurvivors, respectively. The survivors received a mean parotid dose of 29 Gy at both sides and the nonsurvivors received a mean parotid dose of 45 Gy at both sides. Between the two groups, we also compared the flow ratio as a function of the mean parotid dose at 6 weeks, 6 months, and 12 months using regression analysis. This analysis showed a significant difference, in favor of the survivors at 6 weeks ($p = 0.018$) and at 6 months ($p = 0.018$), but this difference was not found at 12 months ($p = 0.182$). Thus, the patients who did survive had a greater parotid flow ratio at 6 weeks and 6 months than the patients who did not survive, but this difference diminished with time.

NTCP model parameters

The NTCP parameter TD_{50} increased from 34 Gy at 6 weeks to 46 Gy at 5 years (Table 4). The corresponding dose-response curves (Fig. 3) showed a tendency toward recovery of the parotid gland function with time. The TD_{50} was 34, 40, 42, and 49 Gy at 6 weeks, 6 months, 12 months, and 5 years, respectively, without adding artificial zero-dose DVHs. However, the small number of patients should be noted.

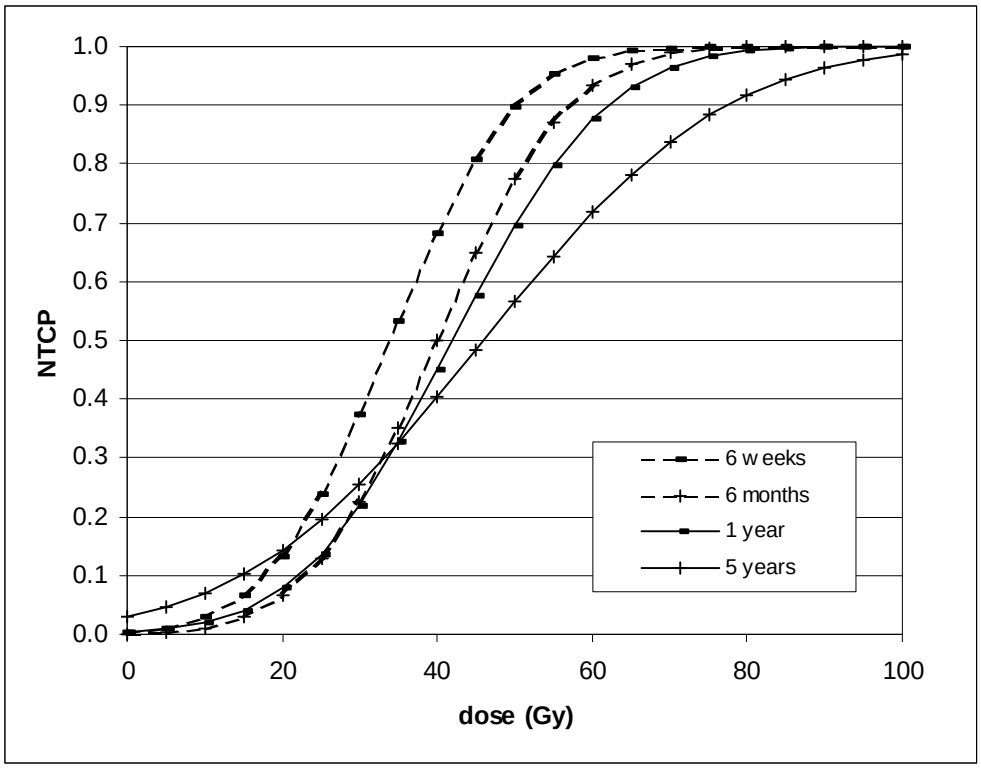

Figure 3. Normal tissue complication probability (NTCP) curves as function of reference dose calculated after fitting of data to NTCP model proposed by Lyman. Complication defined as stimulated parotid flow rate <25% of the preradiotherapy rate. Reference volume was whole organ.

Discussion

This study describes the pattern of parotid salivary flow with time in a group of patients with head-and-neck cancer treated with RT who had a minimal follow-up of 3.5 years. For most patients, the flow rate improved with time. This indicates the possibility of partial recovery of parotid gland function with time, not only the first few months after RT, but also continuing after 1 year. This could also be observed from the TD_{50} values obtained from fitting the Lyman model. At 6 weeks, 6 months, and 12 months after RT, the TD_{50} value was 34, 40, and 42 Gy, respectively. At 5 years after RT, the TD_{50} value was 46 Gy. In earlier published data, of which this patient group is a subset, a dose dependency of the salivary function and a recovery with time until 12 months after RT was found. This is in accordance with other data. Henson *et al*. found an immediate diminishing of the salivary output after RT, with progressive recovery until baseline

values at 1 year of follow-up. However, parotid glands that received a mean radiation dose of 55.0 Gy (SD, 8.5) had a flow rate around 0 at 1 year of follow-up (10). Franzen *et al*. reported a recovery of secretion up to 18 months after RT, with the whole parotid glands included in the radiation field and receiving doses <52 Gy. In most glands with doses >64 Gy, an irreversible depressed parotid function was found (3). Kaneko *et al.* evaluated the salivary function using scintigraphy in 25 patients in whom the parotid glands had been bilaterally and totally included in the radiation volume. The TD_{50} was <33 Gy during the first 6 months and 52.5 Gy after 12 months (11).

Figure 1 shows, in addition to a large scatter in salivary flow rates, a recovery of the flow, even at doses to the parotid gland >50 Gy. Eisbruch et al. showed the presence of a mean dose threshold for stimulated and unstimulated flow rates. In their study, a threshold for stimulated output was found at 26 Gy at 1, 3, and 6 months and 25 Gy at 12 months (8). This feature was not seen in our study and is in accordance with the data reported earlier for the total group of patients (1). Our study demonstrates that a reduction in flow also occurs at low dose levels in accordance with other studies (4, 12-14).

Little is known about the long-term changes in parotid salivary flow. One problem is the difficulty in data collection. Often observations are missing because of illness, study withdrawal, or death. In this study, only 52 (48%) of 108 patients were able and willing to participate and had data to be analyzed. In this study with repeated measurements, it was not possible to achieve the same time points because of practical problems. Because many patients had to travel, we tried to combine the flow measurement with another appointment of the patient in the hospital to achieve the greatest compliance. A considerable variation in the range of stimulated parotid salivary flow rates was found. This is in general agreement with previous reports (15, 16) and also has been demonstrated in healthy individuals. In the latter, variations exceeded up to 40% (17-19). Because of these individual differences, we used multilevel techniques for analysis. They allow great flexibility for modelling individual patterns of change with time and can accommodate data in which the number and timing may vary among patients.

We used the NTCP model developed by Kutcher and Lyman (5, 7, 20). In the previously described study with results to 1 year of follow-up, we found a large volume dependency of n = 1. That assumed a high volume dependence of the parotid salivary flow. Because the present study was of a subset of those patients, we fixated n at 1. It should be

emphasized that a complication was defined as stimulated parotid flow rate < 25% of the pre-RT flow rate, according to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer Late Effects Consensus Conference (8).

Analysis of the flow ratio as a function of the mean parotid dose between the survivors and the nonsurvivors showed a significantly greater parotid flow ratio in favor of the survivors after RT, with a diminishing of this difference over time. At 12 months after RT, no significant difference was found. One explanation could be that a relatively large number of patients with a low flow ratio died between 6 and 12 months follow-up. Patients with a high TNM stage are often treated with large radiation fields and receive high doses, inevitably with the parotid glands in field. As a result, they have low parotid salivary gland function. Because of the small group and the population bias in this present study, we only analyzed the group of surviving patients, knowing that this is a favorable group and not representative of an average population.

Because the consequences of radiation-induced parotid gland injury are still difficult to manage, a lot of effort has been done by different institutions to improve parotid-sparing RT. Accurate and better definition of the areas of the neck to be treated and selective radiation by IMRT are important methods of reducing the dose to the parotid gland without compromising the tumor dose, and thereby, hopefully, diminishing complications such as salivary gland dysfunction. The various TD_{50} values reported in our study were all less than the general prescribed dose of 46-50 Gy for the clinically negative neck at risk for microscopic disease.

Conclusions

Parotid gland function can continue to recover for years after RT. We found an improvement of the salivary flow rate of approximately 32% at 5 years compared with 12 months after RT completion, with TD_{50} values of 34, 40, 42 and 46 Gy at 6 weeks, 6 months, 12 months, and 5 years after RT.

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Chapter 3

Quality of life and salivary output in patients with head-and-neck cancer five years after radiotherapy

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Abstract

Purpose: To describe long-term changes in time of quality of life (QOL) and the relation with parotid salivary output in patients with head-and-neck cancer treated with radiotherapy.

Methods and materials: Forty-four patients completed the EORTC-QLQ-C30(+3) and the EORTC-QLQ-H&N35 questionnaires before treatment, 6 weeks, 6 months, 12 months, and at least 3.5 years after treatment. At the same time points, stimulated bilateral parotid flow rates were measured.

Results: There was a deterioration of most QOL items after radiotherapy compared with baseline, with gradual improvement during 5 years follow-up. The specific xerostomia-related items showed improvement in time, but did not return to baseline. Global QOL did not alter significantly in time, although 41% of patients complained of moderate or severe xerostomia at 5 years follow-up. Five years after radiotherapy the mean cumulated parotid flow ratio returned to baseline but 20% of patients had a flow ratio <25%. The change in time of xerostomia was significantly related with the change in flow ratio ($p=0.01$).

Conclusions: Most of the xerostomia-related QOL scores improved in time after radiotherapy without altering the global QOL, which remained high. The recovery of the dry mouth feeling was significantly correlated with the recovery in parotid flow ratio.

Introduction

Patients with head-and-neck cancer have to cope with many aspects of their life-threatening disease. They have to deal with the diagnosis and the treatment as well as with the impact on physical, psychological and social functioning. Radiotherapy (RT) is a treatment modality, sometimes combined with surgery that can give considerable acute and long-term side effects to the oral cavity. One of the effects is a dry mouth (xerostomia), due to irradiation of the salivary glands. Furthermore, chewing and swallowing difficulties, impaired taste or an increased incidence of dental caries or oral candidiasis can occur (1,2).

Quality of life (QOL) questionnaires have been utilized for several years in the follow-up of patients with head-and-neck cancer, and impaired QOL has been reported until years after RT (3,4). Up to 12 months after RT the xerostomia-related QOL scores follow the general pattern of salivary flow rates (5,6). The long-term relationship between the individual's perception of a dry mouth, the QOL and the objective parotid salivary output however, has not been determined.

We performed a prospective study in patients with head-and-neck cancer receiving RT. The first aim of the study was to assess the long-term change in time of the QOL. The second aim was to investigate the relationship between change in time of the subjective outcome and the objective parotid flow measurements. We also analyzed the relationship between the change in time of the subjective outcome and the mean parotid dose (D_{par}), and the mean submandibular dose (D_{subm}). Earlier we presented the short-term and long-term parotid flow data of this study group (7,8). In this paper, we present results after a minimum follow-up of 3.5 years.

Methods and materials

Patients

From July 1996 till October 1998, patients with head-and-neck cancer that received primary or postoperative RT with curative intent were included in the study. Other inclusion criteria were no previous RT or surgery of the parotid glands, no history of suffering from malignancies or other diseases of the parotid glands and WHO 0-1. Patients with evidence of (p)N2c-N3 (TNM staging system 1997) or distant metastases, were excluded. All patients treated with induction or concomitant chemotherapy were

excluded, because this might influence the parotid function (9). No patient used medication known to affect the function of the salivary glands.

One hundred and eight patients met the inclusion criteria. At minimum follow-up of 3.5 years (hereafter referred to as 5-years follow-up), 27 died, 6 were too ill to participate, 3 had surgery for recurrence, 7 refused participation, 12 had incomplete data and 9 were lost to follow-up. This resulted in 44 patients who were able to fill in the questionnaire and could be assessed (Table 1). Only data received from these 44 patients were analyzed. Patients were treated predominantly with 6-MV X-rays from a linear accelerator using parallel-opposed lateral beams. The irradiation varied with the diagnosis, according to generally accepted treatment strategies. The mean dose prescribed to the primary target was 61.1 Gy, ranging from 40 to 70 Gy. The right D_{par} was 28.3 Gy (range 1-62 Gy) and the left D_{par} was 27.9 Gy (range 0–62 Gy). The right D_{subm} was 39.9 Gy (range 1-71 Gy) and the left D_{subm} was 41.0 Gy (range 0-70 Gy). The distribution of the mean doses of the different glands is presented in Fig. 1. Due to the different tumor sites with 43% laryngeal cancer, these relatively low doses to the parotid glands were obtained.

Questionnaire

Patients completed a questionnaire before treatment and 6 weeks, 6 months, 12 months, and at least 3.5 years (mean 56 months, range 44-72 months) after treatment. The questionnaire consisted of the EORTC QLQ-C30(+3) and QLQ-H&N35.

The EORTC QLQ-C30 is a widely used questionnaire and contains QOL issues relevant to a broad range of cancer patients. It includes five functional scales, three symptom scales, a global QOL scale and six single items (10). Version 30(+3) contains two additional items on role functioning and one additional item on overall health. The EORTC QLQ-C30(+3) is meant to be used in conjunction with a tumor specific module. The EORTC QLQ-H&N35 is a module used for the assessment of health-related QOL in patients with head-and-neck cancer (11). It contains seven symptom scales and six symptom items. It is designed to be used together with the core QLQ-C30 and has been validated in 622 head-and-neck cancer patients from 12 countries (12).

After transformation all items and scales range in score from 0 to 100. High scores for a functional or global QOL scale represent good functioning, or a high QOL, whereas a

Table 1. Patient and tumor characteristics (*n* = 44)

Mean age (*y*, range)	56	24-78
Gender (*n*)		
Female	10	23%
Male	34	77%
Mean follow-up time (*months,* range) since end of radiotherapy	56	44-72
Tumor site (*n*)		
Larynx	19	43%
Floor of mouth/oral cavity	7	16%
Oropharynx	4	9%
Nose (nasal cavity)	4	9%
Hypopharynx	1	2%
Nasopharynx	1	2%
Other	8	18%
Preradiotherapy surgery (*n*)		
Local	6	14%
Local + regional	11	25%
No	27	61%
Stage* (*n*)		
T1	7	22%
T2	16	50%
T3	5	16%
T4	4	12%
Not applicable	12	
N stage* (*n*)		
N0	27	84%
N1	4	13%
N2b	1	3%
Not applicable	12	

* TNM staging system, 1997.

high score for a symptom scale or single item represents a high level of symptomatology or problems (10).

Saliva collection

Parotid flow rates were measured at the same time points as the QOL measurements. No oral stimulus was permitted for 60 min before saliva collection. Stimulated parotid saliva was simultaneously collected separately from left and right parotid gland using Lashley cups. These cups were placed over the orifice of the Stenson's duct. Stimulation was achieved by applying three drops of a 5% acid solution to the mobile part of the tongue every 30 seconds and collection was carried out for 10 min. The volume of the saliva was measured in tubes by weight. It was assumed that the density of the parotid saliva was 1g/ml. The flow rate was expressed for each separate gland in milliliters per minute (ml/min). The left and right parotid flow rates were added together and converted

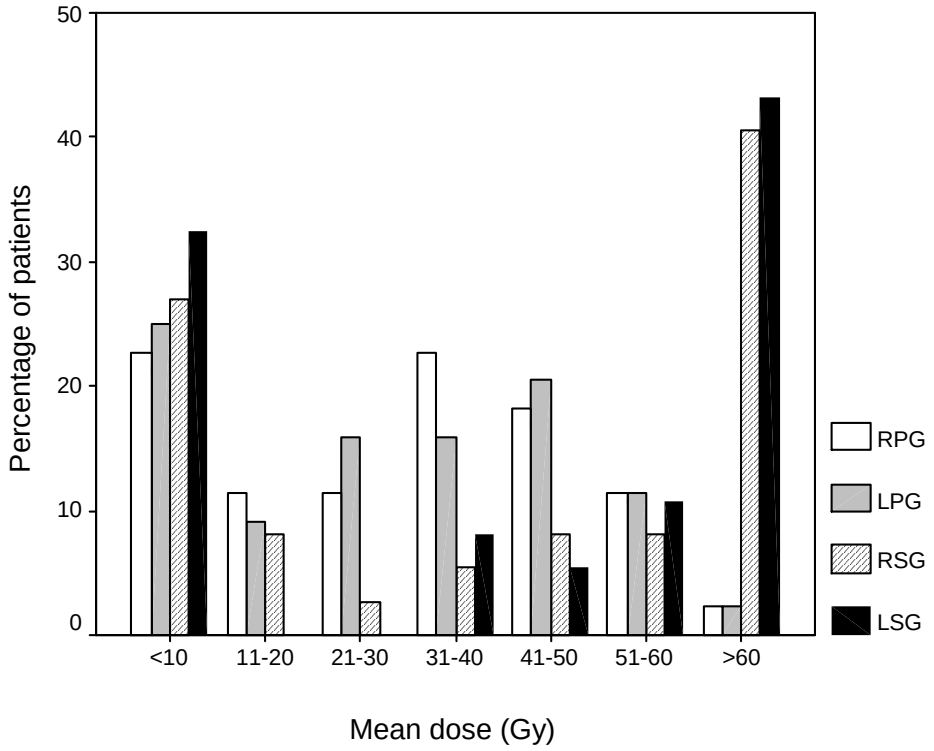

Figure 1. Distribution of the mean dose (Gy) of the different glands presented as the percentage of patients. *Abbreviations*: RPG = right parotid gland; LPG = left parotid gland; RSG = right submandibular gland; LSG = left submandibular gland.

into the percentage of baseline flow rates (flow ratio). A complication was defined as cumulated stimulated parotid flow rate of <25% of the pre-RT flow rate.

Statistics

The data of all items and scales of the EORTC QLQ-C30(+3) and the EORTC QLQ-H&N35 were transformed to a 0-100 scale for presentation according to the guidelines of the EORTC (Table 2, Fig. 2, Fig. 3). For the analysis we decided to use the non-transformed data, because of the discrete and ordinal characteristics of the response. Missing data were excluded from analyses. Mixed effects ordinal regression techniques were used to account for dependency between observations in time and to examine relationships between the response of interest and possible explanatory variables time, D_{par}, D_{subm} and parotid flow ratio. Dr Hedekers software package Mixor was used to obtain estimates of the model parameters.

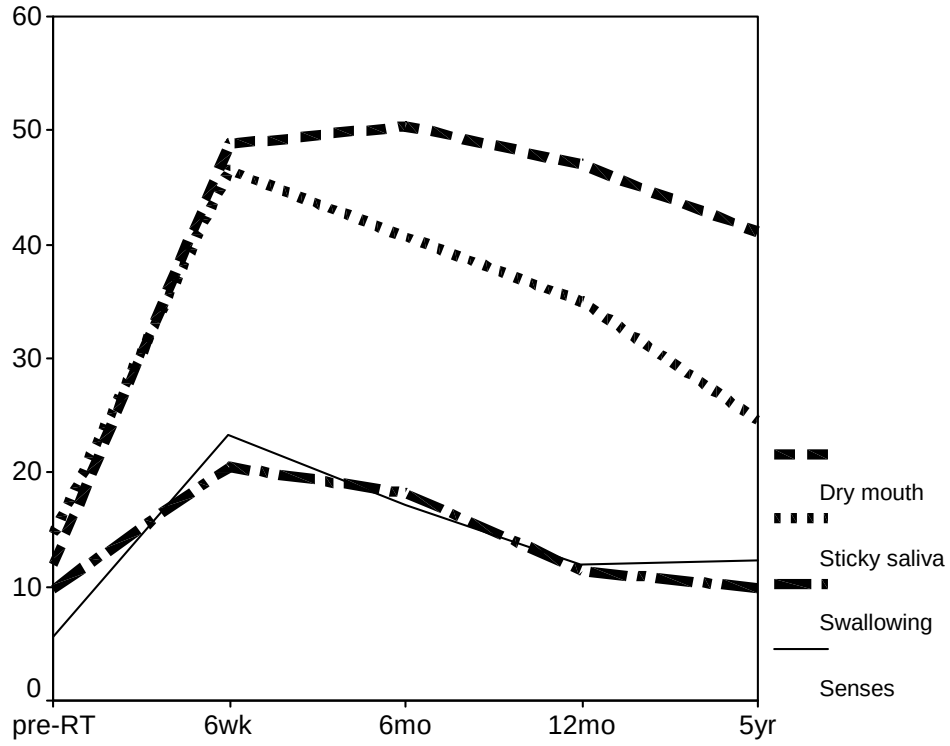

Figure 2. Mean scores over time of the single items dry mouth, sticky saliva, swallowing and senses (QOL-H&N35). High scores imply a high level of symptoms.

Results

QOL

A deterioration of almost all scales and items in QLQ-H&N35 was noted after RT and generally no effect was seen in the QLQ-C30(+3) questionnaire (Table 2). Most items improved in time but not all reached baseline values (Fig. 2). The specific xerostomia related items dry mouth and sticky saliva showed deterioration 6 weeks after RT, which continued for dry mouth till 6 months. Thereafter both items showed an improvement but at 5 years after RT their values remained higher than baseline. We investigated the relation between the change in time of the various parameters starting after RT and not the relation at specific time points. At 12 months follow-up, 49% of the patients complained of a moderate or severe dry mouth, which slightly improved to 41% of the patients at 5 years. The functional scales of the QLQ-C30(+3) showed no significant alteration after RT. The mean scores before RT were already relatively high and showed

Table 2. Mean scores of the scales and single items of questionnaire for patients with cancer of the head-and-neck treated with radiotherapy with or without surgery. A significant outcome presents a significant change in time towards improvements starting 6 weeks after radiotherapy.

	pre-RT	6 weeks	6 mo	12 mo	5 years	Significance
EORTC QLQ-C30(+3)						
Functioning scales*						
Cognitive	90.1	88.0	88.6	90.2	87.3	NS
Emotional	75.8	83.5	83.2	85.5	83.7	NS
Physical	80.6	85.0	85.0	87.0	85.1	NS
Role	75.8	83.5	83.2	85.5	83.7	NS
Social	86.9	88.8	89.4	93.6	87.8	NS
Global QOL*	71.6	73.3	80.1	81.6	80.6	NS
Symptom scales†						
Fatique	24.3	30.5	26.8	23.4	27.5	p<0.01
Pain	14.3	11.6	15.0	8.6	12.0	NS
Nausea and vomiting	3.6	7.4	1.2	2.2	0.8	p<0.01
Single items†						
Dyspnoea	16.7	13.2	18.7	15.4	14.3	NS
Insomnia	24.6	25.6	21.1	17.0	15.5	p<0.01
Appetite loss	7.9	14.0	8.9	7.7	10.1	p<0.05
Constipation	3.2	10.1	5.7	7.7	7.0	NS
Diarrhoea	1.6	2.3	1.6	6.0	0.0	NS
Financial problems	5.6	5.4	4.1	5.1	5.7	NS
EORTC QLQ-H&N35						
Symptom scales-single items†						
Pain	10.6	19.4	19.1	15.5	9.5	p<0.01
Swallowing	9.8	20.5	18.2	11.4	9.9	p<0.01
Senses (taste/smell)	5.6	23.3	17.1	12.0	12.3	p<0.01
Speech	23.8	17.8	15.0	11.5	14.4	p<0.01
Social eating	7.9	19.8	14.8	10.7	10.6	p<0.01
Social contact	4.0	6.2	2.6	3.8	4.6	NS
Sexuality	14.8	78.7	17.1	20.7	25.4	NS
Teeth	10.5	31.8	21.1	19.8	18.7	NS
Open mouth (trismus)	11.1	14.0	15.5	9.4	13.9	NS
Dry mouth	11.9	48.8	50.4	47.0	41.1	p=0.01
Sticky saliva	14.6	46.5	40.7	35.0	24.6	p<0.01
Cough	17.5	23.3	26.0	18.8	13.5	p<0.01
Nutrition supplements	7.3	32.6	12.2	12.8	4.9	p<0.01

*Higher score indicates better function. †Higher score indicates more symptoms. ‡ Significance based on ordinal regression model using non-transformed data. QLQ, quality of life; RT, radiotherapy; NS, not significant.

only slight differences in time, but no significant change caused by RT. The global QOL was also not significantly altered in time in spite of the remaining dry mouth complaints.

Table 3. Percentage of patients divided into three groups by the flow ratio at different time points (n=44)

		6 weeks	6 mo	12 mo	5 years
Flow ratio	< 25%	46	35	24	20
	≥ 25% - < 75%	28	30	35	24
	≥ 75%	26	35	41	56

Parotid flow measurements

Parotid flow rate diminished immediately after RT with a maximal deterioration at 6 weeks, and increased progressively in time. The mean stimulated parotid flow rate was 0.29 (SD 0.19) ml/min before RT. Six weeks after RT the mean stimulated parotid flow rate decreased to 0.14 (SD 0.08) ml/min, with thereafter an increase to 0.19 (SD 0.13) ml/min, 0.19 (SD 0.13) ml/min and 0.26 (SD 0.17) ml/min, respectively 6 months, 12 months and 5 years after RT. Figure 3 shows the mean parotid flow ratio at the different measurement time points. Because of the variability in flow rates, the flow ratio can reach percentages above 100%. The respective median parotid flow ratios were 35%, 47%, 69%, and 79% for 6 weeks, 6 months, 12 months, and 5 years. The percentage of patients with a complication declined from 46% at 6 weeks after RT to 20% at 5 years after RT (Table 3).

Relationship between subjective and objective parameters

Global QOL, dry mouth, sticky saliva and flow ratio

We investigated the relationship between the change in time of the subjective outcome of the questionnaire and the change in time of the objective stimulated parotid flow ratio. As objective explanatory variable we used the sum of the left and right parotid flow ratio. No significant relation was found between the change in global QOL and the change in flow ratio ($p = 0.60$). A significant relation between the flow ratio and dry mouth was found ($p = 0.01$). We found no evidence that the reduction of problems with sticky saliva could be explained by parotid flow ($p = 0.79$), adjusting for time revealed only a significant time effect ($p = 0.003$). In other words, the improvement of problems with sticky saliva could be explained by time and was not due to the improvement of the parotid flow.

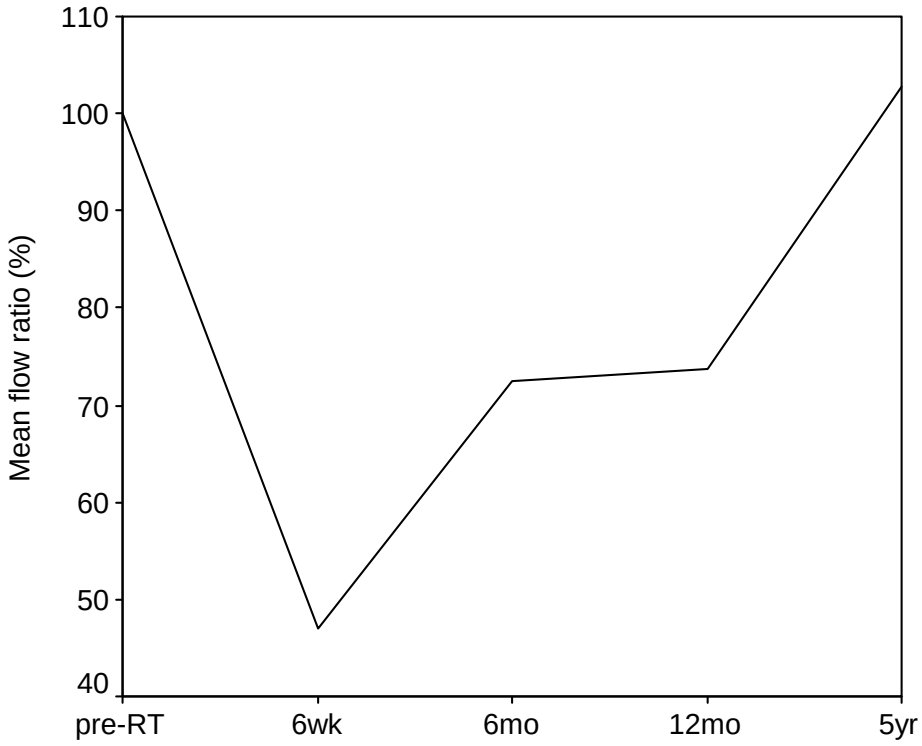

Figure 3. Stimulated parotid flow rates (mean value) at different timings after radiotherapy. Pre-RT means before radiotherapy. The cumulated flow rates are expressed as the percentage of the pre-radiotherapy flow rates. Note: the x-axis is non-linear.

Global QOL, dry mouth, sticky saliva and mean dose

No clear relation was found between the change in time of the dry mouth item and D_{par} or D_{subm}. We found no significant relation between the change in time of the global QOL or sticky saliva and the mean dose to the various salivary glands. We also did not find a combined relationship.

Discussion

This is the first long-term prospective study of the QOL combined with parotid salivary output of patients with head-and-neck malignancies treated with RT. We found a deterioration of most of the QOL items after completion of radiotherapy compared with baseline, with improvement during 5 years follow-up, even after 12 months. The specific xerostomia-related items improved, but did not return to baseline. Global QOL did not

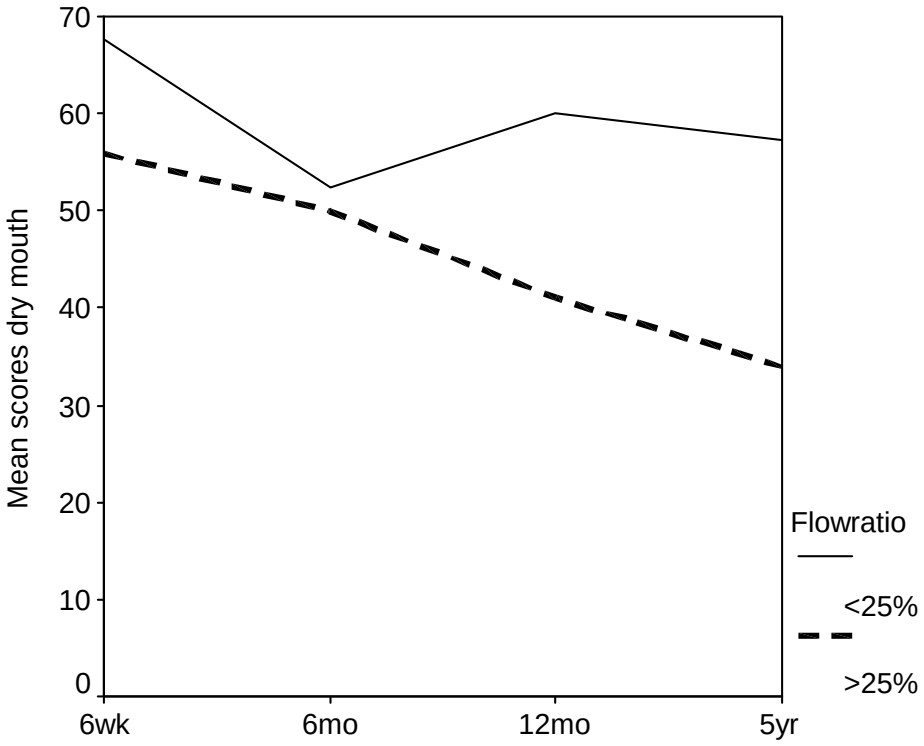

Figure 4. Mean scores over time of the single item dry mouth (QOL-H&N35). High scores imply a high level of symptoms. A division has been made between patients with and without a complication, defined as stimulated cumulated parotid flow rate <25% of the pre-radiotherapy flow rate.

alter significantly in time, despite the fact that 41% of patients complained of a dry mouth at 5 years follow-up. Similar to the partial recovery of the dry mouth, the stimulated parotid flow rates gradually improved after radiotherapy, even after 12 months. We have presented this recovery in more detail previously (7). This improvement of the dry mouth was significantly related with the improvement of the parotid flow ratio (p = 0.01).

The finding of a moderate to severe dry mouth years after treatment and a normalized quality of life is consistent with other studies (4,13-16). It might be explained by adaptation of the patients to their disabilities, as I quote a patient: “doctor, I feel fine and I do not have a dry mouth” after which he took a sip of water out of a bottle he carried with him. It is known that the QOL varies according to gender and age and that gender and age have to be taken into consideration for analyses (17). But because of the relatively small number of patients in the present study, differentiation between men and

women and age could not be studied. It should be remarked that at baseline most patients were preoperative with the tumor still in situ or just post-operative. Both situations may affect the QOL and related parameters and improvement in time. As all patients had this baseline situation, the analyses should be viewed in this perspective.

This study population consisted of 44 survivors derived from a larger group of patients. We only analyzed the group of surviving patients knowing that this is a favourable group and not representative of an average population. Analyses between survivors and non-survivors have been reported previously, and showed statistical difference between the flow ratio in favour of the survivors, but only at 6 weeks and 6 months and not at 12 months (7). This report shows that in patients who do survive, improvement over time can be seen.There are various ways of recording parotid gland toxicity. Several head-and-neck cancer specific QOL questionnaires have been conducted and validated for subjective measurement (10-12,18,19). We used the EORTC-QLQ-C30(+3) and the EORTC-H&N35 questionnaires which are well-validated and widely used. For objective methods salivary flow measurement using sialometry or scintigraphy have been reported (20-23). The most adequate parameter to evaluate the function of the parotid gland is objective stimulated parotid flow measurement and consequently we used this method (24). Recently MRI, SPECT, and PET have been used to quantify the parotid gland radiation response, but they still have to prove their value (25-28).

Several institutions have reported on subjective QOL and xerostomia in relation with salivary flow rates in the short-term with analysis at fixed time points. Henson et al found that the xerostomia-related QOL scores followed the general pattern of parotid flow rates, till 1-year follow-up (6). Parliament et al reported an inverse correlation between the unstimulated and stimulated whole salivary flow and xerostomia-specific items at one month, which disappeared three months and twelve months after treatment (29). Blanco et al found a strong correlation between the stimulated salivary function and the QOL scores 6 months after RT and a nonsignificant trend towards improvement in the mean QOL scores between 6 and 12 months (5). In our long-term analysis in which we focused on changes in time and not at relations at fixed time points, a significant correlation was found between the flow ratio recovery and the changes in the dry mouth item ($p = 0.01$). Previously we found a significant association between time and flow ratio (7). Five years after RT the mean parotid flow ratio returned to baseline while 41% of patients still experienced a moderate to severe dry mouth. A possible explanation is that

patients who had a flow ratio <25% complained the most of a dry mouth. A flow ratio <25% appeared to be the best definition for objective parotid gland toxicity (24). The number of this group of patients diminished in time, constituting almost one-fifth of the total at 5 years. The number of patients with a flow ratio between 25% and 75%, became smaller and the number of patients with a flow ratio >75% (and exceeding 100%) became larger in time (Table 3). In subanalyses we made a division between patients with and without a complication (flow ratio <25%, as defined earlier). A difference between the two groups in time was seen. At all the time points, patients with a complication had higher score results (more complains) but this was not statistically significant (Fig. 4). The low number of patients in the two groups combined with the large number of possible answers [4] may obscure the difference between the two groups. Further research using a larger group of patients is required. Another explanation is that not only the parotid glands are responsible for the dry mouth feeling. There might be an influence of the submandibular glands and/or the minor salivary glands of the palate. In our analysis neither the D_{par} nor the D_{subm} was conclusively associated with the xerostomia-specific items. This is in agreement with others who looked at fixed time points (30). We also did not find a combined influence of the D_{par} and the D_{subm}. As can be seen in Fig. 1, the D_{subm} was not normally distributed. Most patients either received a very low or a very high dose. This can contribute to the negative outcome. Eisbruch et al found a significant correlation between the mean dose to the oral cavity and the xerostomia scores at different time points (18). In their report, the oral cavity mean dose represented the RT effect on the minor salivary glands. This indicates that it may be beneficial to spare the noninvolved oral cavity to further reduce xerostomia. In the contrary Jellema et al showed no significant association between xerostomia and the oral cavity mean dose (30). As there is till now to our knowledge, unfortunately, no conclusive relation, the oral cavity mean dose is not used at our institute.

Conclusions

Xerostomia-related QOL improved in time after radiotherapy without accompanying changes in global QOL. The global QOL remained high during time and no statistically significant changes were observed. The recovery of the dry mouth feeling was significantly related with the change in parotid flow ratio. Although the parotid flow rates

recovered till baseline at 5 years follow-up, 41% of the patients complained of a moderate to severe dry mouth.

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Chapter 4

Location of cervical lymph node metastases in oropharyngeal and hypopharyngeal carcinoma: implications for the cranial border of elective nodal target volumes

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Abstract

Purpose: To analyze the exact location of the most cranial metastatic cervical lymph node in patients with oropharyngeal or hypopharyngeal carcinoma. This was done to specify the cranial border of the elective nodal target volume for improvement of parotid-sparing irradiation.

Methods and materials: The most cranial metastatic lymph node, ipsilateral and, when present, contralateral, was delineated on 58 diagnostic CT scans of patients with node-positive oropharyngeal or hypopharyngeal carcinoma. The distances from the delineated lymph node to the base of the skull were measured in all planes.

Results: The mean ipsilateral and contralateral distance to the base of the skull in the coronal plane was 25.6 mm (range 2.6-73.8; SD 14.7) and 34.7 mm (range 10.4-78.9; SD 14.0), respectively ($p = 0.002$). Ipsilateral and contralateral metastatic lymph nodes were located within 20 mm below the base of the skull in 24 patients (41%) and 3 patients (5%), respectively.

Conclusions: Contralateral metastatic lymph nodes are more caudally located than are ipsilateral metastatic lymph nodes. In elective irradiation, lowering the cranial border of the contralateral nodal target volume with 20 mm below the base of the skull should be considered.

Introduction

Oropharyngeal and hypopharyngeal tumors may be treated by surgery, primary irradiation (RT), or a combination of both. When RT is the treatment of choice, this might be complicated by xerostomia, which can cause great impairment of quality of life (1). A lot of effort has been made by different institutions for parotid gland-sparing RT (2-6). Using conventional methods, sparing the parotid gland bilaterally, and even unilaterally, is very difficult, because the primary tumor is in the vicinity. Research has shown that significant sparing of the parotid gland can be achieved using intensity-modulated RT (IMRT), compared with three-dimensional conformal RT (3, 5, 7, 8). A significant dose to the parotid gland, however, cannot be avoided, because the glands are located adjacent to the lymph node regions.

For RT of the cervical neck nodes, we used the boundaries depicted by Shah et al. (9), based on surgical experience. Level I includes the submental and submandibular nodes; Level II-IV, the upper, medial, and lower deep cervical nodes, respectively, and Level V, the dorsal cervical or superficial cervical nodes, along the accessory nerve. No consensus has been reached in the literature about the cranial border of the RT target volume of the Level II neck nodes. According to Shah et al. (9), the cranial border of Level II is the transverse process of the atlas (C1). Nowak et al. (10), however, suggested, using an anatomical study, that the cranial border should be at the top of the corpus of the atlas. Gregoire et al. (11) proposed, on the basis of surgical experience, that the cranial border should be at the bottom of the corpus of the atlas. Other recently published CT or MRI-based guidelines correspond to surgical anatomic boundaries, landmarks, or other normal anatomical structures (12-15).

The dose to the parotid glands obviously depends on the cranial border of the lymph node target volume. Lowering this border consequently results in a significant reduction of the dose to the parotid glands. This dose reduction has been quantified in a parallel study (8). It is unclear whether the borders of the neck node levels, as determined by anatomic and surgical information, are related to the clinical microscopic spread of malignant cells. One way to investigate this relation is to determine the macroscopic spread of metastatic lymph nodes. The objective of this study was to analyze the exact location of the most cranial metastatic cervical lymph node in oropharyngeal and

hypopharyngeal cancer, to specify the elective target volume and possibly reduce the complication rate.

Methods and materials

For this study, the eligibility criteria were primary oropharyngeal or hypopharyngeal squamous cell carcinoma, with metastatic cervical lymph nodes, and a diagnostic CT scan of the head and neck made in our institution. A positive or metastatic lymph node was defined as a lymph node with a short-axis diameter at least 1 cm or containing inhomogeneities suggestive of necrotic center, or, if it was pathologically examined, confirmed positive. From all eligible patients, gender, tumor stage, and ipsilateral or bilateral lymph node metastases were determined. Histologic confirmation of the disease was acquired. Staging was according to the TNM staging system of the International Union Against Cancer (1997). Between January 1995 and December 2001, a total of 364 patients with primary squamous cell carcinoma of the oropharynx or hypopharynx were seen in our hospital, of whom 139 had cervical metastatic lymph nodes. Of the 139 patients, 58 underwent CT in our hospital. Most of the other patients were referred to our hospital with CT performed at the referring hospital. The patients were grouped by clinical neck status before treatment in the case of inoperability or primary RT (31 patients) and by pathologically examined lymph nodes in the case of neck dissection (27 patients). All cervical metastatic lymph nodes were examined using CT data with mostly a 2-mm slice thickness. The most cranial cervical metastatic lymph node was contoured manually by one clinician and examined by another clinician. Nodal masses, which were not distinguishable as discrete nodes, were contoured as a single mass. In case of doubt, the lymph nodes were labelled as metastatic. In 7 cases, because of borderline nodes, an experienced radiologist interpreted the CT scan. The delineation was done using in-house-developed software. This software package can be used to delineate in a truly three-dimensional fashion (16). The contouring technique also allows delineation in the coronal and sagittal views, resulting in very rapid target/node definition and an accurate determination of the extension of a structure (Fig. 1). The software package was also used to extract geometrical properties and volumetric data from the delineated CT sets. The distance of the delineated lymph node to the base of the skull was measured in three directions (AP, mediolateral, and craniocaudal) resulting in four

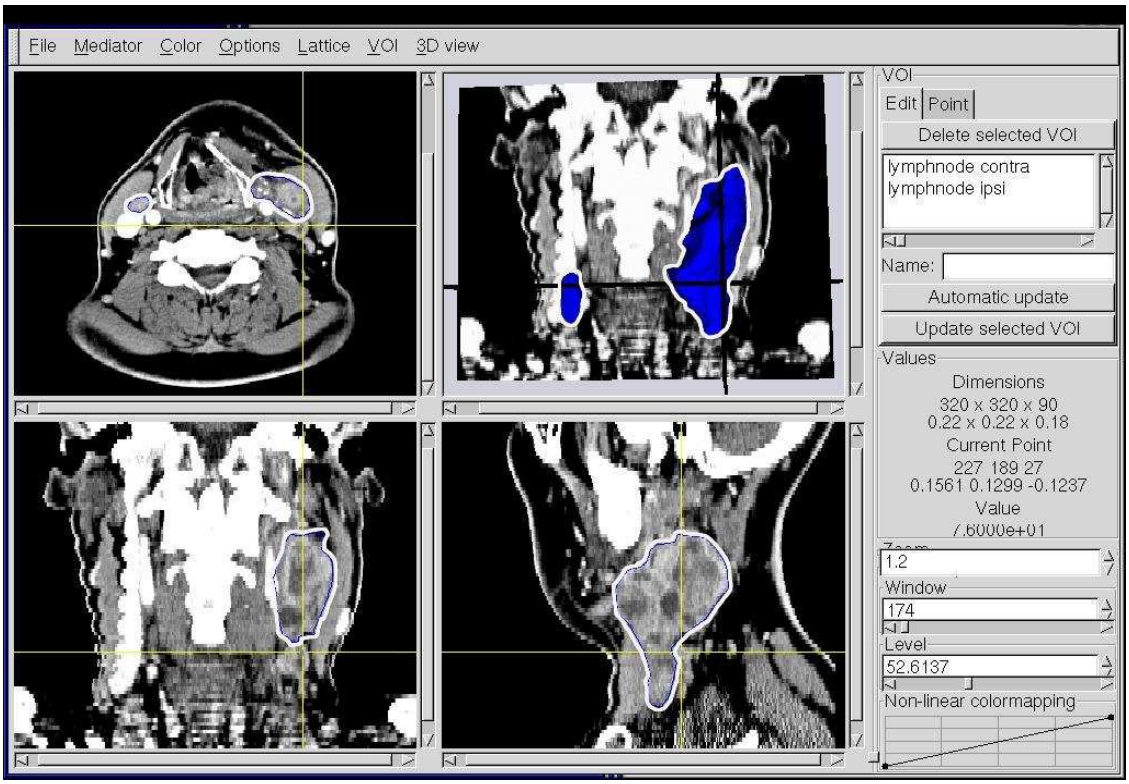

Figure 1. Three-dimensional lymph node delineation. The ipsilateral (left side of patient) and contralateral (right side of patient) most cranial cervical metastatic lymph nodes are contoured. Borders contoured on transverse view (upper left), coronal view (lower left), and sagittal view (lower right). (Upper right) three-dimensional presentation.

distances for each lymph node. These distances were measured in each direction from the external border of the delineated lymph node (Fig. 2). For definitions of the distance measurements, see Table 1. The intersection of lines through the base of the skull is referred to as the base of skull reference point (BOS). Positive distances were defined in the anterior, lateral, and cranial directions. Negative distances were in the posterior, medial, and caudal directions. The distances between the BOS, anterior process of the atlas (C1), and middle of the anterior process of the axis (C2) were also measured.

Data analyses were performed using a statistical software package (Statistical Package for the Social Scineces, version 10.1 and Excel 97). Statistical analysis was performed using the Pearson correlation (one-tail), paired samples *t* test (two-tail), and independent samples *t* test. *p*-values <0.05 were considered statistically significant.

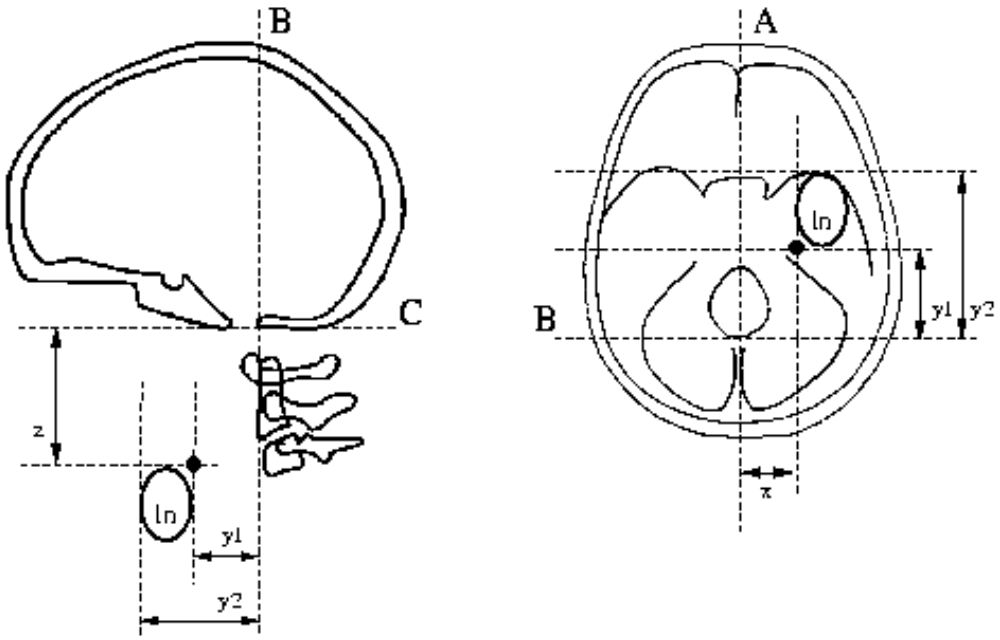

Figure 2. Distance measurements performed on each CT scan. Distances were measured from external borders of delineated lymph node to base of skull as defined in Table 1. Transverse plane (A, x); sagittal plane (B, y); and coronal plane (C, z). Black dot indicates crossing point of two borders. ln = lymph node.

Table 1. Definitions of the different values used for measuring in three dimensions

Value	Definition
x	Distance between medial border of delineated lymph node and midline through base of the skull
y1	Distance between posterior border of delineated lymph node and line through posterior border of the base of skull (foramen magnum)
y2	Distance between anterior border of delineated lymph node and line through posterior border of the base of skull (foramen magnum)
z	Distance between cranial border of delineated lymph node and line through caudal border of the base of skull

Table 2. Patient characteristics

Variable	Oropharynx	Hypopharynx
Patients	40 (69)	18 (31)
Gender		
Male	34 (85)	16 (89)
Female	6 (15)	2 (11)
cT stage		
T1	1 (2.5)	0 (0)
T2	9 (22.5)	1 (5.6)
T3	5 (12.5)	7 (38.9)
T4	25 (62.5)	10 (55.6)
cN stage		
N1	6 (15)	2 (11.1)
N2A	1 (2.5)	4 (22.2)
N2B	21 (52.5)	5 (27.8)
N2C	7 (17.5)	4 (22.2)
N3	5 (12.5)	3 (16.7)
CT-based nodal metastases		
Ipsilateral	40 (100)	18 (100)
Contralateral	19 (48)	8 (44)

Data presented as the number of patients, with the percentage in parentheses.

Results

Of the studied patients, 50 were men and 8 were women. The primary tumors were located in the oropharynx in 40 patients and hypopharynx in 18 patients (Table 2). No statistically significant differences according to tumor stage, gender, or side of nodal metastases were found between the two groups, and the two groups were combined. In total, 58 ipsilateral and 27 contralateral cervical lymph nodes were delineated. No retropharyngeal metastatic lymph nodes were found. Summaries of the distances for each plane are shown in Table 3. Ipsilateral, 9 metastatic lymph nodes had z values <10 mm. No contralateral metastatic lymph nodes with a z value <10 mm were observed. Fifteen ipsilateral and three contralateral metastatic lymph nodes had z values between 10 and 20 mm. Between 20 and 30 mm below the BOS, 21 ipsilateral and 7 contralateral cranial borders of metastatic lymph nodes were found. Cumulatively, 45 ipsilateral (78%) and 10 contralateral (17%) metastatic lymph nodes were located within 30 mm of the BOS (Fig. 3).

No correlation was found between the ipsilateral and contralateral z values (p = 0.92). Also, the other distances at the ipsilateral side did not correlate with those at the contralateral side (p > 0.20). The mean z value of the ipsilateral metastatic lymph nodes

Table 3. Distance of the most cranial cervical metastatic lymph node to BOS in each plane

Value	Side	Minimum (mm)	Maximum (mm)	Mean (mm)	SD	*p* (*t* test, two-tail)
z	I	-2.6	-73.8	-25.6	14.7	0.005
	C	-10.4	-78.9	-34.7	14.0	
y1	I	23.2	104.4	56.2	14.8	0.26
	C	18.2	70.9	52.7	11.8	
y2	I	3.7	66.3	34.3	12.8	0.10
	C	8.9	60.9	38.6	11.5	
x	I	10.7	45.3	31.1	7.4	0.21
	C	22.3	44.6	33.6	5.0	

Abbreviations: SD = standard deviation; BOS = base of skull reference point; I = ipsilateral; C = contralateral. Values x, y, and z are defined in Table 1 and presented in Fig. 2. Negative values in posterior, medial, and caudal directions; positive values in anterior, lateral, and cranial direction.

was significantly smaller than it was for the contralateral side (p = 0.005). In other words, most of the cranial borders of the delineated ipsilateral lymph nodes were located significantly higher in the neck than those of the contralateral delineated lymph nodes. No significant differences were observed between the other ipsilateral and contralateral mean distances (Table 3). The z values of patients with only ipsilateral metastatic lymph nodes were not different from those of patients with both ipsilateral and contralateral metastatic lymph nodes (p = 0.80). In the latter group, the z values of the ipsilateral metastatic lymph nodes, did not correlate significantly with the z values of the contralateral metastatic lymph nodes (p = 0.18). Thus, the location of the cranial border of the ipsilateral metastatic lymph node does not predict the location of the cranial border of the contralateral metastatic lymph node.

No correlation was found between the location of the delineated lymph node and its volume, tumor type, T stage, N stage, or gender. The mean volume was significantly greater for the ipsilateral metastatic lymph nodes than for the contralateral metastatic lymph nodes (p= 0.006 one-tail; Fig. 4).

The mean distance from the BOS to the anterior process of the atlas was 4.9 mm, (range -21.9 to +8.3; SD 6.8) and to the anterior process of the axis was 27.2 mm, (range -13.2 to -40.4; SD 5.9). The maximal value of 8.3 mm is above the level of the BOS. Because of a very long neck of 1 patient, the maximal supine position of that patient's head, and our definition of the BOS, it was possible to have the anterior process of the atlas located above the BOS.

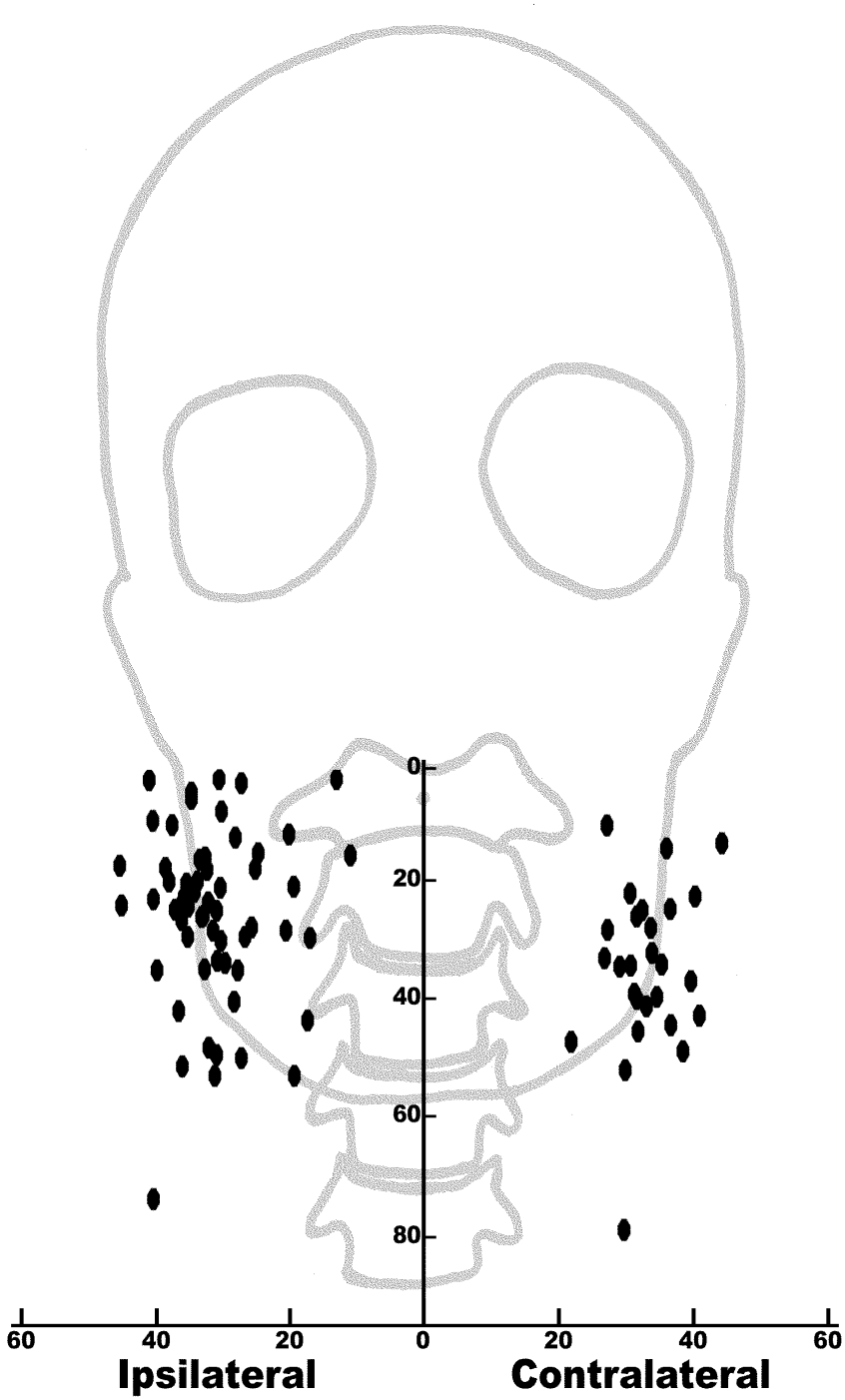

Figure 3. Most cranial metastatic lymph nodes. Crossing points (black dot) of cranial (z) and medial (x) border of metastatic lymph nodes. Division made between ipsilateral and contralateral nodes. Distances given in millimeters.

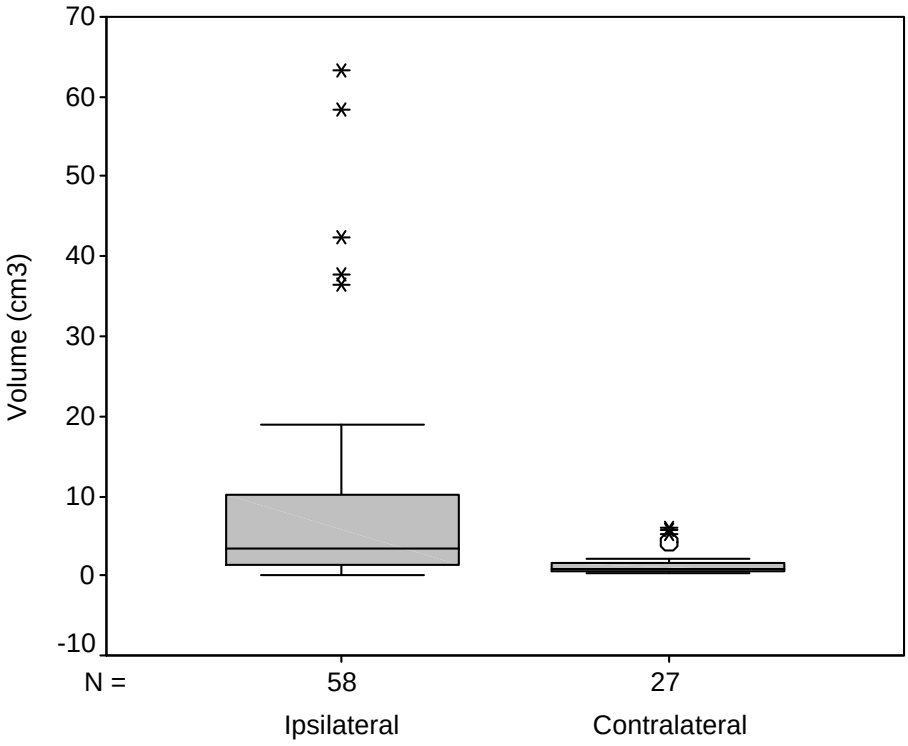

Figure 4. Distribution of volumes of delineated ipsilateral and contralateral lymph nodes. Median, quartiles, and extreme values within each category shown.

Discussion

This study described the location of the most cranial metastatic cervical lymph nodes, expressed in the distance from their external borders to the base of the skull. This was done using data from patients with oropharyngeal or hypopharyngeal carcinoma who were node positive at presentation. These data demonstrate that contralateral metastatic lymph nodes are located more caudally than are ipsilateral metastatic lymph nodes, in light of these tumor types. Although the study group was small, the difference was statistically significant. This is an important finding for the specification of the nodal target volume of the elective radiation field, and for parotid-sparing RT. A parallel study in our department investigated the influence of lowering the cranial border of the Level II radiation field on the probability of radiation-induced xerostomia. In that study, it was found that it is possible to obtain a considerable reduction in the complication rate (approximately 30%) when lowering the cranial border from C1 to C2, using IMRT.

Comparing three-dimensional conformal RT with IMRT, the impact was much larger for IMRT (8). For the Level II lymph nodes, no consensus has been reached in the literature about the cranial border of the target volume. Different guidelines have proposed different levels, ranging from the base of the skull to the bottom of the atlas (9-12,15). No discussion has to be made about the base of the skull as the anatomic border of the Level II cervical lymph nodes. The question remains to what extent this border is relevant in the clinical setting. In fact, one would like to know the location of any microscopic metastases. That answer remains unknown, but now we know now the location of the most cranial macroscopic cervical lymph nodes in advanced disease. To answer the question about the exact location of metastatic lymph nodes, more possibilities exist. One can look at data from surgical neck dissections. These data are available; however, the dissections are often not to the base of the skull because of surgical limitations. Another problem is that these data are not as detailed as is necessary to know the exact location of these lymph nodes. Another possibility is to consider the pretherapeutic data such as from CT scans. A limitation of the diagnostic CT is that subclinical or microscopic disease is not visible. We posed the hypothesis that data on the localization of clinical metastatic lymph nodes or macroscopic disease (N+) can predict the possible subclinical metastatic localization when no clinical metastatic disease (N0) can be diagnosed. Therefore, we enrolled patients with already advanced neck disease.

When specifying the target volume, it is preferable to use the BOS as the bony landmark. The base of the skull and the anterior process of the atlas, and their boundaries, were both clearly visible and determinable at CT slices. It was more difficult to determine the anterior process of the axis (C2) as a single point, even using three-dimensional CT data. When we measured the distances among the base of the skull, anterior process of the atlas, and anterior process of the axis, we found large differences in distance with a SD of >5 mm in all patients. The most probable explanation for these differences is individual anatomic variation. Another explanation could be the immobilization of the patients' head. The patients were not immobilized during diagnostic CT scanning. During RT, patients are normally fixated with an immobilization mask with the head in maximum supine position. However, because the base of the skull is the center of anatomic rotation, no large differences among the position of the atlas, base of the skull, and lymph nodes would be expected while immobilizing the patient's head.

Table 4. Percentage of most cranial metastatic lymph nodes included in elective nodal target volume when lowering the cranial border from BOS in craniocaudal direction

Distance (cm)	Ipsilateral (%)	Contralateral (%)
0.5	88	100
1.0	85	100
1.5	81	95
2.0	59	95
2.5	35	88
3.0	22	83
3.5	22	74
4.0	16	67
4.5	12	62
5.0	5	57
>5.0	0	

Abbreviation: BOS = base of skull reference point.

According to the literature, 31% and 20% of patients with oropharyngeal or hypopharyngeal carcinoma, respectively, and node positive at presentation develop contralateral cervical metastatic lymph nodes (11,17). In our study, approximately 46% of the patients had contralateral metastatic cervical lymph nodes. This high contralateral cervical metastatic rate might have been caused by the large number of T3-T4 and N2b lesions in our study. Also, we labelled any suspect lymph node (diameter >1 cm or containing inhomogeneities suggestive of a necrotic center) without pathologic information as metastatic. Therefore, we might have delineated lymph nodes not containing tumor cells, causing false-positive results.

When failure occurs after treatment, in a large majority of patients, this occurs at the primary site. Pigott et al. (18) showed that 97% of the local recurrences were located at the site of the gross tumor and 93% of the regional failure was located at the original site of disease. Chao et al. (19) found that of 52 patients undergoing primary RT for squamous cell carcinoma of the head and neck, 6 (12%) had persistent or recurrent nodal disease, of which four were located in the clinical target volume (CTV). They used a modified Robbins classification to determine the CTV, in which the base of the skull was the cranial border of Level II neck nodes. Of 74 patients receiving postoperative RT, they found only 7 patients (9%) with failure in the nodal region, four of these within the CTV. All other failures outside the CTV were located in the lower neck (19). Dawson et al. (20) recently analyzed the patterns of locoregional recurrence in patients treated with IMRT. Lymph node targets at the side of the neck at greatest risk included the high

Table 5. Comparison of recommendations for cranial boundary of level II neck nodes in case of node-negative neck

Author	Boundary	Comment
Nowak et al. (10)	Top of corpus C1	Anatomical study
Grégoire et al. (11)	Bottom of corpus C1	Surgical experience
Shah et al. (26)	Transverse process C1	Designed for surgical procedures
This study	Base of the skull	Ipsilateral nodal target volume
	2 cm below base of the skull	Contralateral nodal target volume

jugular nodes at the base of the skull. Four regional recurrences (of 58 patients) extended superior to the jugulodigastric node in the high jugular and retropharyngeal nodes near the base of the skull. At the side of the neck at low risk (contralateral to the primary tumor and with no clinical evidence of metastatic disease), the cranial border was at the jugulodigastric nodes. These nodes are located below the level at which the posterior belly of the digastric muscle crosses the jugular vein. No recurrences were seen in the nodes superior to the jugulodigastric nodes in their study (20).

Their results correspond with our findings, except that we did not find any retropharyngeal metastatic lymph nodes. According to the literature, the incidence of pathologic retropharyngeal lymph node involvement in oropharyngeal or hypopharyngeal carcinoma ranges from 0% to 62% (11,21). This discrepancy between our results and those in the literature might be a result of the imaging modality used. It has been suggested that MRI is superior to CT in the detection of lesions in the retropharyngeal nodes, based on research of nasopharyngeal carcinoma (22). Others have reported considerable variation in the sensitivity and specificity of both CT and MRI in detection of all neck node metastases (23-25). The main limitation of both imaging modalities is the detection of micrometastases. Possibly positron emission tomography or single photon emission CT might further enhance the accuracy in future.

In Table 4, we detailed the percentage of the most cranial metastatic lymph nodes within the nodal target volume when lowering the cranial border from the BOS. When lowering the border 2 cm below the BOS, 59% of the ipsilateral and 95% of the contralateral of the metastatic neck lymph nodes were within the target volume in this study. Depending on the risk of metastatic disease and the complication rate, the cranial border can be defined. A comparison of the cranial border of the elective nodal target volume between

some proposed guidelines is presented in Table 5. These cranial borders correspond to the CTV and do not include margins for patient motion or setup inaccuracy. In this study, we delineated the gross tumor volume of the most cranial metastatic lymph node in patients with positive nodes at presentation. Lymph nodes with positive subclinical disease have a short-axis diameter of <10 mm according to the definition.

Assuming the center to be in the same position, the upper border of these lymph nodes with positive subclinical disease will not be located as cranially as the upper border of the clinical metastatic lymph nodes in this study. We pose that the gross tumor volume found includes the margin of microscopic invasion in the case of subclinical disease. In other words, the cranial border of the gross tumor volume found in this study could be used as the cranial border of the CTV in case of elective field RT.

Conclusions

We have shown that none of the patients with already advanced neck disease had the top of the highest contralateral metastatic lymph node within a distance of <10 mm from the BOS; for 5%, it was <20 mm and for 17%, it was <30 mm. This is in contrast to the top of the ipsilateral metastatic lymph nodes, of which 15% had a distance of <10 mm from the BOS and 41% <20 mm. The position of the highest ipsilateral metastatic lymph node cannot be used as a prognostic factor for the location of the highest contralateral metastatic lymph node. Lowering the border of the contralateral elective target volume with 2.0 cm from the base of the skull might be used safely without risking a high incidence of neck node failure and could possibly diminish the complication rate. Lowering the border at the ipsilateral site is not advised.

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Chapter 5

Cranial location of level II lymph nodes in laryngeal cancer: implications for elective nodal target volume delineation

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Abstract

Purpose: To analyze the cranial distribution of level II lymph nodes in patients with laryngeal cancer to optimize the elective radiation nodal target volume delineation.

Methods and materials: The most cranially located metastatic lymph node was delineated in 67 diagnostic CT data sets. The minimum distance from the base of the skull (BOS) to the lymph node was determined.

Results: A total of 98 lymph nodes were delineated including 62 ipsilateral and 36 contralateral lymph nodes. The mean ipsilateral and contralateral distance from the top of the most cranial metastatic lymph node to the BOS was 36 mm (range, -9-120; SD 17.9) and 35 mm (range, 14-78; SD 15.0), respectively. Only 5% and 12% of the ipsilateral and 3% and 9% of the contralateral metastatic lymph nodes, were located within 15 mm and 20 mm below the BOS, respectively. No significant differences were found between patients with only ipsilateral metastatic lymph nodes and patients with bilateral metastatic lymph nodes. Between tumors that do cross the midline and those that do not, no significant difference was found in the distance of the most cranial lymph node to the BOS and the occurrence ipsilateral or contralateral.

Conclusions: Setting the cranial border of the nodal target volume 1.5 cm below the base of the skull covers 95% of the lymph nodes and should be considered in elective nodal irradiation for laryngeal cancer. Bilateral neck irradiation is mandatory, including patients with unilateral laryngeal cancer, when elective irradiation is advised.

Introduction

Head-and-neck malignancies are relatively rare. With an incidence of 650 patients a year (1:25.000), cancer of the larynx is the second most common form of head-and-neck cancer in the Netherlands. Treatment consists of radiotherapy, surgery, or a combination of both. Primary or postoperative radiotherapy includes the primary tumor or tumor bed and pathologic lymph nodes. Elective nodal treatment is suggested for a risk of subclinical involvement of ≥ 20% (1,2).

With the advances in computer technology, radiation treatment planning and delivery have changed extensively recent years. Intensity modulated radiotherapy (IMRT) offers the great opportunity to selectively treat target volumes while minimizing the dose to normal structures. As the parotid glands are positioned near the level II lymph nodes, they are likely to receive a considerable radiation dose. Radiation-induced xerostomia will appear dependent on the dose and volume irradiated (3). Reduction of the dose to the parotid gland has been achieved using IMRT, in combination with lowering the cranial border of level II target border (4-10).

With the advancements of radiotherapy techniques like IMRT, the need for adapted delineation guidelines grew. In recent years much attention has been paid to the development of guidelines, not only based on surgical experience, but also based on imaging (11-18). The cranial border of the level II lymph nodes mentioned in these guidelines varied from boundaries of the transverse process of the atlas (C1), the top of corpus C1 or the bottom of the corpus C1 (13,16,19). As there remained a call for standardization of target volume delineation, in 2003 a consensus guideline for delineation of the node levels in the node-negative neck was reached and presented, derived from the Brussels guidelines and Rotterdam guidelines (13,14,16). This consensus guideline was discussed and agreed with representatives of the major cooperative groups in Europe (DAHANCA, EORTC, GORTEC) and in North America (NCIC, RTOG) (14). According to the consensus guideline, the cranial border of the level II lymph nodes is set at the caudal edge of lateral process of C1. The question remains whether an anatomic or imaging based guideline is best to use for clinical treatment. It is still unclear whether these boundaries are related to clinical microscopic spread of the malignant cells. Investigating the pattern of macroscopic lymph node spread can reveal possible pathways of microscopic spread. With this knowledge and the possibility of

selective irradiation, the elective target volumes might be adjusted and possibly complications like xerostomia reduced. Furthermore the consensus guidelines for target volume delineation in the clinically negative neck were proposed for all head and neck primary sites. However, one may expect that different primary sites may be associated with different patterns of nodal spread. Therefore the consensus guideline should be tailored to specific primary sites. Earlier we presented implications for the cranial border of the level II elective nodal target volume delineation in patients with oropharyngeal or hypopharyngeal cancer. We found that contralateral metastatic lymph nodes were more caudally located than ipsilateral metastatic lymph nodes. And therewith the cranial border of the contralateral elective nodal target volume could be set 20 mm below the base of the skull. Setting the ipsilateral border beneath the base of the skull was not advised (20).

The purpose of the present study was to investigate the exact position of the most cranial metastatic lymph node in laryngeal cancer. The objective of the study was to specify the cranial border of the elective nodal target volume and therewith optimize the consensus guideline. In this study we restricted our interest to the top edge of level II.

Methods and materials

For this retrospective study, eligibility criteria were patients with primary laryngeal cancer and clinically metastatic lymph nodes, no previous treatment for the laryngeal tumor and a diagnostic contrast-enhanced computed tomography (CT) of the head-and-neck made at our hospital with maximum slice thickness of 3-mm. The diagnosis of a positive or metastatic lymph node by CT was defined as a lymph node with short-axis diameter greater than 1 cm, any node containing inhomogeneities suggestive of necrosis, extracapsular extension or, if it was pathologically examined confirmed positive. From all included patients, gender, tumor stage, and ipsilateral, contralateral, or bilateral lymph node metastases were determined. Histologic confirmation of the disease was acquired. Staging accorded to the American Joint Committee on Cancer staging classification of malignant tumors (sixth edition, 2002) (21).

Between January 1995 and September 2004, a total of 152 patients with primary laryngeal cancer and with cervical lymph node metastasis were seen in the joint clinics of head-and-neck surgery and radiotherapy. Of these patients, 95 had CT scanning of

Table 1. Definitions of the different values used for measuring

Value	Definition
z_{cran}	Distance between the cranial border of delineated lymph node and the caudal border of the base of the skull
z_{caud}	Distance between the caudal border of the delineated lymph node and the caudal border of the base of skull
z_{center}	Distance between the center of the delineated lymph node and the caudal border of the base of skull

the head and neck performed in our hospital. Some of the remaining 57 patients received magnetic resonance imaging (MRI) instead of CT, but most of them were referred to our hospital with CT scanning performed at an outside facility and not available for digital registration in our hospital. In ten cases of the 95 patients, the thickness of the CT slices was more than 3-mm, nine CT scans were taken postoperatively without the digital availability of the diagnostic CT data, and in nine cases there was a synchronic second primary. These cases were not included in the study, which left us with CT data of 67 patients that could be analyzed.

Only the most cranial metastatic lymph node was delineated manually by one clinician and examined by another clinician. One experienced head-and-neck radiologist reviewed some CT images in case of borderline nodes. Nodal masses not distinguishable as discrete nodes were contoured as a single mass. In case of malignant-appearing lymph nodes, the lymph nodes were labeled as metastatic. Delineation was done using in-house developed software as presented before (20,22). Distances were measured to the caudal border of the base of the skull (BOS), defined as the most caudal and dorsal edge of the foramen magnum. The distance of the top edge of the lymph node to the BOS (z_{cran}) and the distance of the bottom of the lymph node to the BOS (z_{caud}) were measured. Also the distance between center of the lymph node and the BOS was measured (z_{center}) (Table 1). According to the definition a metastatic lymph node is clinically diagnosed with a short-axis diameter >1-cm. When we assume a lymph node to grow from its center, the cranial border of a metastatic lymph node extends at least 5-mm from the center. We calculated the center of the delineated lymph node, and added 5-mm cranially (z_{center} + 5-mm). This border was taken as the cranial border of clinically nonmetastatic lymph nodes. The number of cranial lymph nodes included in the nodal target volume when taken this 5 mm margin from the center was calculated.

Statistical analysis was performed using the Statistical Package for Social Sciences, version 10.1 (SPSS Inc., Chicago, IL). Data were analyzed using the paired samples

Table 2. Patient and tumor characteristics (*n* = 67)

Variable		
Gender		
Male	55	(82)
Female	12	(18)
Tumor type		
Supraglottic	56	(84)
Glottic	7	(10)
Transglottic	4	(6)
T stage		
T1	5	(8)
T2	25	(37)
T3	16	(24)
T4	20	(30)
Tx	1	(1)
N stage		
N1	24	(36)
N2a	3	(5)
N2b	21	(31)
N2c	17	(25)
N3	2	(3)
CT-based nodal metastases		
Ipsilateral	62	(93)
Contralateral	35	(52)

t-test, the Pearson correlation, and the independent samples *t* test. All statistical tests were two-tailed as appropriate, and a criterion of $p < 0.05$ was accepted for significance.

Results

This report is based upon the retrospective analysis of 67 patients with squamous cell carcinoma of the larynx. Most patients were male (82%) and in 84% of the cases the primary tumor was located in the supraglottic larynx. Patient and tumor characteristics are presented in Table 2. A total of 98 lymph nodes were delineated including 62 ipsilateral and 36 contralateral lymph nodes.

The mean volume of the ipsilateral metastatic lymph nodes was 5.7 cm^3 (range, 0.4 to 42.3 cm^3; SD 8.9) and of the contralateral metastatic lymph nodes 3.0 cm^3 (range, 0.3 to 22.2 cm^3; SD 4.8). This difference was statistically significant ($p = 0.001$).

The metastatic lymph nodes at the ipsilateral side of the tumor had a mean z_{cran} of 36 mm (SD 18) and at the contralateral side there was a mean z_{cran} of 35 mm (SD 15)

Table 3. Distances of the top of the most cranial cervical metastatic lymph nodes to the BOS

Value	Side	Minimum (mm)	Maximum (mm)	Mean (mm)	SD	*p* (t test, two-tail)
z_{cran}	I	9	-102	-36	17.9	0.73
	C	-14	-78	-35	15.0	
Z_{center}	I	0.5	-114	-50	18.7	0.42
	C	-25	-84	-47	14.9	

Abbreviations: SD = standard deviation; I = ipsilateral; C = contralateral.
Values z_{cran} and z_{center} are defined in table 1. Positive values are in cranial direction, negative values are in caudal direction.

(Fig. 1 and Fig. 2a, Table 3). This difference was not significant (p = 0.73). Table 4 shows the percentages of the most cranial metastatic lymph nodes included in the nodal target volume when lowering the cranial border from the BOS in craniocaudal direction. When assuming a lymph node to grow from its center, a margin of 5-mm of radiologic detection is added to the center and the percentages included in the elective nodal target volume are also shown.

No significant difference was observed between the z_{cran} of patients with only ipsilateral metastatic lymph nodes and the z_{cran} of patients with metastatic lymph nodes on both sides (p = 0.19). In the latter group we investigated whether the location of the contralateral lymph node could be predicted by the location of the ipsilateral lymph node. There was a significant correlation between the z_{cran} (p = 0.01). In other words, the cranial location of the ipsilateral metastatic lymph node can predict the cranial location of the contralateral lymph node.

To determine whether irradiation can be restricted unilateral in case of tumors that do not cross the midline, we investigated the difference in number and location of lymph node metastases between tumors that did cross the midline and those that did not. Nineteen patients had strictly unilateral tumors and of those, 11 patients had only ipsilateral lymph node metastases (58%), 2 patients had only contralateral lymph node metastases (10%) and 6 patients had lymph node metastases on both sides (32%). The 2 patients with only contralateral lymph node metastases had T2 glottic carcinoma. Of the 48 patients with tumors that did cross the midline, 21 patients had only ipsilateral lymph node metastases (44%), 3 patients had only contralateral lymph node metastases (6%) and 24 patients had metastatic lymph nodes on both sides (50%) (Table 5). No significant differences between the distances of the top of the highest metastatic lymph nodes and

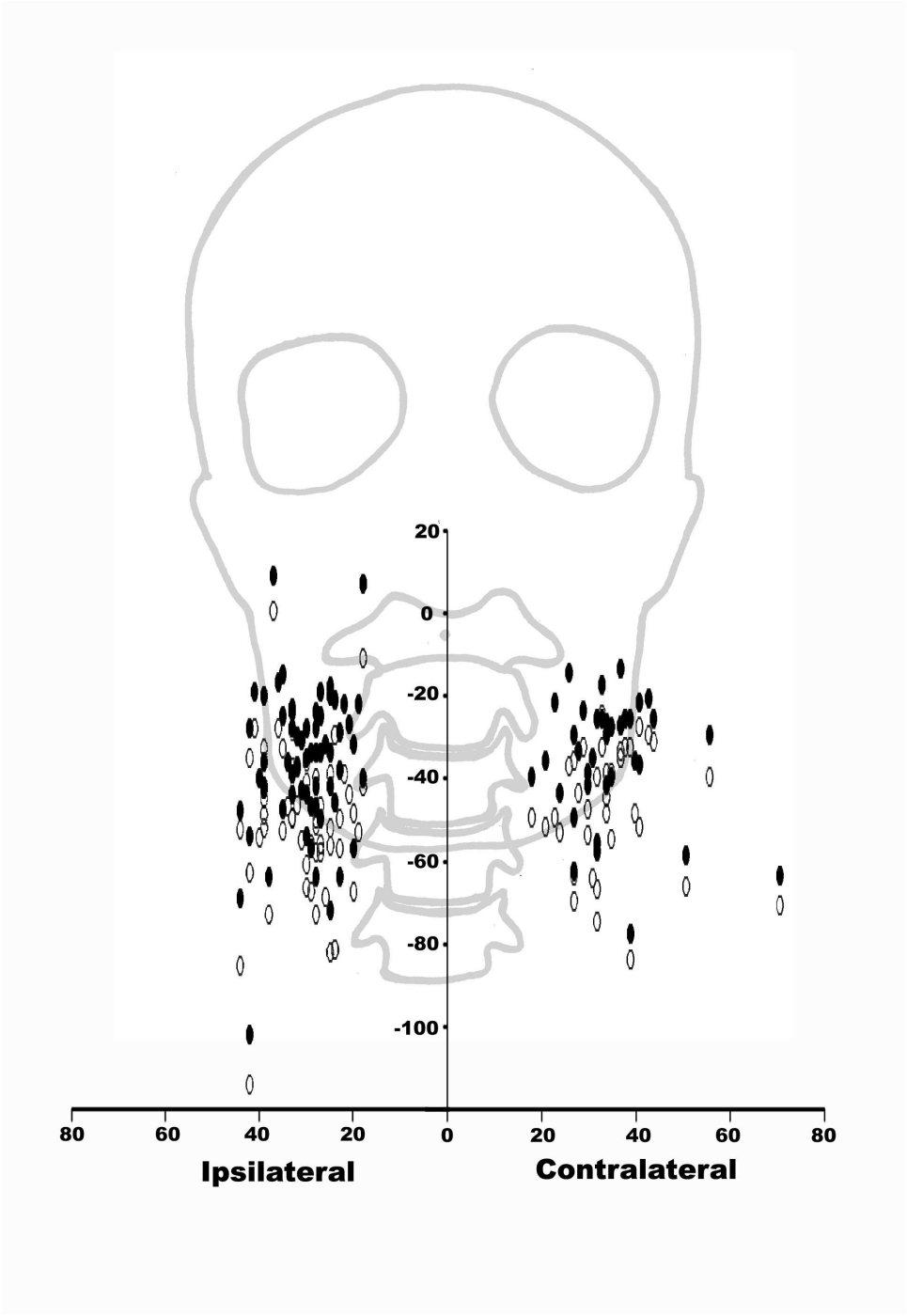

Figure 1. Distribution of distances of the top (z_{cran}, black dot) and center (z_{center}, open dot) of delineated metastatic lymph nodes to the base of the skull. A division has been made between ipsilateral and contralateral lymph nodes. Distances in millimetres.

Figure 2a

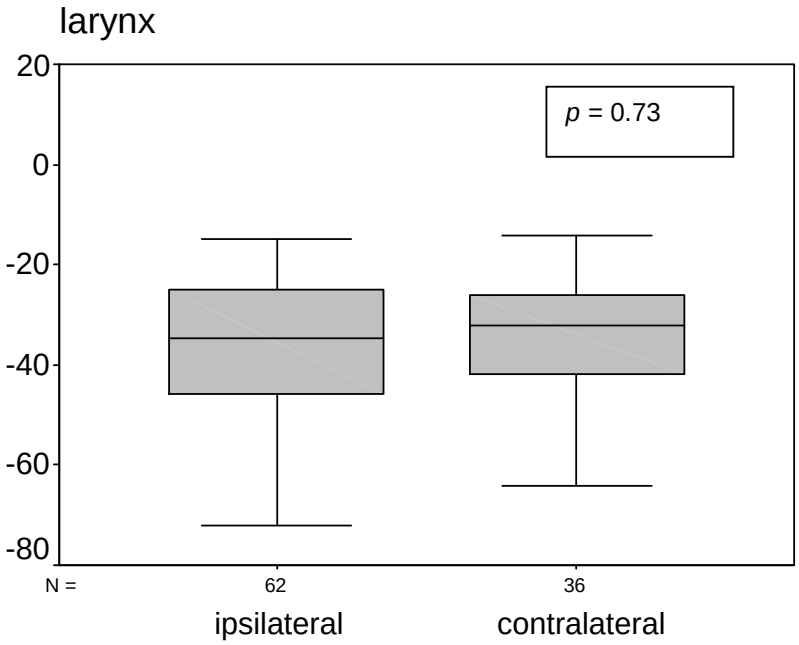

Figure 2b

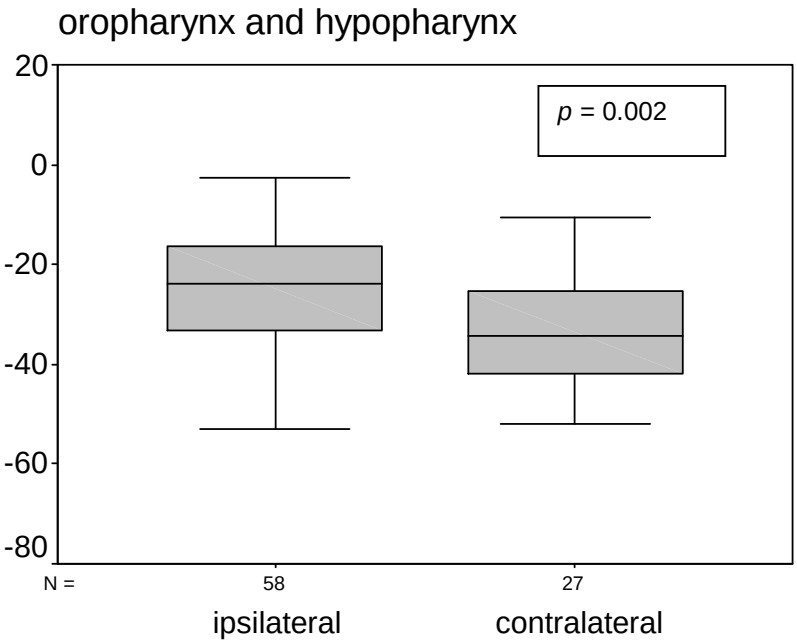

Figure 2. Distribution of the distances between the top of the delineated ipsilateral and contralateral lymph nodes to the base of the skull. A division has been made between tumor groups. Median and quartiles within each category are shown. Fig 2b results adapted from a report presented earlier (20).

Table 4. Percentage of the most cranial metastatic lymph nodes included in the elective nodal target volume when lowering the cranial border from the base of the skull (BOS) in craniocaudal direction

Distance from the BOS (cm)	Ipsilateral (%)	Ipsilateral (%) center + 5-mm	Contralateral (%)	Contralateral (%) center + 5-mm
0.5	96	98	100	100
1.0	96	96	100	100
1.5	95	96	97	100
2.0	88	96	91	100
2.5	75	90	80	94
3.0	62	83	58	72
3.5	50	72	47	58
4.0	40	61	33	52
4.5	29	51	19	41
5.0	17	32	16	25
> 5.0	< 17	< 32	< 16	< 25

When assuming a lymph node to grow from its center, a margin of 5-mm of radiologic detection is added to the center and the percentages given of distance to the base of the skull (center + 5-mm). A division has been made between ipsilateral and contralateral metastatic lymph nodes.

the base of skull could be found between tumors that did cross the midline and tumors that did not ($p = 0.49$).

Previously we presented the results of the cranial location of metastatic lymph nodes of patients with oropharyngeal or hypopharyngeal cancer (20). When comparing these results with the results found in this study, the distance of the cranial border to the BOS of the metastatic lymph nodes differed from oropharyngeal and hypopharyngeal tumors (Fig. 2a and Fig. 2b). The ipsilateral nodal metastases are located more caudal in patients with laryngeal cancer than in patients with oropharyngeal or hypopharyngeal cancer (mean 36-mm and 26-mm from the BOS, respectively) ($p < 0.005$).

Discussion

In this study of 67 patients with advanced laryngeal cancer, we found that more than 50% of the ipsilateral and contralateral cervical metastatic lymph nodes had their cranial edge >3.5 cm below the BOS. There was no statistically significant difference between the cranial border of ipsilateral and contralateral metastatic lymph nodes. No significant difference was found between patients with only ipsilateral metastatic lymph nodes and patients with bilateral metastatic lymph nodes.

The lymphatic drainage in laryngeal cancer occurs along predictable pathways. Level II, III and IV are most frequently involved in decreasing number (23-26).

Table 5. The number of ipsilateral and contralateral delineated lymph nodes

	Unilateral tumors	Bilateral tumors
Ipsilateral lymph nodes	17	45
Contralateral lymph nodes	8	27

A division has been made between tumors that did cross the midline (bilateral, *n* = 48) and tumors that did not cross the midline (unilateral, *n* = 19).

Transglottic carcinoma cross the laryngeal ventricle and involve both true and false vocal cords. They characteristically spread within the paraglottic space and invade into the laryngeal framework and outside the larynx. Cervical lymph node metastases are common and an incidence of 26-52% has been reported (27). Supraglottic tumors have a higher prevalence of regional metastases compared with cancer of the other laryngeal sites. The supraglottic area is richly supplied by lymphatics that drain into the cervical lymph nodes. An incidence of 40% overall metastatic cervical lymph nodes has been reported and 27-38% of occult metastatic lymph nodes (28, 29). Approximately only 1-8% of all laryngeal tumors are subglottic tumors. Glottic tumors with subglottic extension however are more prevalent, ranging from 11-33%. They spread primarily to the paratracheal lymph nodes. The incidence of lymph node metastases has been reported to be generally less than 10% (30).

Before the consensus guideline was reached, several guidelines have been presented for delineation of the nodal target volumes. Most recommended nodal target volumes for the node-negative patient are based on surgical dissection limits and clinical experience (11, 13, 16, 18, 31). A population-based atlas of the normal lymph node anatomy has also been described (32). There is no definitive evidence that demonstrates the superiority of one over the others. The consensus guideline for elective nodal delineation in the node negative neck is based on anatomic landmarks that are visible on axial CT data (14). In this guideline the cranial border of level II was set at the lateral process of C1 in the node-negative neck. The question remains whether a uniform definition of borders for the head-and-neck is suited for specific head and neck tumors. Earlier we have shown that in patients with oropharyngeal and hypopharyngeal tumors, ipsilateral metastatic lymph nodes reach till the base of skull. Of the contralateral metastatic lymph nodes, 95% were included in the target volume when the cranial border was set at 2-cm from the base of the skull (20). In the present study we have shown that there was no statistically significant difference between the cranial border of ipsilateral and

contralateral metastatic lymph nodes for laryngeal cancer (Fig 1.). Also the distance of the cranial border to the BOS of the metastatic lymph nodes differed from oropharyngeal and hypopharyngeal tumors (Fig. 2a and Fig. 2b). The ipsilateral nodal metastases are located more caudal in patients with laryngeal cancer than in patients with oropharyngeal or hypopharyngeal cancer. As can be seen in Table 4, setting the cranial border of the target volume at 1.5 cm from the BOS still covers 95% of the metastatic lymph nodes in laryngeal cancer and might be executed for elective irradiation. This will result in significant sparing of the parotid glands, and therewith diminishing xerostomia compared with the historically used cranial border located at the base of the skull and with the caudal border of the lateral process of C1 of the current consensus guideline. The latter border is located approximately 1 cm below our defined BOS (4). When assuming a lymph node to grow from its center, the percentage of lymph nodes covered in the nodal target volume even increases when further lowering the cranial border (Table 4). Within the total distribution of delineated ipsilateral lymph nodes, two extreme z_{cran}'s were found (Fig. 1). These cranial borders extended 7 mm and 9 mm above BOS. The first mentioned delineated lymph node measured 1.8 cm^3 in volume and belonged to a patient with pT4pN2c supraglottic laryngeal carcinoma. This appeared to be a very extensive obliquely oriented parapharyngeal lymph node, which is a rare incidence in laryngeal cancer. The extensive appearance explained why the z_{center} amounted to 11 mm below the BOS. This patient also had a contralateral lymph node with a z_{cran} of 14 mm below the BOS and a volume of 5.4 cm^3. The second extreme z_{cran} of 9 mm above BOS belonged to a patient with only an ipsilateral metastatic lymph node measuring 2.4 cm^3 in volume. This patient had cT2N2b supraglottic laryngeal carcinoma. The z_{center} only moved a little bit downward to 0.5 mm above the BOS. The tumors of both patients were growing across the midline. Because of the extreme z_{cran} in comparison with the other z_{cran}, an experienced radiologist interpreted both CT-data and confirmed our delineation.
In our study group a significant correlation between the z_{cran} of the ipsilateral metastatic lymph nodes and the contralateral metastatic lymph nodes in patients with bilateral metastatic lymph nodes was found. Thus the location of the ipsilateral metastatic lymph node can to some extent predict the location of the metastatic lymph node at the other side of the neck. No other significant correlation was found between the different distances. Earlier we investigated the location of metastatic lymph nodes in oropharyngeal and hypopharyngeal carcinoma and in that study we did not find this

correlation (20). The significant correlation found in this study might be based on a coincidence in this relatively small patient group. Another more plausible explanation is the similarity of z_{cran} of the ipsilateral nodes compared to the contralateral nodes. The mean z_{cran} of the ipsilateral metastatic lymph nodes was 36.6 mm and the mean z_{cran} of the contralateral metastatic lymph nodes was 35.9 mm, as can be seen in Table 3. Possibly the differences in z_{cran} between the 2 sides were too small to be significantly different. Despite the significance found, clinical reserve should be maintained.

We questioned whether elective lymph node irradiation is necessary for patients with only unilateral laryngeal cancer. By making two subgroups of patients, one group of patients with tumors that where strictly unilateral and another group of patients with tumors that crossed the midline, we were able to investigate the question. In the group of patients with only unilateral tumors we saw that in almost half of the patients (42%) contralateral metastatic lymph nodes were visible. And two patients only had contralateral lymph node metastases. This highlights the need for bilateral neck irradiation and confirms today's policy.

The present study has some limitations. One limitation is the delineation of the metastatic lymph nodes on CT. The Dutch guideline for laryngeal carcinomas recommends CT scan or MRI to be performed for almost all larynx carcinomas (2). CT and MRI have comparable sensitivity and specificity for the detection of lymph node metastases (33,34). FDG-PET/CT has been proven superior to CT alone for localization of metastatic lymph nodes (35,36). FDG-PET alone seems not to be superior in the detection of occult lymph node metastases in patients with a palpable negative neck (37). As this is a retrospective study, the first patients included were diagnosed for laryngeal cancer in 1995. At that time MRI or multimodality imaging was not standard at our clinic.

Our study consisted of only patients with advanced stage disease. A translation to the negative neck can be made but the study results are not specific to early stage disease. We delineated the gross tumor volume of the most cranial metastatic lymph node and pose that this gross tumor volume includes the margin of microscopic invasion in case of subclinical disease. That is the cranial border of the gross tumor volume found in this study could be used as the cranial border of the CTV in elective field radiotherapy. Lymph nodes are considered to be enlarged if they have a short-axis diameter greater than 1 cm. Assuming the lymph node to grow from its center, the cranial edge will be

located at higher distance from the BOS than the cranial edge of the clinical metastatic lymph nodes measured in this study. Probably taking a distance of 1.5 cm below the BOS as the cranial CTV border overestimates the number of lymph nodes covered, which keeps us on the safe side. This cranial CTV border does not include margins for patient motion or setup inaccuracy.

Conclusions

This study provides more evidence for selective nodal target volume delineation. In advanced laryngeal cancer, more than 50% of the cervical metastatic lymph nodes were located > 3.5 cm below the caudal border of the base of the skull. This counts for ipsilateral and for contralateral nodes. We found no difference between the location of the most cranial lymph node of patients with an unilateral tumor or patients with a tumor that crosses the midline.

Setting the cranial border of the nodal target volume 1.5 cm from the caudal border of the base of the skull covers 95% of the cranial metastatic lymph nodes and should be considered in elective nodal level II irradiation for laryngeal cancer. When assuming the lymph node to grow from its center, even a further distance from the base of the skull of 2.0 cm can be achieved. Bilateral neck irradiation is mandatory, including patients with unilateral laryngeal cancer, when elective irradiation is advised.

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Chapter 6

Intensity-modulated radiotherapy significantly reduces xerostomia compared with conventional radiotherapy

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Abstract

Purpose: Xerostomia is a severe complication after radiotherapy for oropharyngeal cancer, as the salivary glands are in close proximity with the primary tumor. Intensity-modulated radiotherapy (IMRT) offers theoretical advantages for normal tissue sparing. A phase II study was conducted to determine the value of IMRT for salivary output preservation compared with conventional radiotherapy (CRT).

Methods and materials: A total of 56 patients with oropharyngeal cancer were prospectively evaluated. Of these, 30 patients were treated with IMRT and 26 patients with CRT. Stimulated parotid salivary flow was measured before, 6 weeks, and 6 months after treatment. A complication was defined as a stimulated parotid flow rate <25% of the preradiotherapy flow rate.

Results: The mean dose to the parotid glands was 48.1 Gy (SD 14 Gy) for CRT and 33.7 Gy (SD 10 Gy) for IMRT ($p < 0.005$). The mean parotid flow ratio 6 weeks and 6 months after treatment was respectively 41% and 64% for IMRT and respectively 11% and 18% for CRT. As a result, 6 weeks after treatment, the number of parotid flow complications was significantly lower after IMRT (55%) than after CRT (87%) ($p = 0.002$). The number of complications 6 months after treatment was 56% for IMRT and 81% for CRT ($p = 0.04$).

Conclusions: IMRT significantly reduces the number of parotid flow complications for patients with oropharyngeal cancer.

Introduction

Xerostomia is a severe complication after radiotherapy of head-and-neck tumors resulting from the unavoidable irradiation of the salivary glands. This is mainly seen in treatment of cancer of the oropharynx and nasopharynx, and when there is nodal metastatic involvement that requires definitive or postoperative radiotherapy. Conventional radiotherapy (CRT) limits the sparing of the parotid glands in patients with oropharyngeal carcinoma as for irradiation generally 2 opposed lateral fields are used. Intensity-modulated radiotherapy (IMRT) has the potential to reduce the dose to healthy tissue without compromising the dose to the tumor volume. Since the development of IMRT, reduction of the dose to the parotid gland has been used to demonstrate the theoretical advantages of IMRT over conventional techniques (1-4). Although some parotid sparing can also be obtained using conventional techniques, it is generally accepted that IMRT is a valuable tool for reducing the dose to the parotid gland (5-9).

Dose-response relationships for the parotid gland have been determined using a variety of methods in small patient groups (10,11). Two dose-response curves obtained from relatively large patient groups are available. Both studies conclude that the mean dose to the parotid gland best predicts its function after radiotherapy, and this parameter is currently the best parameter to characterize dosimetrically a parotid-sparing IMRT technique (9,12). The facts that IMRT reduces the dose to the parotid glands and that a dose-response relationship exists that predicts a reduction in xerostomia complications has lead to a widespread use of IMRT to spare the parotid glands.

Various studies report subjective measurements; however the most adequate parameter to evaluate the function of the parotid gland is objective stimulated parotid flow measurement (13). Consequently in this report we will focus on objective measurements. One prospective study that objectively compares IMRT vs. CRT in oropharyngeal carcinoma has been reported. In this nonrandomized study of a heterogeneous group of 41 patients (19 oropharyngeal tumors), the radiation technique did not independently influence the functional outcome of the parotid glands (14). It is the aim of this study to compare prospectively the salivary function after CRT and IMRT in a homogeneous group of patients. As most parotid gland sparing can theoretically be achieved in oropharyngeal cancer treatment, we selected these tumors.

Methods and materials

From 1996 to 2005, a total of 56 patients with oropharyngeal cancer were enrolled in prospective salivary function studies at our department. Of these patients, 26 patients were treated with CRT 30 patients were treated with IMRT. None of the patients received previous radiotherapy or surgery of the parotid glands or had other malignancies or diseases of the parotid glands. No concomitant or induction chemotherapy was allowed, as this might influence the parotid function (15). The use of any medication known to affect salivary gland function was prohibited. Patients with evidence of distant metastatic disease were not included in the study, and a World Health Organization status of 0 to 1 was required. In all patients the diagnosis was histologically confirmed. Pretreatment evaluation at our department included a computed tomography (CT) scan, and, since 2001, magnetic resonance imaging (MRI) and positron emission tomography (PET) of the head-and-neck region. Staging for analysis accorded to the American Joint Committee on Cancer staging classification of malignant tumours (sixth edition, 2002). Written informed consent was obtained from each patient before entering the study.

CRT

A total of 26 patients received external beam radiotherapy with 6-MV photons using isocentric techniques. Treatment was according to standard methods at that time and no specific effort to spare the parotid glands was made. Opposing lateral fields were used for target volume coverage and an anterior field was used for the supraclavicular regions. To boost the primary tumor generally a lateral field and an oblique opposed lateral field were used. To boost the posterior neck region, electron beams were used after shielding the spinal cord at 40 Gy. The supraclavicular regions were treated with an anterior field using independent collimators. Four patients received postoperative 3-D radiation treatment planning. The clinical target volume included the operation area, abnormal nodes as seen on CT data and other ipsilateral and contralateral neck nodes at risk. The radiation dose varied with the diagnosis, according to generally accepted treatment strategies. The patients received 2 Gy daily fractions, 5 days per week. Prescribed target doses were as follows: 46 to 50 Gy for the clinically negative neck; 50 to 70 Gy for postoperative tumor beds and dissected neck sites, depending on the pathologic review; and 70 Gy for definitive radiotherapy. Most of the treatment fields

were set up using radiographs. From each patient, contrast-enhanced CT imaging of the head-and-neck region including whole major salivary glands, was performed with 3-mm slice thickness in the treatment position. When treatment fields were designed using radiographs, reconstruction of these fields took place on the CT slices. When 3-D treatment planning was used, this was performed using PLATO RTS (Nucletron BV, Veenendaal, The Netherlands). Dose distributions were calculated as prescribed previously (12).

IMRT

A total of 30 patients received parotid-sparing, inverse-planned, step-and-shoot IMRT with integrated boost. Contrast-enhanced CT imaging with 3-mm slice thickness was performed in treatment position with the patient immobilized with the mask. The CT-data were transferred to the planning system (PLATO RTS; Nucletron BV, Veenendaal, The Netherlands). The data of MRI and PET were, when available, matched with the CT data and used to delineate the target volumes. MRI was especially useful in target volume determination and delineation of the parotid glands in case of dental artefacts. PET was used to confirm or exclude borderline lymph nodes as seen on CT. The definition of the target volume followed the description in the International Commission on Radiation Units (ICRU) Report 50 and 62. The gross tumor volume (GTV), the clinical target volume (CTV) of the elective lymph nodes and the organs at risk (spinal cord, brain, and parotid glands) were delineated on each slice. The level II to IV nodes were included in the elective CTV. Neck nodes were treated bilaterally. The cranial border of level II on the ipsilateral side was the transverse process of C1 and on the contralateral side the transverse process of C2 (6,16). The CTV for the primary tumor and metastatic neck nodes was defined as the GTV plus a margin for potential microscopic spread, and was expanded uniformly 1 cm in three dimensions according to the protocol of our institute. The dorsal margin expanded until the anterior part of the vertebra. The planning target volume (PTV) was defined as the CTV plus a margin of 5 mm.

Intensity-modulated radiotherapy plans were obtained using the inverse treatment-planning module PLATO-ITP, version 1.1 (Nucletron BV). Five equidistant beams, starting at 0º, were used. Beam numbers, dose constraints and penalties have been reported previously (17). After 21 patients had been treated, a seven-beam technique was applied. The mean number of segments was 72 (range 44-110). All plans were

dosimetrically verified on the treatment machine using ionisation chamber and film measurements. Verification of patient position was performed the first 3 fractions and then once a week. The prescribed dose to the GTV of the macroscopic tumor was 69 Gy in 2.3 Gy daily fractions and to the CTV 66 Gy in 2.2 Gy daily fractions. For the elective irradiation of the lymph nodes a dose of 54 Gy in 1.8 Gy daily fractions was prescribed. Patients were treated 5 times per week.

Treatment delivery

During treatment, all patients were immobilized in supine position using customized facial masks for reproducible positioning. A continuous course of radiotherapy consisting of daily fractions 5 days per week was delivered to all patients. The patients treated with CRT received 33 fractions (mean; range, 25-40) delivered in 47 days (mean; range, 33-57). Patients were treated with IMRT in 30 fractions in a time period of 42 days (mean; range, 40-49). An example of the dose distribution for CRT and IMRT is shown in Fig. 1.

Parotid gland delineation

For both CRT and IMRT, the left and right parotid gland of each patient was outlined on multiple axial CT slices. The CT slices had a maximum slice thickness of 3 mm. The entire parotid gland was delineated without differentiation between the deep and superficial lobe. Dose distributions were calculated using a 3-D pencil beam convolution algorithm. The information from the calculated dose distribution was condensed into dose-volume histograms for the entire organ, as presented before (12). Separate dose-volume histograms were generated for the left and right parotid gland.

Parotid flow measurements

The parotid salivary flow rates were measured before treatment, 6 weeks, and 6 months after radiotherapy as previously described (12,18). In brief, bilateral stimulated parotid saliva was collected using Lashley cups, which were placed over the orifice of the Stenson’s duct. The left and the right parotid gland were measured separately. Stimulation was created by application of a 5% acid solution on the mobile part of the tongue. Patients were instructed not to eat or drink 60 min before saliva collection. The parotid flow measurements at each visit were converted into the percentage of baseline

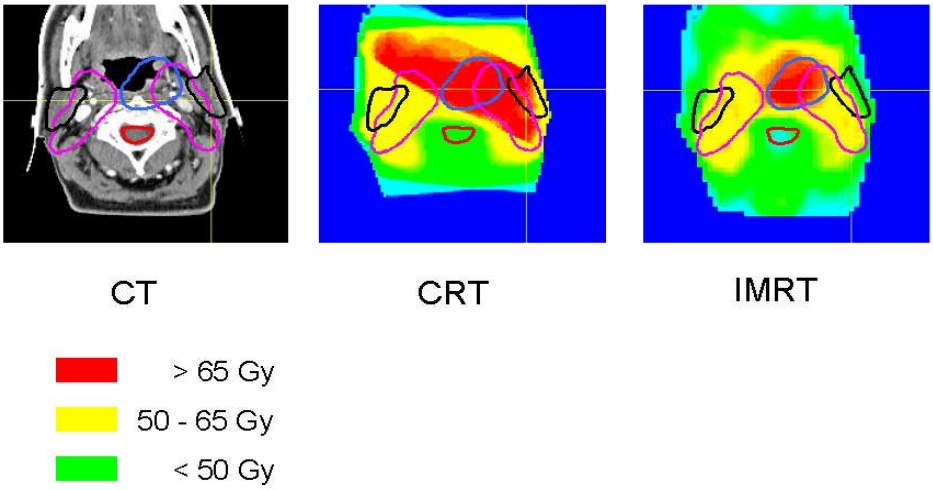

Figure 1. An example of the dose distribution achieved with conventional radiotherapy (CRT) and with intensity-modulated radiotherapy (IMRT) for the same patient with T3N0 oropharyngeal cancer. Both plans shown for the same axial computed tomography (CT) slice. The tumor bed (dark blue), regional lymph nodes (purple), parotid glands (black), and the spinal cord (red) are delineated. The parotid gland dose is substantially reduced for the IMRT plan compared with the CRT plan.

flow rates. A complication was defined for each individual gland as the stimulated parotid flow rate <25% of the pretreatment parotid flow rate (19).

Statistical analysis

Descriptive statistics (mean, median, proportions) were calculated to characterize the patient, the dose to the parotid gland, the parotid gland volume and the flow ratio. The parotid salivary flow measurements were analyzed separately for the left and right parotid gland. Patient characteristics, the mean dose to the parotid gland, and the parotid gland volume were analyzed for statistical significance using the Mann-Whitney test. To detect statistical difference in proportions Fisher's Exact test was used. All analysis was performed using SPSS 10.1 (SPSS Inc., Chicago, IL). All statistical tests were two-tailed as appropriate, and a criterion of $p < 0.05$ was accepted for significance.

Results

Characteristics of the 56 patients are outlined in Table 1. The IMRT and CRT group had comparable distributions of gender, age, and stage grouping. In the CRT group significantly more patients received postoperative irradiation (n = 20) than in the IMRT group (n = 5) (p <0.005). The mean total dose of patients treated with CRT was 65.9 Gy (range, 50-70Gy). Two patients (9%) received a total dose of 50 Gy, 5 patients (22%) received 60 Gy, 1 patient (4%) received 66 Gy, and 15 patients (65%) received 70 Gy. Of the 15 patients, 10 who received a total dose of 70 Gy did so postoperatively. Of these patients, 5 had local surgery and 5 had surgery of the primary tumor and the neck nodes. Of the patients treated with CRT, 4 patients (15%) had a tumor stage T1, 10 (39%) T2, 4 (15%) T3, and 8 (31%) T4. Of the patients treated with IMRT, 9 patients (30%) had a tumor stage T1, 14 (47%) T2, 6 (20%) T3, and 1 (3%) T4. The difference in T status between the two groups was statistically significant (p = 0.003). Of the patients treated with CRT 11 patients (42%) had nodal status N0, 6 (23%) N1, 1 (4%) N2a and 8 (31%) N2b. Of the patients treated with IMRT, 11 patients (37%) had nodal status N0, 4 (13%) N1, 1 (3%) N2a, 11 (37%) N2b and 3 (10%) N2c. No significant difference was found in N status between the two groups (p = 0.27). Stage grouping is presented in Table 1; the distribution between the two groups is comparable (p = 0.52).

The mean volume of the parotid gland was 23 cc (range, 5-51 cc; SD, 9) and 26 cc (range, 9-60 cc; SD, 10) for CRT patients and IMRT patients, respectively (p = 0.12). The mean dose to the parotid glands was significantly lower for patients receiving IMRT treatment (p < 0.005) (Table 2). Flow measurements 6 weeks and 6 months after radiotherapy were available for respectively 37 and 32 parotid glands in the CRT and respectively 47 and 39 parotid glands in the IMRT patients. The mean parotid flow ratio 6 weeks after IMRT amounted to 41%. This was higher than the mean flow ratio of 11% obtained after CRT. At 6 months, the mean parotid flow ratio was 18% in the CRT patients and 64% in the IMRT patients. Figure 2 shows the parotid flow ratios at 6 weeks and 6 months after treatment as a function of the mean parotid gland dose. The parotid gland complication rate 6 weeks after treatment was 87% (32/37) for CRT and 55% (26/47) for IMRT. This difference is statistically significant (p = 0.002) when independent glands are assumed. At 6 months after treatment the parotid gland complication rate was 81% (26/32) for CRT and 56% (22/39) for IMRT (p = 0.04).

Table 1. Patient and tumor characteristics, *n* (%)

	CRT (*n* = 26)		IMRT (*n* = 30)		*p* - value
Gender					
Male	16	(61)	18	(60)	0.91
Female	10	(39)	12	(40)	
Age (y)					
Median	55		58		0.19
Range	41-76		43-88		
Stage grouping					
Stage I	1	(4)	1	(3)	0.52
Stage II	2	(8)	4	(13)	
Stage III	7	(27)	9	(30)	
Stage IV	16	(61)	16	(53)	
Radiotherapy					
Definitive	6	(23)	25	(83)	<0.005
Postoperative					
Primary site	6	(23)	-		
Neck dissection	-		4	(13)	
Both	14	(54)	1	(3)	

Abbreviations: CRT = conventional radiotherapy; IMRT = intensity-modulated radiotherapy.

Table 2. Parotid gland function parameters for patients with oropharyngeal cancer treated with conventional radiotherapy (CRT) and intensity-modulated radiotherapy (IMRT)

Parameter	CRT (*n* = 26)	IMRT (*n* = 30)	*p* - value
Parotid gland dose (Gy)			
Mean	48.1	33.7	< 0.005
Range	3.6 – 68.7	13.6 – 60.6	
6 Weeks			
Flow ratio (%)	11	41	< 0.005
Complications (%)	87	55	
6 Months			
Flow ratio (%)	18	64	0.04
Complications (%)	81	56	

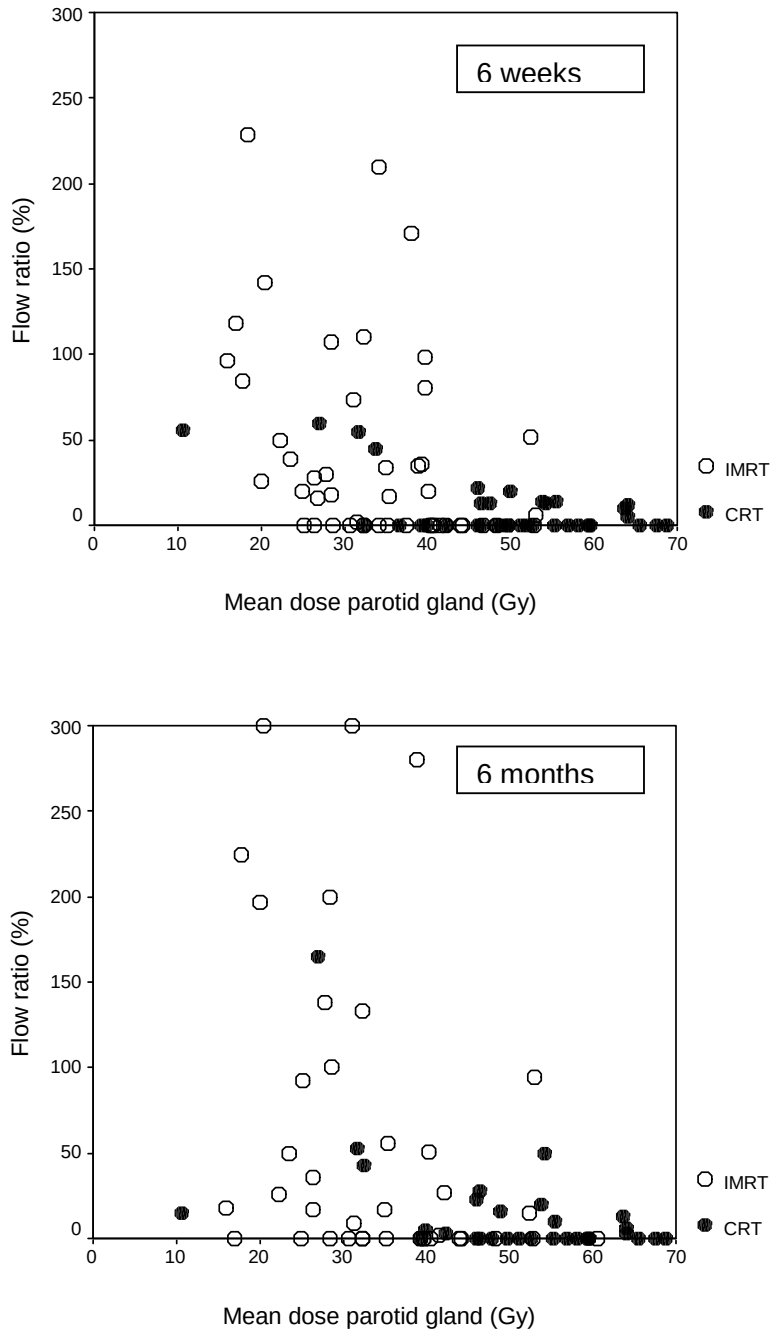

Figure 2. Stimulated parotid flow rates as a function of the mean dose to the parotid gland 6 weeks and 6 months after intensity-modulated radiotherapy (IMRT) compared with those after conventional radiotherapy (CRT). Flow rates are expressed as the percentage of the preradiotherapy (RT) flow rates for each parotid gland. In the lower graph (6 months), two data points with very high flow ratios (315% and 417%) are depicted at 300%.

Discussion

Reducing the dose to the parotid gland is the key for preserving parotid function. This study showed a significant reduction of the dose to the parotid gland reached by IMRT compared with CRT. As a result, 6 weeks and 6 months after treatment, the number of parotid flow complications was significantly lower after IMRT (55% and 56%, respectively) than after CRT (87% and 81%, respectively) for patients with oropharyngeal cancer. To our knowledge, this is the first Phase II study that objectively quantifies the advantages of IMRT compared with CRT for parotid sparing radiotherapy in a homogeneous group of patients with oropharyngeal cancer.

A great absolute improvement of the mean parotid flow ratio, from 41% to 64% for IMRT was found between 6 weeks and 6 months after treatment, and CRT showed an absolute improvement at the same time points from 11% to 18%. The relative improvement between the two time points was 64% for IMRT and 61% for CRT. Despite the flow ratio improvement, the number of complications after IMRT did not decrease (from 55% to 56%) and decreased only slightly after CRT (from 87% to 81%) ($p = 0.55$). This might be explained by the number of patients with a complication that remains quite constant in time and do not show improvement of parotid function, whereas the patients without a complication show recovery of the parotid gland function and therewith show an increase in flow ratio in time.

Several aspects of salivary function were not examined in this study that may have impact on xerostomia. The subjective assessment of salivary function was not examined in this investigation. Not only the parotid glands but also the submandibular and probably the minor salivary glands may have an impact on xerostomia. Patients included in this study were not receiving concomitant or induction chemotherapy and medication known to affect salivary function. We restricted our study to the parotid salivary glands and objective assessment of their function.

One limitation of our study is that it is a nonrandomized study, which inevitable carries the consequence of differences in patients groups. The best assessment of comparing parotid function after IMRT and CRT would be a randomized study. Because IMRT is often adapted as standard therapy due to theoretical advantages, it is however difficult to include patients in such a study. Consequently no randomized study measuring parotid flow has been reported.

Although there was no statistical difference in stage grouping, there was a difference in tumor characteristics between the two patient groups. More patients treated with CRT had a tumor >4 cm in greatest dimension or invading in adjacent structures (46%) compared with patients receiving IMRT (23%). When IMRT was implemented at our department, we started treatment carefully and included only patients with a small tumor and receiving definitive radiotherapy. As our experience increased we also included patients for IMRT with larger tumors and in some cases extensive neck disease was treated by surgery before IMRT. Although not statistically significant, there was a difference in nodal status. Of 30 patients, 15 (50%) receiving IMRT had nodal status 2a or higher, compared with 9 of 26 patients (34%) receiving CRT. The first patients receiving CRT were included in a study in 1996. At that time, surgery of the neck nodes was the standard treatment in our hospital. During the following years radiotherapy was more advocated, resulting in more patients with definitive radiotherapy treatment, as can be seen in Table 1. This might have resulted in more unfavourable irradiation target volumes for patients treated with IMRT and consequently a higher dose to the parotid gland. Despite this, however, the mean dose to the parotid gland was significantly lower in the group of patients treated with IMRT compared with CRT.

Four patients of the CRT group received postoperative 3-D radiation treatment planning (3D-CRT). It is suggested that by using 3D-CRT, the incidence of xerostomia would be less compared with conventional radiotherapy. Partial parotid sparing is feasible using 3D-CRT in unilateral and bilateral head and neck radiation resulting in some salivary function preservation (20,21). Unfortunately, no clinical data objectively comparing xerostomia using 3D-CRT and IMRT in case of oropharyngeal cancer have been published, by our means. A previous planning study of 12 patients with oropharyngeal cancer showed a reduction of the mean parotid gland dose using IMRT compared with 3D-CRT. A mean dose to the parotid gland of 51 Gy using 3D-CRT was found compared with 33 Gy using IMRT (6). These results are very comparable to the mean dose values in this clinical study where a reduction of the mean parotid dose from 48.1 Gy to 33.7 Gy was observed by using IMRT.

The mean parotid dose of 33.7 Gy found in this study is higher than the generally agreed dose goal of approximately 26 Gy, a dose that is considered low enough for parotid gland preservation. This value is based on studies reporting the existence of a dose threshold for the parotid gland at 26 Gy and 32 Gy for stimulated salivary flow (9,14).

However, also reduction in flow at low dose levels has been reported without identification of a dose threshold (12,18).

Two studies with large patient groups are available in which a dose-response curve for parotid function is obtained (9,12). The reported TD_{50} values in these studies amount 39 Gy and 28 Gy for the same endpoint (flow ratio <25% 1year after radiotherapy) and the same method of parotid salivary flow measurements (stimulated parotid flow measured with Lashley cups). The discrepancy might be caused by differences between the radiation techniques CRT, 3D-CRT, and IMRT. Another possibility is that these results are obtained using the mean dose to the parotid gland, which might not be valid. In both studies the parotid gland mean dose was found to be the best predictor of parotid gland function. Chao et al. investigated different mathematical models to characterize the reduction in flow as a function of the dose distribution to the parotid gland. Several fitted dose-volume models (mean dose-exponentional model, equivalent uniform dose-exponentional model, parallel-exponentional model, exponentional-sigmoid model) provided good data description. No superior model was found. These investigators concluded that the mean-dose-exponentional model provided a good representation and had the advantage of being a single parameter model. Using this model they estimated a mean parotid dose of 25.8 Gy likely to reduce the complication rate, regardless of the treatment delivery method (CRT; IMRT) (22). The observation that all three studies demonstrate that the mean dose to the parotid gland best predicts its function after radiotherapy led to our use of this parameter in this study.

One study has been published that objectively compares parotid gland function in patients treated with IMRT and CRT. In this prospective clinical study xerostomia was investigated in a heterogeneous group (50% oropharyngeal tumors) of 27 IMRT patients and 14 patients treated by conventional means. The parotid flow ratio correlated with the mean parotid dose and the mean parotid dose was lower in the IMRT group. However use of IMRT vs. CRT did not independently influence the functional outcome of the salivary glands in this study (14).

Eisbruch et al. reports in several papers on the parotid flow after parotid-sparing conformal radiotherapy and forward-planned IMRT. Improvement in time in xerostomia and increased salivary flow from the spared glands were observed in a heterogeneous group of patients. The mean parotid flow ratio in a study for the contralateral spared parotid gland (mean dose 19 Gy) 1 year after radiotherapy reaches a value >100%. The

number of complications after IMRT cannot be deduced from the published data, however, and a comparison with conventional techniques is difficult to make (9, 23-25). Studies reporting on IMRT results for oropharyngeal cancer without a control group have also been published. Parliament et al. reports on a heterogeneous group of 22 patients treated with IMRT. From the data it can be deduced that 1 year after radiotherapy 7 of 18 patients (40%) had a stimulated whole-mouth salivary flow <25%, compared with 11 of 18 patients (61%) with unstimulated whole mouth salivary flow (26). Saarilahti et al. reports on 17 patients (11 oropharyngeal cancer) treated with IMRT and measured whole saliva to monitor the salivary function. Because whole saliva was measured, no difference could be made between the function of both parotid glands and the submandibular glands, and the number of parotid gland complications is difficult to assess (27).

Conclusions

Our study quantifies objectively the great advantage of IMRT compared with CRT for parotid-sparing radiotherapy in patients with oropharyngeal cancer. By using IMRT we were able to reduce the mean dose to the parotid gland compared with CRT. This resulted in a statistical significant reduction of salivary flow complications of 87% after CRT to 55% after IMRT, 6 weeks after radiotherapy ($p = 0.005$). Six months after treatment, the number of complications was 81% after CRT and 56% after IMRT ($p = 0.04$).

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Chapter 7

Preserved salivary output after intensity-modulated radiotherapy does not result in improved subjective outcome: a comparison with conventional treatment

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Abstract

Purpose: Intensity-modulated radiotherapy (IMRT) has been shown beneficial in head-and-neck cancer regarding sparing the parotid glands. We previously demonstrated significant improvement of objective xerostomia after IMRT compared with conventional radiotherapy (CRT) in patients with oropharyngeal cancer. We now evaluate the objective and subjective outcomes with longer follow-up.

Methods and materials: A total of 56 patients were prospectively enrolled in salivary function studies. Of these, 30 patients were treated with IMRT and 26 with CRT. The stimulated parotid salivary flow, subjective xerostomia using the LENT-SOMA scale, and adverse effects were monitored till 12 months follow-up. A complication was defined as stimulated parotid flow rate <25% of pre-treatment flow rate.

Results: With a median follow-up of 24 months, the 1- and 2-year local recurrence-free survival rates were 86% and 82% for patients treated with IMRT. Twelve months after treatment the mean parotid flow ratio was 73% for IMRT compared with 23% for CRT. At that time the number of complications was 43% for IMRT and 83% for CRT ($p = 0.001$). There was no significant difference in subjective outcome between the two groups at all time points. At 12 months 52% and 24% IMRT and 29% and 43% CRT complained of partial and complete persistent dryness.

Conclusions: Significant long-term preservation of the parotid gland function was achieved using IMRT compared with CRT. However, no difference in subjective xerostomia between the treatment modalities was observed. More than 70% of patients complained of partial or complete persistent dryness at twelve months after parotid-sparing treatment.

Introduction

Xerostomia is a common and severe complication after radiotherapy of head-and-neck cancer resulting from the unavoidable irradiation of the salivary glands. Intensity-modulated radiotherapy (IMRT) has been shown beneficial in head-and-neck cancer regarding sparing the parotid glands, due to its excellent dose conformity (1-5). A reduction of the dose to the parotid glands has been shown using IMRT compared with conventional radiotherapy (CRT) (6-9). A dose-response relationship for the parotid gland has been reported (10;11). Consequently a reduction in dose might result in a reduction of parotid flow complications; defining a complication as a stimulated parotid flow rate <25% of the pre-radiotherapy flow rate. We have reported this reduction in complications following IMRT in oropharyngeal cancer in a previous report (6). Various studies report on subjective xerostomia, however in most cases there is incongruence between the patients' complaints of a dry mouth and the objective parotid salivary flow measurement (12-14). But also a correlation between the two has been reported (15).
Previously we reported a significant reduction in number of parotid flow complications for patients with oropharyngeal cancer using IMRT compared with CRT till 6 months follow-up (6). For the current study, the median follow-up of the cohort has been extended to more than one-year. We investigated whether the reduction in parotid flow complications using IMRT compared with CRT for patients with oropharyngeal cancer continued in time. Second objectives included subjective xerostomia, efficacy of treatment, and toxicity profile.

Methods and materials

From 1995 to 2005, 56 patients with oropharyngeal cancer were enrolled in prospective clinical salivary function studies. Of these patients, a total of 26 patients were treated with CRT and 30 patients were treated with inverse-planned step-and-shoot IMRT with integrated boost. All patients were treated with curative intent. Histological diagnosis was confirmed in all cases. Patients were excluded from the study if they had previous radiotherapy or surgery of the parotid glands, suffered from other malignancies or diseases of the parotid glands, had WHO performance status less than 2, used concomitant or induction chemotherapy, had evidence of distant metastatic disease, or severe concomitant disease (16). Patients using any medication known to affect the

parotid glands were not included. Staging accorded to the 6th edition American Joint Committee on Cancer staging classification of malignant tumors 2002.

Pre-treatment evaluation included a computed tomography (CT) scan and since 2001 magnetic resonance imaging (MRI) and positron emission tomography (PET) of the head-and-neck region. Patients were evaluated regularly during treatment. Generally follow-up consisted of clinical examination of the head-and-neck while additional investigations were performed in case of suspicious findings. In addition, treatment-related adverse events were scored according to the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC) criteria (17).

This phase II study was conducted in compliance with the declaration of Helsinki and good clinical practice guidelines. All patients provided their written informed consent before entering the study.

Radiation techniques

From 1996 till 1998 a total of 26 patients were treated with external beam radiotherapy with 6-MV photons using isocentric techniques. No specific effort was made to spare the parotid glands and treatment was according to standard methods at that time. Prescribed doses were 70 Gy to the macroscopic tumor planning target volumes (PTV), 50-70 Gy for resected tumor bed PTV's and dissected neck sites, and 46-50 Gy for the clinically negative neck (6;10). All patients received 2 Gy daily fractions, 5 days per week. Four patients received postoperative 3-D radiation treatment planning, which was performed using PLATO RTS (Nucletron BV, Veenendaal, The Netherlands). Since 2001, parotid-sparing inverse-planned step-and-schoot IMRT with integrated boost has been used (18), thus a second group of 30 patients received IMRT. IMRT plans were obtained using the inverse treatment-planning module PLATO-ITP, version 1.1 (Nucletron BV). The prescribed dose to the gross target volume (GTV) of the macroscopic tumor was 69 Gy in 2.3 Gy daily fractions, to the clinical target volume (CTV) 66 Gy in 2.2 Gy daily fractions, and the dose to the clinically negative neck was 54 Gy in 1.8 Gy daily fractions. All treatment plans were dosimetrically in a phantom verified. Patients were treated 5 days per week. Details of the radiation techniques have been reported previously (6;10;18).

Objective and subjective salivary gland function measurements

Stimulated bilateral parotid gland function was objectively measured using Lashley cups. (10;19). The left and right parotid glands were measured separately. Stimulation was performed by application of 5% acid solution on the mobile part of the tongue. At each visit, the stimulated parotid flow rates were converted into the percentage of the baseline flow rates (ratio). A complication was defined as a stimulated parotid flow ratio <25% (20). Subjective salivary gland function was evaluated using the late effects of normal tissue-subjective objective management analytic scoring scale (LENT-SOMA scale) (20;21). Using the LENT-SOMA scale, the patients' perception of a dry mouth is assessed in 4 grades: 0-none, 1-occasional dryness, 2-partial dryness, and 3-complete persistent dryness. Both objective flow measurements and LENT-SOMA scale were measured before treatment, and 6 weeks, 6 months and 12 months after treatment.

Statistical methods

Descriptive statistics (mean, median, range, proportions) were calculated to state the patient characteristics. The overall survival (OS), and local recurrence-free survival (LRFS) for patients treated with IMRT were estimated using the Kaplan-Meier method with the time to event measured from the start of first radiation treatment (22). All recurrences, before or after the detection of distant metastases, were taken into account. For analysis of OS all causes of death were considered. The censor date was 1st of December 2006. Data from patients who remained free of local disease were censored as the date when the last follow-up information was obtained. The parotid salivary flow measurements were analyzed separately for the left and right parotid gland. Statistical analysis of the differences between both treatment groups was performed using the two-independent samples test, and Chi-square test. All tests were two-sided as appropriate. All analysis was performed using SPSS 10.1 (SPSS Inc., Chicago, IL). A criterion of $p < 0.05$ was used for statistical significance.

Table 1. Patient and tumor characteristics, *n* (%)

	CRT (*n* = 26)	IMRT (*n* = 30)
Gender		
Male	16 (61)	18 (60)
Female	10 (39)	12 (40)
Tumor stage		
T1-2	14 (54)	23 (77)
T3-4	12 (46)	7 (23)
Nodal stage		
N0	11 (42)	11 (37)
N+	15 (48)	19 (63)
AJCC stage		
I	1 (4)	1 (3)
II	2 (8)	4 (13)
III	7 (27)	9 (30)
IV	16 (61)	16 (53)
Radiotherapy		
Definitive	6 (23)	25 (83)
Postoperative	20 (77)	5 (16)

Abbreviations: CRT = conventional radiotherapy; IMRT = intensity-modulated radiotherapy; AJCC = American Joint Committee on Cancer.

Results

Patient characteristics

More men than women were included in both groups (Table 1). The median age was 55 years (range, 41-76 years) and 58 years (range, 43-88 years) for CRT and IMRT, respectively (p = 0.91). Fifty-four percent of the patients treated with CRT had a T1-2 primary tumor and 46% were T3-4, which was significantly different from the patients treated with IMRT of whom 77% had a T1-2 primary tumor and 23% a T3-4 (p = 0.003). More patients treated with IMRT had positive or metastatic lymph nodes (63%) compared with 48% in the CRT patient group (p = 0.15). The disease stage distribution between CRT and IMRT was not significantly different (p = 0.52) (Table 1). Twenty-three percent of the CRT patients were treated only with radiotherapy compared with 83% of the IMRT group (p < 0.005). Of the postoperative patients in de CRT group, 6 patients (23%) had only resection of the primary site, and 14 patients (54%) had resection of the primary site and a neck dissection. Of the postoperative patients treated with IMRT, 4 patients (13%) had only a neck dissection and 1 patient (3%) had a resection of both the primary site and a neck dissection.

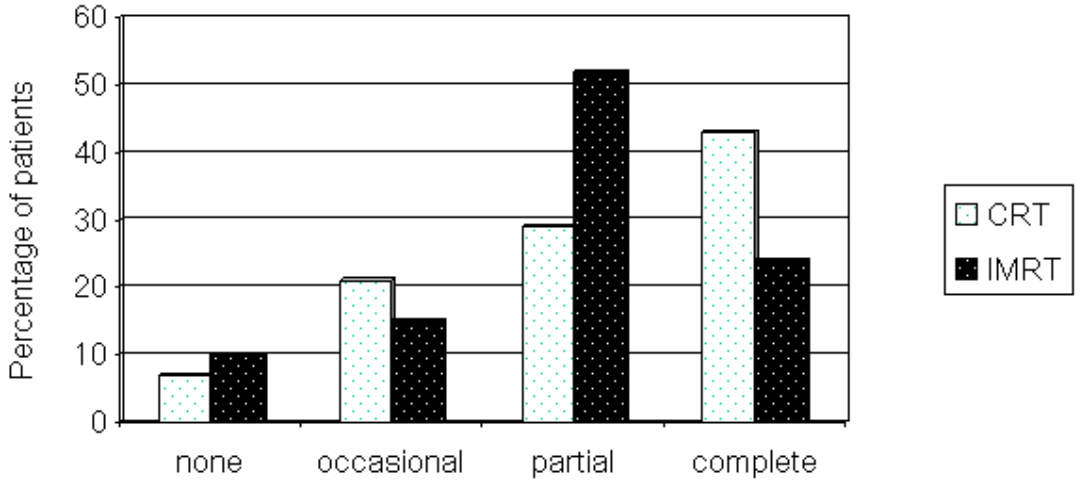

Figure 1. Degree of xerostomia 12 months after finishing treatment according to the LENT-SOMA scale. A division has been made between patients treated with conventional radiotherapy and intensity-modulated radiotherapy.

Objective and subjective parotid gland function

The mean dose to the parotid glands was 48.1 Gy (SD14 Gy) and 33.7 Gy (SD 10 Gy) for patients treated with CRT and IMRT, respectively. This difference was statistically significant ($p < 0.005$). The mean stimulated flow ratio improved in time after CRT from 11% at 6 weeks, to 18% at 6 months and 23% at 12 months after treatment. After IMRT, the mean stimulated flow rate improved from 41% at 6 weeks, to 64% at 6 months and to 73% at 12 months. As a result, the number of parotid flow complications after IMRT (55%) was significantly lower than after CRT (87%) 6 weeks after treatment ($p = 0.002$). This difference in complications remained significantly different between the two treatment groups and was 43% after IMRT and 83% after CRT 12 months after treatment ($p = 0.002$) (Table 2).

Subjective symptoms using the LENT-SOMA scale were not significantly different between the two groups at 6 weeks, 6 months, and 12 months. At twelve months after treatment 52% (11 out of 21) IMRT and 29% (4 out of 14) CRT complained of partial xerostomia, and 24% (5 out of 21) IMRT and 43% (6 out of 14) CRT complained of complete persistent xerostomia, respectively (Table 3, Fig. 1).

Table 2. Number of complications (%) after treatment with CRT and IMRT at different time points. A complication was defined as stimulated parotid flow rate <25% of the pre-radiotherapy flow rate. Number of glands measured between parentheses.

Time point	CRT	IMRT	*p* - value
6 weeks	87 (37)	55 (47)	0.002
6 months	81 (32)	56 (39)	0.03
12 months	83 (29)	43 (40)	0.001

Abbreviations: CRT = conventional radiotherapy; IMRT = intensity-modulated radiotherapy.

Table 3. Subjective xerostomia assessed after radiotherapy using the LENT-SOMA scale. The percentage of patients is presented with the number of patients between parentheses.

	0		1		2		3	
Baseline								
CRT	76	(19)	16	(4)	8	(2)	0	(0)
IMRT	70	(21)	20	(6)	10	(3)	0	(0)
6 weeks								
CRT	10	(2)	25	(5)	40	(8)	25	(5)
IMRT	3	(1)	31	(9)	28	(8)	38	(11)
6 months								
CRT	5	(1)	15	(3)	30	(6)	50	(10)
IMRT	0	(0)	29	(7)	33	(8)	38	(9)
12 months								
CRT	7	(1)	21	(3)	29	(4)	43	(6)
IMRT	10	(2)	14	(3)	52	(11)	24	(5)

Abbreviation: LENT-SOMA: late effects of normal tissue-subjective objective management analytic scoring scale.

Efficacy / treatment outcome after IMRT

With a median follow-up of 24 months (range, 5-49 months) for all patients, the 1- and 2-year estimated overall survival rates were 86% and 77%, respectively. The 1- and 2-year estimated local recurrence-free survival rates were 86% and 82% (Fig. 2). Local recurrence was observed in 5 of the 30 patients. Median time to local tumor progression was 7 months (range 4-13). Three patients underwent salvage surgery for recurrent disease, which made one patient tumor-free, and two patients developed a second local recurrence at later stage. These two patients were then treated palliative. Two patients

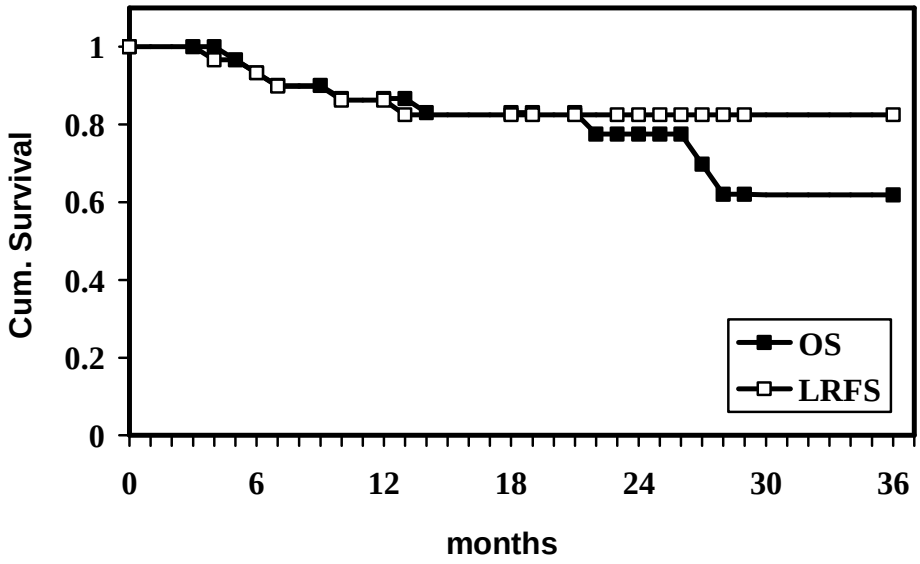

Figure 2. Kaplan-Meier estimates of overall survival (OS) and local recurrence-free survival (LRFS) of patients treated with intensity-modulated radiotherapy.

developed regional recurrence together with the local recurrence. Both patients had metastatic lymph nodes at diagnosis. Of the patients without metastatic lymph nodes, no regional recurrences were seen. One patient developed distant metastases during follow-up, and was treated palliative. At the censor date, mortality from all causes was observed in 8 patients out of 30. Twenty-two patients were still alive (20 without disease and 2 with disease), 5 died of the disease, 1 died due to complications and 2 died for other reasons without disease.

Acute and late toxicity following IMRT

No patient had treatment break due to radiation toxicity or other cause. All patients had mucositis of varying degree during treatment till median 6 weeks (range, 3-13) after finishing treatment. Three patients (10%) suffered from grade 1 mucositis (moderate erythema), 4 (14%) grade 2 (severe erythema), 8 (28%) grade 3 (patchy mucositis), and 14 (48%) grade 4 (confluent mucositis). Thirteen patients (22%) suffered from grade 1 dermatitis (follicular, moderate erythema), 9 (15%) grade 2 (severe erythema, moist desquamation), and 6 (21%) grade 3 (confluent moist desquamation). Seven patients required tube feeding. One patient died caused by the radiation treatment. This patient was a 65-year-old male with T3N0 left tonsil cancer, which was treated with definitive

IMRT. After treatment he remained suffering from pain. Five months after treatment he died caused by an infected ulcer located close to the carotid artery. During autopsy an in-field radiation ulcer was found without residual tumor. This necrotic area was located in the area that received 60-69 Gy.

Discussion

A significant reduction in complications was found using IMRT compared with CRT, not only at short-term, but also 6 and 12 months after treatment ($p = 0.04$ and $p = 0.002$, respectively). No significant difference in subjective symptoms was found. At twelve months after treatment, 76% (52% and 24%) IMRT and 72% (29% and 43%) CRT complained of partial and complete persistent dryness, respectively.

Although this is not a randomized study with only a limited number of patients, the reduction in objective xerostomia was very evident. It has been argued that the best way to establish the reduction in parotid flow complications using IMRT compared with CRT for patients with oropharyngeal cancer would be to conduct a randomized controlled trial. From an ethical perspective however, such a trial will be almost impossible to justify and only one randomized trial concerning early-stage nasopharyngeal cancer has been reported (23). In this initial report at twelve months follow-up the stimulated parotid salivary flow was significantly better using IMRT than CRT. In both groups the dry mouth score showed improvement over time and was lower at twelve months using IMRT than CRT.

In studies reporting on oropharyngeal cancer treated with IMRT without saliva measurements the LENT-SOMA scale, patient-reported questionnaires like the EORTC QLQ-C30/H&N35 or dedicated in-house developed xerostomia questionnaires are applied (17;24-26). A matched case-control study was reported in which 30 IMRT patients with 10-matched CRT patients were compared. Validated questionnaires were used to compare QOL and subjective xerostomia at several time points after treatment. In the IMRT group significant improvement of salivary function in time was observed which could not be shown for the small group of conventionally treated patients. At 12 months after treatment the median xerostomia scores were lower (better) in the IMRT group compared with the CRT group, but this difference did not reach statistical significance (27). Another report showed subjective improvement of xerostomia in 27

IMRT patients (24 oropharyngeal cancer) compared with 183 CRT patients (78 oropharyngeal cancer). This improvement concerned only a subgroup of IMRT patients when the mean dose to the contralateral parotid gland was less than 26 Gy. They used the University of Michigan Xerostomia Questionnaire and measured once, at least 1 year after treatment (28). The subjective xerostomia measured by the LENT-SOMA as used in this study might not be congruent with the reported rate of xerostomia measured by the EORTC questionnaires (29). As both questionnaires exist of only one question on subjective xerostomia, it might be questioned whether these questionnaires are best to use to evaluate xerostomia. Since 1996 the LENT-SOMA questionnaire is used in our clinic. When starting IMRT treatment in 2002, we started also using the EORTC questionnaires and an in-house developed questionnaire. As a consequence for comparison we used the LENT-SOMA outcomes in this study.

A drawback of this study is the use of the RTOG/EORTC toxicity scale. The first patients entered salivary studies at our department in 1996, a time when the RTOG/EORTC toxicity scale was used. When IMRT was introduced our department, we decided to continue scoring of toxicity with this scoring system. However not long after the study was launched a report was published including new guidelines for grading the adverse effects of cancer treatment, the common toxicity criteria (CTC) version 2.0 (30). A pilot study conducted by the RTOG confirmed that this version represented an improvement in the evaluation and grading of acute toxicity (30). In 2003 an updated version was available and published, now called the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (31). This recent version comprises in a comprehensive multimodality grading system the acute and late effects of cancer treatment. We agree that standardized reporting of toxicities improves the comparison of outcomes of different trials and support the use of CTCAE version 3.0.

The submandibular glands are the main contributors of saliva production during rest and therefore might have a higher impact on subjective xerostomia than the parotid glands. As analyzed by Saarilahti et al, lowering the dose to the submandibular glands can reduce subjective xerostomia. As the submandibular glands are included in level IB and located very near level II lymph nodes, sparing cannot be adjusted for a large group of patients and will be available just for a small patient selection who will possibly benefit from the dose reduction (32;33). In our study, no effort was taken for sparing the submandibular glands.

Several studies reported outstanding results using IMRT, with overall survival rates exceeding 85%. However, these results are difficult to compare with our results as different tumor stages are described as well as different IMRT techniques, like IMRT delivery in combination with conventional radiotherapy or IMRT restricted to boost the primary tumor region. Furthermore, many studies report the results of a non-homogeneous group of patients with head-and-neck cancer and not oropharyngeal cancer in specific. Two to 4-year estimates of overall survival rates including patients treated with postoperative or definitive IMRT and some receiving chemotherapy, range from 84.9% to 100% (7;34-36). In this present study of 30 patients receiving radiotherapy without chemotherapy, a 2-year estimated overall survival of 77% and local recurrence-free survival of 82% were found, which is lower than achieved by others mentioned above. The large number of patients with metastatic lymph nodes (63%) treated with IMRT in this study might cause this difference. These patients have a worse prognosis than patients without lymph node involvement.

Conclusions

A reduction of the dose to the parotid glands was achieved using IMRT compared with conventional techniques. This resulted in higher long-term objective flow values and diminished complication rates. Nevertheless a significant difference in subjective xerostomia between the treatment modalities was not observed. Still more than 70% of patients complained of partial or complete persistent dryness 12 months after parotid sparing IMRT.

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Chapter 8

General discussion

Three pairs of major salivary glands and numerous minor salivary glands produce saliva. In healthy individuals 1-1.5 L per day of saliva is produced. The major salivary glands (parotid, submandibular, and sublingual) produce about 90% of the salivary secretions, and the minor salivary glands produce the remainder. The parotid glands produce about 60-65% of the total salivary volume. Their secretion is most maximal during stimulation like eating or chewing. The submandibular and the sublingual glands produce 20-30% and 2-5%, respectively, during stimulation (1;2). At rest, the contribution of the submandibular output is higher and may reach 90% of the total salivary output (3;4). The parotid gland saliva is predominantly serous, consisting almost entirely of water. The submandibular and sublingual glands are mixed serous and mucineus. The minor salivary glands are distributed throughout the oral cavity and pharynx and produce most of the mucins in the saliva (5).

Xerostomia is the most prominent complication after radiotherapy for head-and-neck cancer, caused by irradiation of the salivary glands. The degree of reduction in stimulated salivary flow is directly related to the dose to the parotid glands and is partially reversible (6-8). Lowering the dose to the parotid gland is the key for parotid-preserving radiotherapy. In the following sections several strategies will be addressed for reducing the dose to the parotid glands and therewith diminish radiation-induced salivary dysfunction. Next, submandibular gland sparing treatment is discussed. Finally a conclusion regarding parotid gland sparing radiotherapy and future perspectives are presented.

Parotid gland function preservation

IMRT

Reduction of the dose to the parotid gland can be achieved using intensity-modulated radiotherapy (9-14). We have shown that by using intensity-modulated radiotherapy (IMRT) compared with conventional radiotherapy (CRT) a dose-reduction of 30% to the parotid gland can be achieved (48.1 → 33.7 Gy, p = <0.005), which resulted in a reduction in flow complications from 83% after conventional treatment to 41% after IMRT at 12 months after treatment (Chapter 6 and 7). The mean parotid gland dose of 33.7 Gy however, still resulted in a considerable number of complications. A complication was defined as a stimulated parotid flow rate <25% of the preradiotherapy flow rate. Using

non-IMRT techniques a mean parotid gland dose of < 26 Gy to 30 Gy has gradually been formed as consensus for parotid gland function sparing treatment (15;16). These values are based on studies reporting the existence of a dose threshold for the stimulated parotid salivary flow rates at 26 Gy and 32 Gy (17). But a reduction in flow has also been reported without identification of a dose threshold (8). When evaluating long-term parotid gland function, no dose threshold was found and also a reduced function at low dose levels could be seen (Chapter 2). In the same chapter we showed partial recovery of salivary output years after radiotherapy even after high mean parotid gland doses.

The parotid salivary flow rates are not influenced by the radiation technique used (18). Therefore the data of NTCP models achieved using non-IMRT techniques can be used when analyzing parotid salivary outcome after IMRT treatment. When applying the mean parotid gland dose achieved using IMRT (33.7 Gy, Chapter 7) to the reported complication probability curve achieved using non-IMRT, an expected complication probability of 40% is found (8). This is almost equal to the observed number of complications 1-year after IMRT treatment of 41%. Regarding the dose dependency of the parotid gland for salivary function without a dose threshold, a mean parotid gland dose as low as possible should be aimed.

The clinical use of IMRT is rapidly evolving and has been implemented in an augmenting number of centers around the world and in the Netherlands. Much research and developmental work remains to be done to fully utilize its potential advantages. Progress in computerized optimization, leaf sequencing, and multi-leave collimator (MLC) design are just some of the strategies that are currently under development (19;20).

Target volume definition

In 3D-CRT as well as IMRT accurate delineation of target volumes or organs at risk is essential and is performed following the recommendations of the International Commission on Radiation Units and Measurements (ICRU) reports 50 and 62 (21;22). A standardization of nomenclature has been presented in these reports. Gross tumor volume (GTV) is defined as all known gross disease determined from CT or MRI, physical examination, and endoscopic findings. The clinical target volume (CTV) represents a margin around the GTV for suspected microscopic spread. The planning

target volume (PTV) describes the marginal volumes necessary to compensate for treatment setup variations and organ and patient motion. The margin of the PTV is around the CTV.

Minimizing the margins described above can reduce the dose to the parotid gland and therewith reduce xerostomia (23). This might be achieved by reducing the geometric uncertainties like the patient day-to-day positioning variations, machine-related errors, and the internal organ motion (PTV → CTV) and also by reducing the uncertainty of microscopic extension (CTV → GTV) (24;25). A PTV → CTV reduction in oropharyngeal cancer has been reported to result in a reduction of the mean dose to the parotid gland of 1.3 Gy per mm, and the normal tissue complication probability for a flow ratio <25% of the baseline flow ratio decreased with the application of smaller margins (23).

Cervical lymph nodes are an important prognostic factor in cancer of the head-and-neck, regardless of the size and site of the primary tumor. Elective radiotherapy is usually recommended when the estimated risk of microscopic disease exceeds 10-20%. The most widely accepted classification of the lymph nodes in the neck had been proposed in 1981 by head-and-neck surgeons of the Memorial Sloan-Kettering Cancer Center (26). According to the Memorial Sloan-Kettering-group the cervical lymph nodes are divided into 6 levels: the submental nodes (IA), the submandibular nodes (IB), the upper jugular nodes (II), the middle jugular nodes (III), the lower jugular nodes (IV), the posterior triangle nodes (V), and the anterior nodes (VI). This level classification system was designed for surgical procedures and it uses mainly soft tissue landmarks for definition like the anterior belly of the digastric muscles, carotid bifurcation, or medial borders of the carotid sheath. These soft tissue landmarks are often hard to see or just invisible on CT or MRI. With the advancements of radiotherapy techniques and the possibility of 3D-delineation and treatment planning, there was a call for adapted guidelines for delineation. In recent years different guidelines were proposed (27-34). These guidelines mostly are a translation of the surgical level definitions to imaging based definitions. The question is whether these surgical or anatomical based guidelines are best to use for clinical treatment and whether a uniform definition of nodal target volume delineation is suited for specific tumor sites. The anatomical distribution of cervical lymph node metastases occurs in a predictable pattern. The sequence of most frequently involved lymph nodes has been reported for different tumor sites (28;35-40). In Chapter 4 and 5 we have shown a different tumor spread for different primary sites,

concerning the most cranial cervical metastatic lymph node. The most cranial metastatic lymph node in oropharyngeal or hypopharyngeal cancer was situated much more cranially (near the base of the skull) than the most cranial metastatic lymph nodes were in laryngeal cancer. If we do know the lymph node locations (mainly) affected by tumorcells, selective nodal target volume irradiation can be performed and therewith locations not at risk can be prevented from irradiation. This consequently may result in a reduced number of complications and sparing of the parotid gland function. The normal lymphatic system and the interpatient anatomic variation is well known and has also recently been demonstrated using MRI-data (41;42). But a detailed tumor-site specific three-dimensional atlas of the microscopically involved lymph nodes is not available.

It can be questioned whether the target volumes and organs at risk should only be delineated before the start of the treatment. In current practice imaging is performed before the start of treatment, after which target volumes and organs at risk are delineated, and a treatment plan is generated. Imaging for treatment planning during the radiotherapy course is starting to emerge. It is well known that due to irradiation complications, patients are at high risk for decreased nutritional intake and weight loss during and after treatment. Anatomic changes may occur during treatment, like tumor shrinkage and resolving postoperative changes. A volume reduction of the parotid gland 6 weeks after radiotherapy of 24% has been observed using MRI images, which correlated with the weight loss of the patient (43). Also volume reduction of the parotid gland during treatment has been reported based on repetitive CT images (44). In the latter report, a decrease of the primary tumor volume and involved lymph nodes (GTV) was noted throughout the course of the fractionated radiotherapy. Together with the volume reduction, the center of the parotid gland displaced medially toward the high dose region, with a median shift of 3 mm. Although relatively small, this median shift may result in a higher actual radiation dose to the parotid glands than calculated in the pre-treatment plan. This analysis was performed using data of 14 patients with mainly locally advanced disease at least 4 cm in maximal diameter. Smaller changes can be expected when treating smaller target volumes. But these volume changes and displacements may result in suboptimal treatment and periodic adjustments of the treatment plan might be needed. Extension of this type of research might lead to the development of adaptive radiotherapy treatment plans.

Imaging

Imaging is the cornerstone for accurate delineation of target volumes and organs at risk. The CT scan has become the reference imaging modality in head-and-neck cancers for staging and radiation treatment planning, and is widely available. In routine clinical practice planning CT data are acquired before the start of the treatment. But in some situations CT alone is not sufficient for tumor definition. Small primary tumors are poorly identifiable on CT and subclinical tumor involvement cannot be detected. Another disadvantage of the CT scan are metal artefacts caused by for example dental fillings. In these cases, the delineation of oropharyngeal or oral cavity tumors is highly limited. MRI uses various sequences and has been shown to be more accurate than CT data in evaluating soft tissue or bone extension (45). The use of functional imaging and in particular [^{18}F]fluoro-deoxy-glucose positron emission tomography (PET) has become increasingly popular in head-and-neck cancer. A disadvantage of PET is the limited intrinsic spatial resolution to depict superficial tumor extension (46). The use of PET for target volume delineation requires specific tuning for parameters as image acquisition and processing. Also the segmentation of a PET-image for delineation is not trivial and is still an unresolved issue (47).

The issue regarding sensitivity and specificity of imaging modality is mainly critical in GTV delineation, which inevitably directly influences the corresponding CTV. For delineation of the GTV, equal volumes are received using magnetic resonance imaging (MRI) compared with computer tomography (CT) (46;48). But another study showed larger GTV's using MRI compared with CT (49). In both MRI and CT larger GTV's are delineated compared with (PET) (46;50). One study compared MRI, CT and PET with the surgical specimens of 9 patients with laryngeal cancer, and in this study PET was found to be the most accurate modality. But all three modalities overestimated the tumor extension and the small number of patients should be remarked (46). Fusion of CT and MRI improved the determination of the target volumes (49;51). Also fusion between PET and CT can be useful in the delineation of the GTV and showed reduction in inter-observer volume delineation variability (52;53). But as well as a reduction in target volume an increase has been shown (52;54). In case of delineating the parotid glands, a smaller volume was found when using MRI compared with CT with a comparable inter-observer variation. The smaller volume of the parotid gland observed resulted from the

more accurate and easier delineation of the deep lobe and from the exclusion of the carotid artery using MRI (48).

One of the shortcomings in almost all of these studies is the inability to determine the most accurate imaging modality due to lack of the pathological specimen. Also the results obtained are from a limited number of patients and need to be validated. It should be noted that all imaging modalities thus far failed to visualize superficial tumor extension or microscopic disease. The combined anatomical and functional modality approach for target volume delineation seems promising but the clinical validation still needs to be undertaken and further research is required before implementation in routine clinical practice. Although the CT still remains the “golden standard” in clinical practice for treatment planning, the use of combined modalities as standard is to be expected in the near future.

In current practice the whole GTV is considered as equal regarding tumor load and radiosensitivity. But within a tumor there are areas with different biological characteristics, which might need specific management. There are promising approaches currently under investigation. Molecular imaging may make differentiation possible of the GTV in areas with for example different radiosensitivity or tumor cell burden. The imaging of biological pathways that influence radiosensitivity like hypoxia or proliferation, may contribute to the delineation of a sub-GTV which may allow a heterogeneous dose distribution (55-59). These approaches look promising but still need to be explored and validated before they can enter routine clinical practice.

More accurate delineation of the GTV and of the parotid gland does not necessary result in improved parotid gland sparing radiotherapy. Hypothetically it may also result in an equal or higher mean dose to the parotid gland. Besides a reduction in GTV and delineated parotid gland, also an increase can be received using a multimodality approach. As the deep lobe of the parotid gland is often located in close proximity to the GTV, the PTV or CTV may still partly overlap the parotid gland. A larger GTV results in a larger PTV and a larger parotid gland overlap. Inevitably part of the parotid gland receives a high dose (9;23;60;61). IMRT allows irregular target volume dose distributions. Because of the possibility of accomplishing a dose reduction to the organs at risk, IMRT creates opportunities for selective target dose escalation to improve treatment outcome. When the dose to the (sub)-GTV will be increased this may result in a higher localized dose to part of the parotid gland due to its proximity. Time will tell the

impact of all imaging modalities including molecular or biological imaging on the parotid gland sparing treatment.

Submandibular gland function preservation

It is well known that the submandibular glands and the minor salivary glands are the main contributors of salivary flow during resting periods. The unstimulated salivary output in the resting state might be far more important in the subjective experience of a dry mouth. In Chapter 7 we showed that a reduction in mean parotid gland dose using IMRT resulted in a higher parotid flow ratio and a reduction of objective complications, but no improvement in subjective xerostomia was found using the LENT-SOMA scale. In the long-term, using conventional techniques, no clear relation was found between the dry mouth item of the EORTC QLQ-H&N35, and the dose to the parotid gland (Chapter 3). It might be questioned whether the adverse effects grading system and questionnaire are best to use in evaluating xerostomia. They both exist of only one patient-reported question regarding a dry mouth. Possibly the question regarding a dry mouth has to be asked into detail to receive the most accurate xerostomia experience. Different questionnaires do exist consisting of more questions, like the validated 8-item self-reported xerostomia-specific questionnaire (XQ) developed at the University of Michigan (6). There are studies that show a benefit in xerostomia after IMRT compared with conventional techniques, using this questionnaire (62;63). And the mean dose to the submandibular gland was found to have a significant association with the XQ scores (6).
When starting IMRT treatment in 2002, patients also answered a 12-item xerostomia questionnaire. The validation of this questionnaire is ongoing and the outcome is under investigation.
Independent which questionnaire used, in addition to the parotid gland, protection of the submandibular gland from irradiation should be aimed when attempting to reduce radiation-induced xerostomia. To preserve the submandibular gland function, surgical transfer of the submandibular gland outside the radiation volume may be used. (64;65). In this procedure a single submandibular gland on the side contralateral to the primary tumor is surgically transferred to the submental space before radiotherapy. Afterwards the standard radiation prescription dose can be given. Two years after transferring a single submandibular gland 83% of the patients reported normal amounts of saliva (66).

This method can be performed in patients who receive primary radiotherapy or in patients who are planned to receive postoperative radiotherapy, which is not always predictable. In some patients the submental space cannot be shielded from radiotherapy due to close proximity of the primary tumor or metastatic disease in the lymph nodes. The main concern is the strict patient selection and eligibility criteria. Patients with cancer of the oral cavity, level I involvement or patients with N3 nodes for example are ineligible.

With the development of IMRT xerostomia preventing radiotherapy was generally focused on protecting the parotid gland, part of which has been investigated in this thesis. Submandibular gland sparing might also be achieved using IMRT. In conventional radiotherapy the submandibular glands are almost always included in the irradiated volume. IMRT offers the opportunity to selectively decrease the radiation dose to the submandibular glands. It has been reported, in a small patient number, that sparing the contralateral submandibular gland is feasible using IMRT and resulted in better maintained unstimulated whole salivary flow rates in the short-term and long-term (67;68). Sparing the submandibular glands might be hazardous since the glands are included in the level Ib nodal target volume and are positioned close to the level II lymph nodes which might be at risk for subclinical disease (28;29;69). Compromising the CTV (primary tumor and lymph nodes) for submandibular gland sparing treatment may result in a volume of the CTV (and consequently PTV) outside the prescribed isodose line, which receives underdosage. A potential risk of locoregional recurrence at the site of the spared gland exists. Careful patient selection should be made, like excluding patients who have oral cavity tumors that cross the midline or tumors that originate from the midline.

Conclusions

Prevention of radiation-induced salivary function asks for a multi-modality approach. The improvement of imaging techniques and the use of combined PET/CT and MRI imaging, paves way for optimization of target volume delineation. Clinical and tumor-site specific adjustments of the elective nodal target volume has been proven feasible in oropharyngeal, hypopharyngeal and laryngeal carcinoma (Chapter 4 and 5) and creates an opportunity for reducing the dose to the parotid gland. We have shown that a

reduction of the dose to the parotid gland can be achieved by using IMRT compared with conventional radiotherapy and resulted in a reduced number of objective complications (Chapter 6 and 7). We have also shown in Chapter 2 and 3 that parotid gland function can recover years after radiotherapy as well as subjective xerostomia. However, subjective xerostomia was not necessary reflected in objective flow rates (Chapter 3 and 7). The contribution of the submandibular and minor salivary glands on xerostomia is also important and should be included in future research. It is therefore important to further realize a greater parotid gland dose reduction and treatment should also be focused on submandibular and minor salivary gland sparing. In future optimization of all modalities may contribute to improved salivary gland sparing radiotherapy.

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Chapter 9

Summary / Samenvatting

Summary

Head-and-neck malignancies are relatively rare. With an incidence of 2400 patients in the Netherlands per year, it counts for about 4% of the total newly diagnosed malignancies. Radiotherapy is a common form of treatment for head-and-neck malignancies and one of the most prominent complaints after radiotherapy is xerostomia or a dry mouth. This is caused by hyposalivation due to irradiation of the salivary glands. The main contributor of saliva during stimulation is the parotid gland. The parotid glands are positioned near the neck nodes and are in most cases in the vicinity of the primary tumor. Consequently irradiation of part of the parotid gland cannot be prevented and radiation-induced hyposalivation of the parotid gland will occur.

In this thesis a detailed report is given on long-term objective parotid gland function and the subjective outcome of patients with head-and-neck cancer and treated with radiotherapy. A specification of the superior extent of the nodal target volume is presented to guide the definition of target volumes for head and neck IMRT. Thereafter a comparison of conventional radiotherapy with IMRT for parotid salivary output is reported.

Chapter 2

Little is known about the changes with time of parotid gland function after radiotherapy. Most of the long-term survivors of head-and-neck malignancies that have been treated with radiotherapy complain of moderate to severe xerostomia. Improvement in salivary function has been shown till two years after treatment. In Chapter 2 we described the long-term parotid gland function after radiotherapy of 52 patients with a mean follow-up of 57 months. We used stimulated parotid salivary flow measurements as a parameter for the parotid function. The parotid saliva was collected in 10 minutes from both glands with Lashley cups placed over the orifice of the Stenson’s duct. The measurements were taken before radiotherapy and 6 weeks, 6 months, 12 months and at least 3.5 years after radiotherapy. The normal tissue complication probability model proposed by Lyman was fit to the data. A mean flow rate of 0.31 mL/min was found before radiotherapy. After treatment a reduction of the flow rate was found to 0.14 mL/min at 6 weeks, with recovery to 0.20 mL/min and 0.19 mL/min at 6 and 12 months after treatment,

respectively. The mean stimulated flow rate 5 years after radiotherapy was 0.25 mL/min. This is an increase of 32% compared to 12 months after treatment. The mean dose to the parotid gland resulting in a 50% complication probability increased from 34 Gy at 6 weeks to 40 Gy, 42 Gy and 46 Gy at respectively 6 months, 12 months and 5 years. In conclusion, parotid salivary output can still recover years after radiotherapy.

Chapter 3

Patients with head-and-neck cancer have to cope with many aspects of their life-threatening disease. Quality-of-life (QOL) questionnaires have been utilized for several years in the follow-up of these patients. Impaired QOL and xerostomia have been reported till years after treatment. But the long-term relationship between the patients' perception of a dry mouth, the QOL and the objective parotid gland function has not been determined. In Chapter 3 the analyses of subjective and objective measurements are evaluated. Forty-four patients completed the EORTC-QLQ-C30(+3) and the EORTC-QLQ-H&N35 questionnaires before treatment, 6 weeks, 6 months, 12 months and at least 3.5 years after radiotherapy. At the same time points stimulated bilateral parotid flow rates were measured (as described in chapter 2). Most of the xerostomia-related QOL scores improved in time after radiotherapy but did not return to baseline. The global QOL did not alter significantly and remained high. At 5 years follow-up 41% of the patients complained of moderate to severe dry mouth while the mean cumulated parotid flow ratio returned to baseline. At that time point 20% of patients had a flow ratio < 25%.

Chapter 4

The dose to the parotid gland and therewith the degree of function reduction, clearly depends on the irradiated target volume. Not only the primary tumor may be in the vicinity, but also the nodal target volume is important, especially of the level II lymph nodes. Lowering the border of the nodal target volume consequently results in a reduction of dose to the parotid gland. As consensus for the cranial border of the level II neck nodes, combined anatomical and surgical based borders are currently used. It is unclear whether these borders are related to clinical microscopic disease. We investigated the distance from the base of the skull to the most cranial metastatic lymph node in patients with oropharyngeal and hypopharyngeal carcinoma. This distance was

used to specify the superior extent of the elective nodal target volume for improvement of parotid-sparing irradiation. Contralateral metastatic lymph nodes were more caudally located than ipsilateral metastatic lymph nodes. The mean distance of the top of the most cranial metastatic lymph node to the base of the skull was 34.7 mm contralateral and 25.6 mm ipsilateral. Lowering the cranial border of the contralateral elective nodal target volume with 20 mm from the base of the skull might be used safely without risking a high incidence of neck node failure and could possibly diminish the complication rate. Lowering the border at the ipsilateral side is not advised.

Chapter 5

At a little less extent than in oropharyngeal and hypopharyngeal carcinoma (Chapter 4), the parotid glands are also included in the irradiation volume used to treat laryngeal cancer. The consensus guideline for delineation of node levels in the node-negative neck is not tumor-site specific and the cranial border of the level II lymph nodes is set at the caudal edge of the lateral process of C1. One may expect that different primary sites may be associated with different patterns of nodal spread. In Chapter 5 the results of the delineation of 98 most cranial metastatic lymph nodes from 67 patients with laryngeal carcinoma are outlined. The mean ipsilateral and contralateral distance of the top of these lymph nodes to the base of the skull was 36 mm and 35 mm respectively. According to these results the cranial border of the elective nodal target volume can be lowered by 1.5 cm from the base of the skull. These results are different from the results achieved from oropharyngeal and hypopharyngeal cancer and therefore the guidelines should be tailored to specific primary sites.

Chapter 6

Theoretically IMRT shows advantages for dose reduction to the parotid gland as IMRT offers a high degree of target coverage and normal tissue sparing, especially for complex shapes and concave regions. Chapter 6 reveals the comparison of conventional radiotherapy (CRT) with intensity-modulated radiotherapy (IMRT) for parotid salivary output preservation. Objective measurements (as described in Chapter 2*)* from fifty-six patients with oropharyngeal cancer, 30 IMRT and 26 CRT, were compared. A complication was defined as a stimulated flow rate <25% of the pre-

radiotherapy flow rate. The mean dose to the parotid gland was reduced from 48.1 Gy using CRT to 33.7 Gy using IMRT. A significant reduction of flow complications was found using IMRT compared with CRT. The number of complications 6 weeks and 6 months after treatment was 87% and 81% using CRT compared with 55% and 56% after IMRT, respectively.

Chapter 7

A significant reduction in number of parotid flow complications was found for patients with oropharyngeal cancer using intensity-modulated radiotherapy (IMRT) compared with conventional radiotherapy (CRT) till 6 months follow-up (Chapter 6). In Chapter 7 we investigated whether the reduction in flow complications continued in time. We also evaluated subjective xerostomia, efficacy of treatment and toxicity profile. Stimulated parotid flow measurements were performed (Chapter 2), and the patients' perception of a dry mouth was assessed using the LENT-SOMA scale. At 12 months follow-up the number of complications was significantly reduced using IMRT (43%) compared with CRT (83%), which is a further reduction in time for IMRT but not for CRT. However, there was no significant difference in subjective xerostomia between the treatment modalities at all time points. At 12 months 52% and 24% of the patients treated with IMRT complained of partial or complete persistent dryness, compared with 29% and 43% treated with CRT, respectively. The 2-year estimated overall survival and local recurrence-free survival rates for IMRT were 77% and 82%, respectively. All patients had mucositis, dermatitis and dysphagia of varying degree, during and after treatment. No patient had treatment break due to radiation toxicity or other cause.

Reducing the dose to the parotid gland is the main concept of parotid gland preserving radiotherapy. Using clinically optimized guidelines for target volume delineation a dose reduction can be achieved. Combined with intensity-modulated radiotherapy instead of conventional techniques, a further parotid sparing treatment can be realized. However subjective xerostomia is not necessarily reflected in objective flow rates. Therefore further research should be focused on prevention of all major salivary glands in a multi-modality approach.

Samenvatting

Kwaadaardige aandoeningen (maligniteiten) van het hoofd en halsgebied zijn relatief zeldzaam. Met een incidentie van 2400 patiënten in Nederland per jaar, bestrijken ze ongeveer 4% van het totaal aantal nieuw gediagnostiseerde kwaadaardige tumoren. Radiotherapie speelt een belangrijke rol bij de behandeling van hoofd-hals maligniteiten. Eén van de belangrijkste complicaties na bestraling is xerostomie ofwel een droge mond. Dit wordt veroorzaakt door vermindering van speeksel (hyposalivatie) door bestraling van de speekselklieren. De mens heeft vijf grote en een aantal kleinere speekselklieren. Gedurende stimulatie zoals bijvoorbeeld eten, wordt speeksel met name geproduceerd door de oorspeekselklier (glandula parotis). Deze glandula parotis, in het vervolg afgekort als parotis, bevindt zich zoals de naam al aangeeft, aan beide zijden vlak naast het oor. Aangezien deze lokatie vlakbij de lymfeklieren in de hals gelegen is en in veel gevallen dichtbij de primaire tumor of het wondbed na operatie, kan bestraling van een deel van de parotis meestal niet voorkomen worden. Bestralings-geïnduceerde vermindering van de speekselproductie van de parotis zal dan optreden.
In dit proefschrift worden de lange termijn resultaten besproken van de objectieve parotisfunctie en de subjectieve xerostomie van patiënten met een hoofd-hals maligniteit welke behandeld is met (onder andere) radiotherapie. Voor de functie van de parotis is het belangrijk tot welke hoogte de lymfeklierstations in de hals worden ingetekend. Een specificatie van de craniale uitbreiding van het lymfeklierdoelvolume wordt gegeven om de huidige protocollen voor intekening van doelvolumina voor hoofd-hals intensiteit gemoduleerde radiotheapie (IMRT) te optimaliseren. Daarnaast wordt conventionele radiotherapie (CRT) vergeleken met IMRT betreffende behoud van speekselklierfunctie.

Hoofdstuk 2

Er is weinig bekend over de veranderingen van de parotisfunctie in de loop van de tijd na radiotherapie. De meerderheid van de patiënten met een hoofd-hals maligniteit, welke behandeld is met radiotherapie, heeft last van matige tot ernstige xerostomie. Verbetering hiervan is gezien tot 2 jaar follow-up. In hoofdstuk 2 worden de lange termijn resultaten van de parotisfunctie geëvalueerd in een groep van 52 patiënten met een

gemiddelde follow-up van 57 maanden. Als parameter voor de functie van de parotis werden gestimuleerde parotis speekselsecretie-metingen gebruikt. De speekselsecretie van beide parotiden afzonderlijk werd in 10 minuten verzameld met behulp van Lashley cupjes die over de uitgang van de buis van Stenson werden geplaatst. De metingen vonden plaats voor bestraling en 6 weken, 6 maanden, 12 maanden en tenminste 3,5 jaar na bestraling. Data analyse vond plaats met het NTCP model volgens Lyman. Een gemiddelde speekselsecretie van 0.31 mL/min werd gevonden voor aanvang van bestraling. Deze daalde tot 0.14 mL/min 6 weken na afloop van behandeling en steeg daarna tot 0.20 mL/min op 6 maanden en tot 0.19 mL/min op 12 maanden na behandeling. Vijf jaar na radiotherapie bedroeg de gemiddelde speelselsecretie 0.25 mL/min. Dit is een verbetering van 32% ten opzichte van 12 maanden na behandeling. De gemiddelde dosis op de gehele parotis, resulterend in complicatiekans van 50% nam toe van 34 Gy op 6 weken, tot 40 Gy op 6 maanden, 42 Gy op 12 maanden en 46 Gy op 5 jaar. Een complicatie was gedefinieerd als een gestimuleerde speekselsecretie < 25% van de speekselsecretie voor de behandeling. Concluderend kan de parotis speekselsecretie tot jaren na bestraling nog (deels) herstellen.

Hoofdstuk 3

Patiënten met een hoofd-hals maligniteit moeten omgaan met vele aspecten van hun levensbedreigende aandoening. Kwaliteit-van-leven vragenlijsten worden reeds lange tijd gebruikt in de follow-up van deze patiënten. Vermindering van kwaliteit van leven en xerostomie zijn beschreven tot jaren na afloop van de behandeling. De lange termijn verhouding tussen de beleving van de patiënt van een droge mond, de kwaliteit van leven en de objectieve parotis speekselsecretie zijn niet bekend. In hoofdstuk 3 worden deze subjectieve en objectieve metingen geanalyseerd. Vierenveertig patiënten werden geëvalueerd met behulp van de EORTC-QLQ-C30(+3) en de EORTC-QLQ-H&N35 vragenlijsten die werden ingevuld door de patiënt voor aanvang van de behandeling en 6 weken, 6 maanden, 12 maanden en tenminste 3.5 jaar na behandeling. Op dezelfde tijdstippen werden gestimuleerde tweezijdige parotissecretie metingen verricht (zoals beschreven in hoofdstuk 2). In de loop van de tijd verbeterden de meeste xerostomie gerelateerde scores, maar bleven slechter dan voor de behandeling. De globale kwaliteit van leven veranderde niet significant en bleef hoog. Vijf jaar na de behandeling had 41%

van de patiënten last van een matige tot ernstige droge mond, terwijl de gemiddelde speekselsecretie genormaliseerd was tot de uitgangssituatie. Op dat tijdstip had 20% van de patiënten een flowratio < 25%.

Hoofdstuk 4

De bestralingsdosis op de parotis en daarmee het functieverlies van de parotis, is afhankelijk van de grootte van het bestraalde doelvolume. Niet alleen het doelvolume van de primaire tumor kan dichtbij de parotis liggen, maar ook de grootte van het lymfeklier doelvolume speelt een rol bij de hoogte van de dosis op de parotis. Voor deze laatste geldt met name tot welke hoogte de lymfklierstations naar craniaal (meest naar de kruin toe) worden ingetekend, omdat de hoogjugulaire lymfeklierstations (niveau II) mediaal van de caudale helft van de parotis gelegen zijn. Een verlaging van de craniale grens van het lymfeklier doelvolume resulteert in een lagere dosis op de parotis. Momenteel wordt voor de craniale grens van de niveau II lymfeklieren een grens aangehouden die een consensus is van anatomische en chirurgische begrenzingen. Het is echter niet duidelijk of deze grens ook gerelateerd is aan klinisch microscopische aandoening. In hoofdstuk 4 wordt beschreven hoe de precieze lokatie van meest craniale en door tumor aangedane lymfeklier werd vastgesteld bij patiënten met oropharynx en hypopharynx tumoren. De afstand tussen de schedelbasis en de craniale begrenzing van de lymfeklier werd berekend. Deze afstand werd gebruikt om de craniale grens van het electieve lymfeklier doelvolume te specificeren en op deze manier mogelijk een dosisverlaging in de parotis te bewerkstelligen. De lymfeklieren aan de andere zijde dan de tumor (contralateraal) waren lager gelegen dan de lymfeklieren aan dezelfde zijde als de tumor (ipsilateraal). De gemiddelde afstand tussen de top van de hoogste lymfeklier en de schedelbasis was 34.7 mm voor contralaterale lymfeklieren en 25.6 mm voor ipsilaterale lymfeklieren. In geval van electieve bestraling kan de contralaterale grens van het lymfeklier doelvolume verlaagd worden met 20 mm vanaf schedelbasis. Dit kan zeer waarschijnlijk uitgevoerd worden zonder een hoog risico op recidief in de hals en kan een verbetering geven van complicaties. Het verlagen van de contralaterale electieve craniale grens wordt niet geadviseerd.

Hoofdstuk 5

Bij de behandeling van stembandtumoren (larynx carcinoom) kunnen de parotiden zich ook gedeeltelijk in het bestralingsvolume bevinden, alhoewel in een beperktere mate dan bij oropharynx of hypopharynx tumoren (hoofdstuk 4). Het consensus protocol voor intekening van lymfeklier doelvolumina in de tumorvrije hals is niet tumor specifiek, maar geldt voor verschillende hoofd-hals tumoren. Als craniale grens van niveau II lymfeklieren wordt de caudale zijde van het processus lateralis van C1 geadviseerd. Het ligt voor de hand dat verschillende primaire tumoren een verschillende tumorverspreiding via lymfeklieren vertonen. In hoofdstuk 5 worden de resultaten beschreven van de intekening van 98 lymfeklieren van 67 patiënten met een larynx tumor. Al deze lymfeklieren waren de meest craniale door tumor aangedane lymfeklieren. De gemiddelde afstand van de bovenzijde van deze lymfeklieren tot de schedelbasis bedroeg 36 mm aan de ipsilaterale zijde en 35 mm aan de contralaterale zijde van de primaire tumor. Op basis van deze uitkomsten kan de craniale grens van het electieve lymfeklier doelvolume verlaagd worden met 15 mm vanaf de schedelbasis. Deze resultaten zijn verschillend van de resultaten verkregen bij patienten met oropharynx of hypopharynx tumoren (hoofdstuk 4). Protocollen voor intekening vanlevel II lymfeklier doelvolumina zouden derhalve ook tumorspecifiek moeten worden.

Hoofdstuk 6

In hoofdstuk 6 wordt conventionele radiotherapie (CRT) vergeleken met IMRT wat betreft behoud van speekselsecretie. Theoretisch toont IMRT voordelen voor dosisvermindering van de parotis gezien de mogelijkheid tot zeer conformale dosisverdeling, met name bij complexe vormen en concave gebieden. Objectieve speekselsecretie metingen (zoals beschreven in hoofdstuk 2) van 56 patienten met oropharynx tumoren werden met elkaar vergeleken. Hiervan waren 26 patiënten behandeld met CRT en 30 patiënten met IMRT. De gemiddelde dosis op de parotis was 48.1 Gy bij CRT en deze was gereduceerd tot 33.7 Gy bij IMRT. Na behandeling met IMRT werd een significante vermindering van het aantal complicaties gevonden in vergelijking met CRT. Het aantal complicaties op 6 weken en 6 maanden na behandeling was 87% en 81% na CRT vergeleken met 55% en 56% na IMRT.

Hoofdstuk 7

Na behandeling met IMRT werd in vergelijking met CRT een afname in het aantal complicaties gevonden tot 6 maanden follow-up voor patienten met oropharynx tumoren (hoofdstuk 6). In hoofdstuk 7 is onderzocht of deze afname in complicaties continueert in de loop van de tijd. Tevens zijn subjectieve xerostomie, effectiviteit en toxiciteit van de behandeling onderzocht. Voor objectieve evaluatie werden gestimuleerde parotis speekselsecretie metingen verricht (hoofdstuk 2) en de subjectieve droge mond beleving van de patiënt werd gemeten met behulp van de LENT-SOMA schaal. Twaalf maanden na afloop van de behandeling was het aantal complicaties significant lager na IMRT (43%) vergeleken met CRT (83%). Dit is een verdere reductie in loop van de tijd voor patiënten behandeld met IMRT, maar niet voor de patiënten behandeld met CRT. Er werd geen significant verschil gevonden in subjectieve xerostomie tussen de twee behandelmodaliteiten op alle meetpunten. Van de patiënten behandeld met IMRT had op 12 maanden na behandeling 52% last van matige en 24% van ernstige droge mond. Van de patiënten behandeld met CRT was dit respectievelijk 29% en 43%. De twee-jaars overleving en 2-jaars tumorvrije overleving na IMRT waren 77% en 82%. Alle patiënten hadden in verschillende mate klachten van mucositis, dermatitis en slikklachten gedurende en na afloop van behandeling. Bij geen patiënt hoefde de behandeling hierdoor of door een andere oorzaak vroegtijdig afgebroken te worden.

Reductie van de dosis op de parotis is de basis voor parotissparende radiotherapie. Met het gebruik van klinisch geoptimaliseerde protocollen voor intekening van doelvolumina, kan een dosisvermindering behaald worden. Wanneer dit gecombineerd wordt met IMRT in vergelijking met CRT kan een verdere parotissparende behandeling gerealiseerd worden. Echter subjectieve xerostomie wordt niet noodzakelijk teruggezien in objectieve parotis speekselsecretie. Daarom is het belangrijk om in de toekomst preventie van alle grote speekselklieren voor bestraling als doel te beschouwen, middels een multi-modale benadering.

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Spuug, spog, speeksel, kwijl, kwiel, tuf. Iets wat zoveel benamingen kent kan onmogelijk oninteressant zijn. De Dikke van Dale spreekt zelfs van het werkwoord speekselen, wat herhaaldelijk spuwen betekent. Zo bestaan er ook de spuugbak, de spuugdrank (braakdrank), de kwijlslab (slab om kwijl op te vangen), de speekselpomp, het spuugbeestje (schuimbeestje), speekselwortel (weegbree), speekselchromosoom (bijzonder groot chromosoom dat in speekselklieren van verschillende insekten voorkomt), kwijlebabber of kwijlebal (iemand die altijd kwijlt), speekselkruid (kwijlwortel) en de spuuglok. En dit zijn slechts een paar voorbeelden, er zijn er nog veel meer.
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Curriculum vitae

Pètra Braam werd op 1 april 1974 geboren te Etten-Leur. In 1992 behaalde zij het VWO-diploma aan het Katholieke Scholengemeenschap Etten-Leur. Hierna startte zij met de studie geneeskunde aan de Rijksuniversiteit Utrecht, waar zij het artsexamen haalde in december 1999. Vanaf 2000 was zij 1 jaar als AGNIO werkzaam binnen de dermatologie en 6 maanden bij de chirurgie. Sinds september 2001 is zij werkzaam in het UMC Utrecht, aanvankelijk als parttime AGNIO radiotherapie gecombineerd met parttime onderzoek welke gefinancierd werd door de Nederlandse Kankerbestrijding. Vanaf juli 2003 is zij radiotherapeut in opleiding onder leiding van Prof. Dr. J.J. Battermann, in combinatie met het onderzoek (AGIKO). Pètra is getrouwd met Bart-Jan Prins en samen hebben zij twee dochters, Lokke en Tess.