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

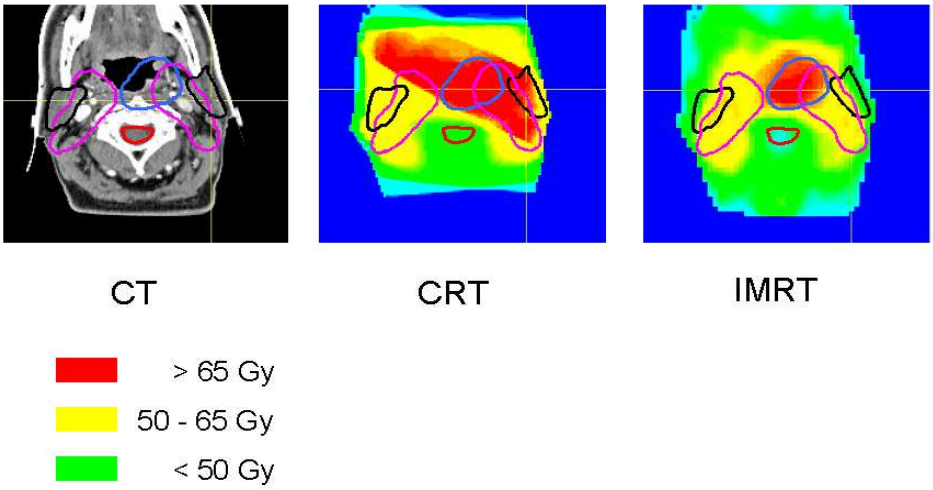

Figure 1. An example of the dose distribution achieved with conventional radiotherapy (CRT) and with intensity-modulated radiotherapy (IMRT) for the same patient with T3N0 oropharyngeal cancer. Both plans shown for the same axial computed tomography (CT) slice. The tumor bed (dark blue), regional lymph 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	

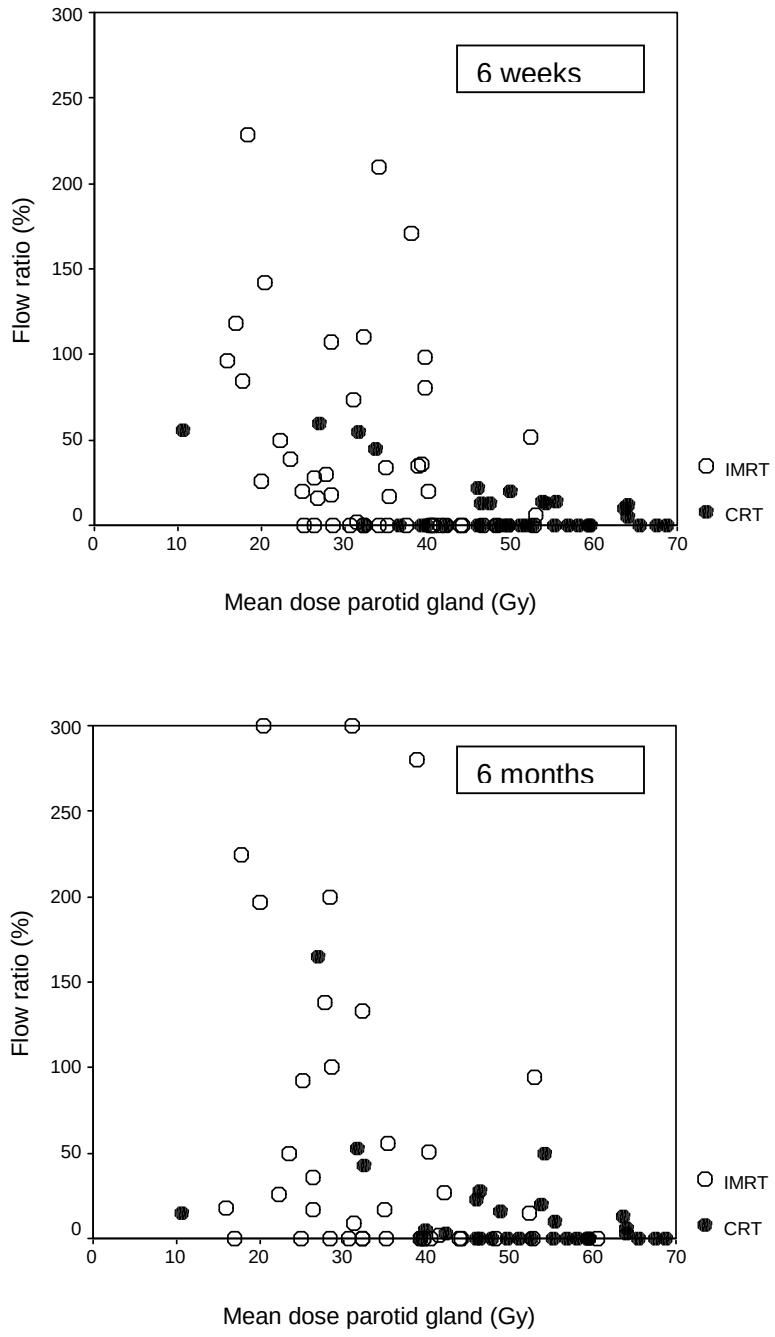

Figure 2. Stimulated parotid flow rates as a function of the mean dose to the parotid gland 6 weeks and 6 months after intensity-modulated radiotherapy (IMRT) compared with those after conventional radiotherapy (CRT). Flow rates are expressed as the percentage of the preradiotherapy (RT) flow rates for 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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