# CHAPTER 2

# Intensity modulated radiotherapy reduces radiation-induced morbidity and improves health-related quality of life: Results of a non-randomized prospective study using a standardised follow up program

Marije R. Vergeer, Patricia A.H. Doornaert, Derek H.F. Rietveld,
C. René Leemans, Ben J. Slotman, Johannes A. Langendijk

Int J Radiat Oncol Biol Phys. 2009 May 1;74(1)

## Abstract

Purpose: The purpose of this study was to compare intensity-modulated radiation therapy (IMRT) and 3D-conventional radiotherapy (3D-CRT) with regard to patient-rated xerostomia, Radiation Therapy Oncology Group (RTOG) acute and late xerostomia and health-related quality of life (HRQoL) among patients with head and neck squamous cell carcinoma (HNSCC).

Methods and Materials: Included were 241 patients with HNSCC treated with bilateral irradiation ± chemotherapy. Since 2000, all patients treated with HNSCC were included in a program, which prospectively assessed acute and late morbidity according to the RTOG and HRQoL on a routine basis at regular intervals. Before October 2004, all patients were treated with 3D-CRT (n=150). After clinical implementation in October 2004, 91 patients received IMRT. In this study, the differences regarding RTOG toxicity, xerostomia and other items of HRQoL were analyzed.

Results: The use of IMRT resulted in a significant reduction of the mean dose of the parotid glands (27 Gy versus 43 Gy ($p<0.001$). During radiation, grade 2 RTOG xerostomia was significantly less with IMRT than with 3D-CRT. At 6 months, the prevalence of patient-rated moderate to severe xerostomia and grade 2 or higher RTOG xerostomia was significantly lower after IMRT versus 3D-CRT. Treatment with IMRT also had a positive effect on several general and head and neck cancer specific HRQoL dimensions.

Conclusions: IMRT results in a significant reduction of patient- and observer-rated xerostomia, as well as other head and neck symptoms compared to standard 3D-CRT. These differences translate into a significant improvement of the more general dimensions of HRQoL.

## Introduction

In many patients with head and neck squamous cell carcinoma (HNSCC), bilateral irradiation of the upper neck levels is indicated because of the presence or high probability of nodal metastases. When the upper nodal levels are treated with conventional radiation techniques (e.g., by using two opposing lateral fields), the radiation dose administered to the salivary glands is generally beyond the threshold dose, resulting in a high probability of xerostomia (1). New radiation delivery techniques, such as intensity modulated radiotherapy (IMRT), enable a significant reduction of the radiation dose to the salivary glands without compromising the dose distribution to the planning target volume (PTV) (2). It is generally accepted that post-radiation salivary flow worsens with increasing mean parotid gland dose (3,4) and several authors have shown significantly improved preservation of salivary flow rates after IMRT compared to conventional radiotherapy (5-7). However, comparative studies reporting on differences between IMRT and conventional radiation techniques regarding patient-rated xerostomia and health –related quality of life (HRQoL) are scarce (8-10). Moreover, the main caveats of these studies are the limited number of patients included or study designs that included neither baseline and longitudinal assessments nor comparisons with conventionally treated patients.

Therefore, the main purpose of this prospective cohort study was to test the hypothesis that IMRT reduces the likelihood of patient-rated xerostomia compared with 3D-CRT among patients with HNSCC in whom bilateral irradiation was indicated. In addition, the impact on xerostomia according to the European Organization for Research and Treatment of Cancer/ Radiation Therapy Oncology Group (EORTC/RTOG) acute and late radiation morbidity scoring scheme, other patient-rated head and neck cancer symptoms and HRQoL were investigated.

## Methods and Materials

***Study population***

The study population of this prospective non-randomized cohort study was composed of 241 patients. Eligible patients had HNSCC arising from the oral

cavity, oropharynx, hypopharynx, nasopharynx or larynx; they were treated with bilateral irradiation with either conventional 3D-CRT or IMRT, with or without chemotherapy. Patients with neck node metastases from a squamous cell carcinoma from an unknown primary tumor were also included. Patients with malignancies originating from the salivary glands and paranasal sinuses were excluded, as were those treated with unilateral irradiation, distant metastases, and those previously treated for head and neck cancer.

From January 1999 until October 2004, all patients were treated with conventional 3D-CRT, (i.e., using 3D-CRT without attempts to spare the salivary glands). In October 2004, IMRT was clinically introduced at our department and subsequently, all consecutive patients in whom bilateral irradiation was indicated were treated with IMRT. The pre-treatment and treatment characteristics of the patients included are listed in Table 1.

***The standardized follow up program***

Since 1999, all patients treated for head and neck cancer were included in a standardized follow up program (SFP), which prospectively assessed toxicity and HRQoL on a routine basis. Acute and late toxicity were graded according to the RTOG Radiation Morbidity Scoring Criteria (11). HRQoL was assessed using the EORTC QLQ-C30 and the additional head and neck cancer module, the EORTC QLQ-H&N35 (12,13) at baseline, 6 weeks post-treatment and at 6 month intervals thereafter.

***Target volume definition***

In all patients, a planning CT-scan with contrast-enhancement was performed in treatment position. Target volume definition was similar in both treatment groups. Target volumes and organs at risk, such as the parotid and submandibular salivary glands, were delineated on the planning CT-scan. All patients were treated with definitive radiotherapy (± chemotherapy), or with postoperative radiotherapy. Radiotherapy was delivered using megavoltage equipment, with a 6 MV linear accelerator. In case of primary radiotherapy, the clinical target volume of the initial field (CTV1) was composed of the primary tumor and pathological lymph nodes plus a 1.0 cm margin, and the elective nodal areas on both sides of the neck, selected according to the guidelines reported by Gregoire, et al (14). The CTV of the boost (CTV2) consisted of the primary tumor and pathological lymph nodes with a 0.5 cm margin. In case of

**Table 1:** Pre-treatment and treatment characteristics.

| Variable | Radiotherapy technique | | | | p-value |
|---|---|---|---|---|---|
| | 3D-CRT (%) | | IMRT (%) | | |
| Sex | | | | | p =0.04 |
| Male | 104 | (69%) | 51 | (56%) | |
| Female | 46 | (31%) | 40 | (44%) | |
| Age | | | | | ns |
| 18-65 years | 95 | (63%) | 68 | (75%) | |
| > 65 years | 55 | (37%) | 23 | (25%) | |
| T-classification | | | | | ns |
| T0 | 1 | ( 1%) | 3 | ( 3%) | |
| T1 | 12 | ( 8%) | 6 | ( 7%) | |
| T2 | 63 | (42%) | 24 | (26%) | |
| T3 | 41 | (27%) | 40 | (44%) | |
| T4 | 33 | (22%) | 18 | (20%) | |
| N-classification | | | | | p =0.01 |
| N0 | 83 | (55%) | 33 | (36%) | |
| N1 | 17 | (11%) | 12 | (13%) | |
| N2a | 4 | ( 3%) | 9 | (10%) | |
| N2b | 23 | (15%) | 16 | (18%) | |
| N2c | 19 | (13%) | 18 | (20%) | |
| N3 | 4 | ( 3%) | 3 | ( 3%) | |
| Stage UICC | | | | | p =0.02 |
| Stage I | 8 | ( 5%) | 1 | ( 1%) | |
| Stage II | 50 | (33%) | 20 | (22%) | |
| Stage III | 21 | (14%) | 18 | (20%) | |
| Stage IV | 71 | (47%) | 52 | (57%) | |
| Primary site | | | | | p =0.01 |
| Oral cavity | 16 | (11%) | 13 | (14%) | |
| Oropharynx | 46 | (31%) | 34 | (37%) | |
| Nasopharynx | 5 | ( 3%) | 3 | ( 3%) | |
| Hypopharynx | 12 | ( 8%) | 17 | (18%) | |
| Larynx | 69 | (46%) | 21 | (23%) | |
| Unknown primary | 2 | ( 1%) | 3 | ( 3%) | |
| Chemotherapy | | | | | ns |
| Yes | 53 | (35%) | 39 | (43%) | |
| No | 97 | (65%) | 52 | (57%) | |
| Radiotherapy | | | | | p =0.004 |
| Primary | 109 | (73%) | 82 | (90%) | |
| Postoperative | 35 | (23%) | 8 | (9%) | |
| Both * | 6 | ( 4%) | 1 | (1%) | |
| Fractionation | | | | | ns |
| Accelerated (6 times / week) | 56 | (37%) | 43 | (47%) | |
| Conventional (5 times/week) | 94 | (63%) | 48 | (53%) | |
| Surgery of the neck | | | | | p =0.002 |
| Yes | 38 | (25%) | 8 | ( 9%) | |
| No | 112 | (75%) | 83 | (91%) | |

ns = not significant (i.e., p>0.05)

* Neck dissection for lymph node metastases followed by primary radiotherapy at the primary site and postoperative radiotherapy of the operated neck.

postoperative radiotherapy, the CTV1 consisted of the original primary tumor region with a 1.0 cm margin, the neck node levels containing lymph node metastases, the elective nodal areas on both sides of the neck and the surgical area. The CTV2 included the original primary tumor with a 0.5 cm margin and the neck node levels that contained lymph node metastases. In all cases, a 0.5 cm margin was applied for the planning target volume (PTV).

***3D-CRT***

In patients treated with 3D-CRT, the PTV1 was generally irradiated using 2 opposing lateral fields for the upper neck nodes and the area of the primary tumor with an anterior field (plus a posterior field if appropriate) for the level IV and low level V nodes. In some patients (mainly those with bilateral or contralateral lymph node metastases), a 5-field technique was used to allow sufficient sparing of the spinal cord without compromising the required dose for the PTV (15). In the primary irradiated patients, the PTV1 was treated with 46 Gy in 2 Gy fractions. PTV2 (boost) was treated with 2 Gy per fraction up to a total dose of 70 Gy. In case of primary radiotherapy, an accelerated fractionation schedule was used using a concomitant boost technique (CCB). The CCB accelerated fractionation schedule included the primary field (23 fractions of 2 Gy, 5 times per week) plus an extra fraction on Fridays including the boost with an interval of at least 6 hours. After finishing the primary field, we continued with the boost 6 times per week with a second fraction each Friday with an interval of 6 hours between two fractions. In this way, 35 fractions could be administered in 40 days.

Patients with locally advanced and unresectable tumors were generally treated with concomitant chemoradiation (3 cycles of cisplatin 100 mg/$m^2$ given on days 1, 22 and 43). In case of concomitant chemoradiation, a conventional fractionation schedule was used with a sequential boost.

Patients treated in the postoperative setting also received 46 Gy to PTV1 in 2 Gy daily fractions. At the primary site and nodal metastases, the total dose to the PTV2 was 56 Gy or 66 Gy depending on surgical margin status and the presence of pathological lymph nodes with or without extranodal spread, respectively. In the postoperative setting, only conventional fractionation was used without chemotherapy.

***IMRT***

We used dynamic IMRT with a sliding window technique. The target volumes for the initial fields and boosts were similar as described for the 3D-CRT patients. In general, a seven-field equidistant, non-opposing beam configuration was applied. Treatment planning was optimized by the Helios inverse planning module incorporated in the Eclipse (Varian, Palo Alto, CA) treatment planning system. Patients were treated with a simultaneous integrated boost technique (IMRT-SIB). Sparing of parotid tissue without compromising the dose in the PTV's was the aim in all patients. Sparing of the contralateral gland was given priority compared to the ipsilateral gland and mean parotid doses were aimed as low as possible, preferably under 26 Gy. When it was not possible to spare the ipsilateral parotid gland (e.g. positive ipsilateral level II nodes or primary tumor in proximity to the parotid gland), the contralateral gland was spared as much as possible.

Patients treated with IMRT were all treated with a simultanuous integrated boost (SIB) technique. In cases of primary radiotherapy, we used an accelerated schedule with 6 fractions per week, with the 6$^{th}$ fraction on Fridays at an interval of at least 6 hours. In these cases, the same SIB technique was used for all fractions. In cases of primary radiotherapy, with or without chemotherapy, the PTV1 was treated with 35 fractions of 1.55 Gy up to a total dose of 54.25 Gy. The total dose of 54.25 Gy was chosen to compensate for the lower dose per fraction and the longer overall treatment time and is radio-biologically equivalent to 46 Gy in 2 Gy fractions. The PTV2 was treated with 35 fractions of 2 Gy up to a total dose of 70 Gy.

In the postoperative setting, the dose per fraction to the PTV1 was 1.64 Gy to a total dose of 54.12 Gy in case the total dose to the PTV2 was 66 Gy. When the PTV2 was irradiated to a total dose of 56 Gy, PTV1 received 1.8 Gy fractions of to a total dose of 50.4 Gy.

***Study design and statistical considerations***

In a non-randomized cohort study with prospectively scored RTOG morbidity and HRQoL, we compared IMRT with 3D-CRT. We composed a historical control group of 150 patients treated with 3D-CRT. To calculate the number of IMRT patients required for this study, we estimated the potential benefit of IMRT compared to 3D-CRT using the data of a planning comparative study among 20 consecutive patients who were treated with 3D-CRT. In these

patients an alternative IMRT plan was made. The risk reduction on moderate or severe patient-rated xerostomia to be expected with IMRT versus 3D-CRT was estimated based on the model described in a previous publication (16). From this analysis we expected a risk reduction from 65% to 40%. On the basis of these assumptions, the power analysis revealed that 90 patients in the IMRT cohort were required to determine a difference of 25% ($\alpha = 0.05$, 2-sided; power: 0.80) taking into account a fall out of 20% at six months.

In the univariate analysis, the Wilcoxon signed ranks test or the Student's t-test were used when appropriate to compare mean values. For comparison of percentages between groups, a chi-squared test was used. Because the two groups were not well balanced with regard to various pre-treatment characteristics, a multivariate logistic regression analysis was performed to account for possible confounding. Changes in symptoms and HRQoL items were evaluated on an exploratory basis with repeated measurement analysis of variance (ANOVA). All tests were two-tailed, and differences were considered statistically significant at the 0.05 level.

## Results

***Salivary gland dose***

In the parotid glands and the contralateral submandibular gland, the mean doses in the IMRT patients were significantly lower compared to those observed among the patients treated with 3D-CRT (Table 2). No differences were noted with regard to the dose in the ipsilateral submandibular glands. To reveal whether the IMRT patients were comparable to the 3D-CRT patients regarding parotid dose, additional 3D-CRT treatment plans were made among 10 randomly selected IMRT patients. In these 10 patients, the mean parotid dose of the 3D-CRT plans was 45 Gy, which was comparable to that observed among the patients actually treated with 3D-CRT (43 Gy) (ns).

**Table 2:** Comparison of salivary gland dose between 3D-CRT and IMRT.

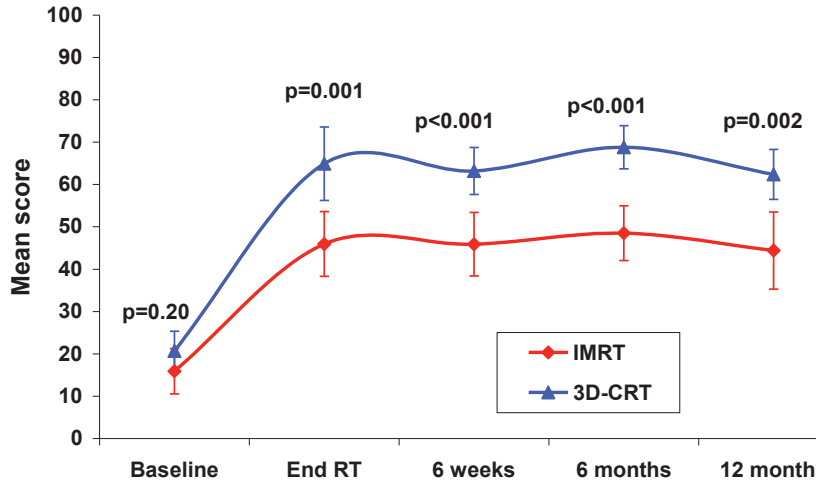
| Salivary glands | Mean dose | | p-value |
|---|---|---|---|
| | 3D-CRT (SD) | IMRT (SD) | |
| Parotid ipsilateral | 44.4 (16.7) Gy | 28.7 (11.9) Gy | p<0.001 |
| Parotid contralateral | 41.6 (14.5) Gy | 23.3 (11.2) Gy | p<0.001 |
| Parotid both | 43.0 (15.4) Gy | 27.1 (12.0) Gy | p<0.001 |
| Submandibular ipsilateral | 57.9 (15.7) Gy | 61.2 ( 9.0) Gy | p=0.144 |
| Submandibular contralateral | 59.6 (13.3) Gy | 55.2 ( 9.7) Gy | p=0.004 |
| Submandibular both | 59.6 (13.0) Gy | 59.0 ( 8.4) Gy | p=0.625 |

***Patient-rated xerostomia***

At 6 months, 29 of 71 patients (41%) treated with IMRT reported moderate or severe xerostomia compared to 82 of 122 patients (67%) treated with 3D-CRT (odds ratio (OR) 0.34; 95% confidence interval (CI) 0.18-0.62; p<0.001). To account for the unbalanced distribution with regard to pre-treatment and other treatment characteristics at baseline, a multivariate logistic regression analysis was performed. After adjustment for these factors, the corrected OR was 0.27 (95% CI 0.13-0.54; p<0.001), with primary tumor site as the only significant confounder.

When converted to a 0 to 100 scale, no differences were noted with regard to the mean score of xerostomia at baseline (Figure 1). Post-treatment, the mean scores for patient-rated xerostomia among 3D-CRT patients were significantly worse compared to those observed after IMRT at all time points.

**Figure 1:** Patient-rated xerostomia assessed with the EORTC QLQ-H&N35.




**Note: Higher scores represent higher degrees of patient-rated xerostomia.**

***RTOG acute toxicity***

During treatment, significantly more patients in the 3D-CRT group suffered from grade 2 acute xerostomia (Figure 2). Similar results were observed for acute mucositis. The prevalence of grade 3 or higher mucositis during radiotherapy was significantly higher among the 3D-CRT patients compared to the IMRT patients (Figure 3). No differences were found with regard to acute skin toxicity, except at week 7, when grade 2 or higher skin toxicity was reported in 86% of the IMRT patients compared to 74% of 3D-CRT patients (p=0.03). However, this difference disappeared at week 8.

**Figure 2:** Acute xerostomia grade 2 according to the RTOG Acute Morbidity Scoring System.

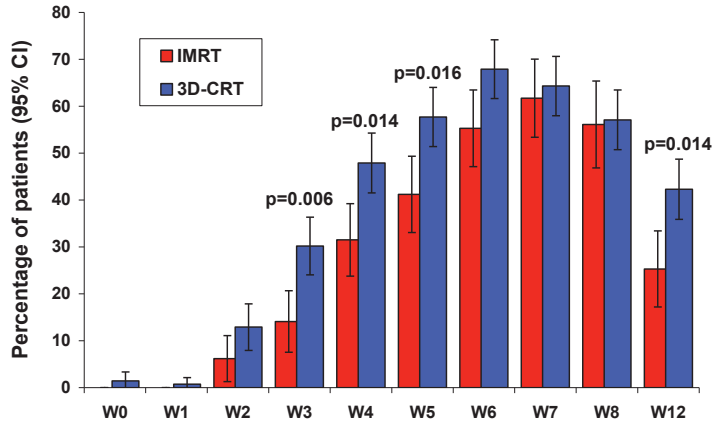
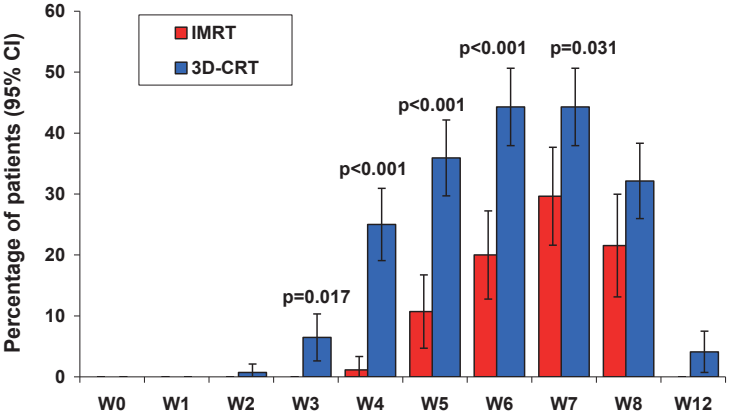



**Figure 3:** Acute Mucositis grade 3 or higher according to the RTOG Acute Radiation Morbidity Scoring System.




**Note: The prevalence of grade 3 or higher mucositis was significantly lower among IMRT-treated patients. This is most likely due to the SIB-technique used with a lower dose per fraction and a longer overall treatment time of radiation for the elective part of the target volume.**

***RTOG late toxicity***

At 6 months, 22 of 74 patients (32%) treated with IMRT reported grade 2 or higher RTOG xerostomia compared to 74 of 134 patients (56%) treated with 3D-CRT (OR 0.38; 95% CI, 0.25-0.70; p=0.002). To account for the unbalanced distribution with regard to pre-treatment and other treatment characteristics at baseline, a multivariate logistic regression analysis was performed (Table 3). After adjustment for these factors the corrected OR was 0.24 (95% CI 0.12-0.51; p<0.001), again with primary tumor site as the only significant confounder.



**Table 3:** Results of the univariate and multivariate logistic regression analysis. For the multivariate analysis, a stepwise backward procedure was used. Only the ultimate results of the multivariate model are shown.

| Variable | | B | SE | OR | 95% CI | P-value |
|---|---|---|---|---|---|---|
| **Univariate analysis** | | | | | | |
| Radiation technique | IMRT reference to 3D-CRT | -0.969 | 0.311 | 0.38 | (0.25 - 0.70) | p=0.002 |
| Age | > 65 years reference to 18-65 years | -0.657 | 0.315 | 0.52 | (0.28 - 0.96) | p=0.037 |
| Sex | Male reference to female | -0.786 | 0.301 | 0.46 | (0.25 - 0.82) | p=0.009 |
| T-classification | T3-T4 reference to T0-T2 | 0.591 | 0.285 | 1.81 | (1.03 - 3.16) | p=0.038 |
| N-classification | N+ reference to N0 | 0.734 | 0.286 | 2.08 | (1.19 - 3.65) | p=0.010 |
| Tumour site | Oropharynx/nasopharynx reference to other sites | 1.978 | 0.332 | 7.23 | (3.77 - 13.8) | p<0.001 |
| Chemotherapy | Yes reference to No | 0.470 | 0.291 | 1.60 | (0.90 - 2.83) | p=0.107 |
| Radiotherapy | Postoperative reference to primary | 0.901 | 0.351 | 2.46 | (1.24 - 4.89) | p=0.010 |
| Fractionation schedule | Accelerated reference to conventional | -1.187 | 0.294 | 0.31 | (0.17 - 0.54) | p<0.001 |
| Surgery of the neck | Yes reference to No | 1.091 | 0.371 | 2.98 | (1.44 - 6.17) | p=0.003 |
| **Multivariate analysis** | | | | | | |
| Radiation technique | IMRT reference to 3D-CRT | -1,420 | 0.353 | 0.24 | (0.12 - 0.51) | p<0.001 |
| Tumour site | Oropharynx/nasopharynx reference to other sites | 2.117 | 0.353 | 8.30 | (4.15 - 16.6) | p<0.001 |

***Other head and neck symptoms and health-related quality of life***

The outcome with regard to the other head and neck symptoms are shown in Table 4. The analysis was performed with repeated measures ANOVA on an exploratory basis, taking into account only the cases with complete data sets. The mean scores for dry mouth and sticky saliva were significantly lower among the IMRT patients. In addition to these head and neck symptoms directly related to salivary function, significantly lower scores were also found for other head and neck symptoms, including opening mouth, head and neck pain, swallowing, problems with social eating, sexuality, problems with

teeth and feeling ill. For most symptoms, significant linear effects were noted, indicating a difference in time between 3D-CRT and IMRT, which is linear in time, i.e., the difference remained present at 6 weeks and 6 months.

In the repeated measurement ANOVA, the differences with regard to head and neck symptoms were also translated into differences in the more general dimensions of HRQoL, as shown in the lower part of Table 4. Patients treated with IMRT scored significantly better with regard to global quality of life, role functioning, cognitive functioning, social functioning, fatigue, insomnia and appetite loss. A temporary effect was observed for pain.

## Discussion

The results of this prospective non-randomized study showed that both observer-rated and patient-rated radiation-induced xerostomia can be reduced significantly with the use of IMRT. These findings are in agreement with those reported by others that compared conventional radiation techniques with IMRT (8,10,17). Recently, Pow et al. (8) reported on the results of a clinical trial that randomly assigned patients with early-stage nasopharyngeal carcinoma to receive IMRT or conventional radiotherapy. In that study, salivary functions in terms of stimulated whole salivary and parotid flow, as well as patient-rated xerostomia and sticky saliva (EORTC QLQ-H&N35) were significantly better after IMRT. Similar results were found in a matched-pair cross-sectional study (17) and a matched-case longitudinal study (10). The findings of these clinical studies, including those of the current study, comparing conventional techniques and IMRT with regard to clinical outcome measures, confirm what already has been suggested by other investigators who observed a significant association between the mean parotid dose and post-radiotherapy salivary flow (3, 4, 18) and patient-rated xerostomia and sticky saliva (19).

With regard to determining the efficacy of IMRT regarding the prevention of xerostomia, it should be emphasized that both observer-rated and patient-rated outcome measures are important. In an earlier study, we showed that late RTOG xerostomia had a significant impact on the more general dimensions of HRQoL (16). However, physicians generally tend to underestimate the severity of xerostomia compared to that reported by patients (20). Moreover, patient-rated xerostomia also depends on other factors than the mean parotid dose (e.g., on

the dose distribution in the submandibular glands) (19). Taken into account that we observed a dose reduction in the parotid glands as well as in the contralateral submandibular glands, patient self-reported scores may provide important additional information. We found that both observer-rated and patient-rated endpoints were significantly better with IMRT compared to 3D-CRT.

A surprising finding was the lower prevalence of grade 3 or higher acute mucositis among patients treated with IMRT. This may be explained by the reduced dose per fraction to the elective target volumes in cases of SIB-IMRT as applied in this study. Another explanation could be that preservation of salivary gland function itself has a protecting effect with regard to acute mucositis and secondary oral infections (21).



In this study, significantly lower scores were also observed for a number of other head and neck symptoms after IMRT reference to 3D-CRT, including for pain, swallowing, and problems with teeth and opening mouth. These findings are in line with those reported by Graff et al, who found significantly lower scores after IMRT for exactly the same symptoms (17). The lower scores for pain and swallowing may result from preserved salivary function, but may also be due to a lower dose to organs at risk involved in swallowing, e.g. the pharyngeal constrictor muscles (22, 23), the lower prevalence of radiation-induced grade 3 or higher mucositis, or both.

Although the results of our study indicate that some side effects and subsequent treatment-related symptoms can be reduced by using IMRT, some critical issues should be pointed out. First, IMRT aimed at dose reductions to specific structures implies an increased dose to other normal tissues which may result in unusual side effects that were uncommon with 3D-CRT. Recently, Rosenthal et al. showed that patients treated with IMRT received a significantly higher dose to a number of anatomical structures, such as the brainstem and the occipital scalp, resulting in higher incidences of headaches, nausea and vomiting and occipital alopecia (24). Second, a number of recent publications reported on local-regional recurrences just outside the clinical and planning target volume that might have been prevented using conventional radiation techniques (25, 26). Although the probability of these marginal recurrences is considered low (26), it stresses the importance of accurate surveillance and the need for recurrence analysis (i.e. evaluation of local-regional recurrence reference to the actual dose distribution).

Table 4: Head and neck cancer symptoms and health-related quality of life among patients treated with 3D-CRT compared among those treated with IMRT. The p-values are based on the repeated measures ANOVA.

| Scale | Baseline | | 6 weeks | | 6 months | | p-value linear [1] | p-value quadratic [2] |
|---|---|---|---|---|---|---|---|---|
| | IMRT | 3D-CRT | IMRT | 3D-CRT | IMRT | 3D-CRT | | |
| **EORTC QLQ-H&N35** | | | | | | | | |
| **Head and neck pain** | 31.1 (26.4) | 27.9 (25.4) | 19.9 (17.0) | 33.0 (25.7) | 18.9 (23.4) | 28.3 (24.7) | p=0.030 | p=0.046 |
| **Swallowing** | 24.1 (27.5) | 23.2 (27.2) | 35.5 (28.7) | 36.1 (31.3) | 21.1 (24.7) | 33.7 (26.9) | p=0.042 | ns |
| **Senses** | 6.7 (20.3) | 10.2 (20.9) | 32.7 (23.8) | 34.0 (28.2) | 16.7 (17.9) | 26.8 (25.7) | ns | ns |
| **Speech** | 58.0 (27.3) | 64.7 (29.2) | 23.0 (27.7) | 31.2 (30.5) | 19.8 (24.9) | 29.9 (28.1) | ns | ns |
| **Social eating** | 15.5 (26.1) | 14.7 (25.0) | 23.0 (24.0) | 35.7 (31.4) | 15.9 (24.4) | 30.9 (30.3) | p=0.011 | ns |
| **Sexuality** | 21.3 (32.1) | 28.6 (35.2) | 30.7 (33.6) | 45.5 (37.3) | 13.3 (23.6) | 38.1 (37.4) | p=0.003 | ns |
| **Teeth** | 15.9 (31.6) | 14.9 (27.4) | 4.3 (11.5) | 19.6 (29.4) | 7.2 (20.0) | 24.3 (33.0) | p=0.015 | ns |
| **Opening mouth** | 16.0 (29.8) | 18.3 (31.4) | 8.6 (14.9) | 27.1 (30.8) | 17.3 (31.2) | 30.2 (35.5) | ns | p=0.026 |
| **Xerostomia** | 12.3 (22.9) | 20.5 (29.1) | 43.2 (34.4) | 62.2 (34.3) | 48.1 (28.2) | 68.6 (31.2) | p<0.001 | ns |
| **Sticky saliva** | 12.0 (19.0) | 17.2 (26.4) | 41.3 (32.3) | 61.3 (34.9) | 32.0 (29.6) | 56.9 (34.1) | p=0.001 | ns |
| **Cough** | 32.1 (23.5) | 32.0 (29.3) | 35.8 (26.0) | 33.3 (32.0) | 27.2 (24.5) | 35.4 (30.3) | ns | ns |
| **Felt ill** | 11.1 (20.7) | 12.6 (21.8) | 21.0 (29.5) | 18.1 (26.1) | 6.2 (16.1) | 19.1 (24.7) | p=0.011 | ns |
| **EORTC QLQ-C30** | | | | | | | | |
| **Global quality of life** | 69.2 (19.1) | 67.1 (22.7) | 76.0 (15.9) | 64.9 (21.3) | 79.2 (19.5) | 65.6 (22.9) | p=0.004 | ns |
| **Physical functioning** | 83.3 (21.4) | 84.3 (17.9) | 77.4 (16.6) | 73.3 (21.8) | 80.7 (18.4) | 74.4 (20.8) | ns | ns |
| **Role functioning** | 77.2 (40.0) | 76.4 (30.1) | 81.5 (22.8) | 65.6 (30.7) | 82.1 (25.3) | 70.8 (26.3) | p=0.042 | ns |
| **Emotional functioning** | 76.2 (19.6) | 66.8 (25.6) | 78.2 (20.0) | 73.5 (22.5) | 85.3 (16.6) | 73.2 (26.7) | ns | ns |
| **Cognitive functioning** | 91.0 (14.3) | 86.5 (22.0) | 87.8 (24.3) | 83.9 (20.2) | 93.6 (14.2) | 84.6 (17.9) | p=0.033 | ns |
| **Social functioning** | 80.7 (25.3) | | 82.7 (22.3) | 76.1 (25.4) | 92.0 (13.7) | 76.5 (22.7) | p<0.001 | ns |
| **Fatigue** | 27.1 (28.0) | 27.2 (26.4) | 30.9 (23.9) | 40.5 (25.7) | 24.2 (19.4) | 40.4 (33.7) | p=0.026 | ns |
| **Nausea and vomiting** | 3.2. (8.2) | 4.2 (12.5) | 12.8 (20.7) | 13.6 (21.9) | 6.4 (18.9) | 8.4 (18.0) | ns | ns |
| **Pain** | 24.4 (25.9) | 21.0 (23.4) | 14.1 (17.4) | 25.2 (25.8) | 19.2 (30.4) | 23.3 (26.3) | ns | p=0.042 |
| **Dyspnoea** | 17.9 (26.4) | 24.7 (33.0) | 11.9 (22.6) | 19.1 (28.4) | 10.7 (15.9) | 22.4 (30.5) | ns | ns |
| **Insomnia** | 32.7 (33.3) | 30.3 (32.0) | 27.4 (28.8) | 26.3 (28.8) | 16.7 (28.0) | 30.1 (32.7) | p=0.021 | ns |

Table 4: Continued

| Scale | Baseline | | 6 weeks | | 6 months | | p-value linear [1] | p-value quadratic [2] |
|---|---|---|---|---|---|---|---|---|
| | IMRT | 3D-CRT | IMRT | 3D-CRT | IMRT | 3D-CRT | | |
| **Appetite loss** | 21.0 (33.5) | 10.0 (22.0) | 19.8 (31.0) | 32.5 (32.9) | 12.3 (26.4) | 24.2 (32.6) | p=0.018 | ns |
| **Constipation** | 8.0 (14.5) | 9.0 (20.3) | 10.7 (15.9) | 17.1 (26.4) | 10.7 (18.6) | 12.1 (22.4) | ns | ns |
| **Diarrhoea** | 6.4 (16.4) | 9.3 (21.2) | 11.5 (28.2) | 7.8 (19.7) | 2.6 (9.1) | 8.5 (20.9) | ns | ns |
| **Financial difficulties** | 20.5 (29.9) | 14.2 (26.3) | 16.7 (25.4) | 12.6 (24.3) | 15.4 (25.4) | 14.8 (25.6) | ns | ns |

[1] A significant linear effect indicates difference between 3D-CRT and IMRT which is linear in time, i.e., remains present a 6 weeks and 6 months.
[2] A significant quadratic effect indicates a significant but temporary difference between 3D-CRT and IMRT.
Note: In the repeated measures ANOVA, only cases with a complete set of data up to 6 months after completion of radiotherapy are taken into account.

An important finding of our study is that the reduction of radiation-induced side effects and head and neck symptoms translated into higher and thus better scores for a number of the more general dimensions of HRQoL. The results of an earlier study showed that HRQoL was significantly affected by late RTOG xerostomia and that this impact increased with time, in particular after 18 months (16). Given the relatively short follow up of this report (6 months), it cannot be excluded that the differences with regard to HRQoL between IMRT and 3D-CRT will increase further when the interval with the completion of radiotherapy progresses.

One of the main caveats of the present study is its non-randomized design. In an earlier study we found that after bilateral irradiation, patient-rated xerostomia significantly depended on the mean parotid and submandibular dose (19). Moreover, we showed that HRQoL was significantly affected by late RTOG xerostomia (16). Because the planning comparative study we performed revealed major differences between 3D-CRT and IMRT regarding the mean parotid dose, it is likely that the clinical introduction of IMRT would result in a major and clinically relevant benefit from the patient's perspective. Therefore, we considered it unethical to withhold IMRT to patients in whom bilateral irradiation was indicated. For this reason, we checked the comparability of the two treatment groups with regard to parotid dose by producing an alternative 3D-CRT plan among 10 randomly selected patients who were actually treated with IMRT. The mean "mean parotid dose" in these 3D-CRT plans was similar to that observed among the patients actually treated with 3D-CRT, indicating that the two treatment groups were comparable regarding the mean parotid dose. Further, the prospective longitudinal design of our study also allowed for a comparison of both primary and secondary endpoints at baseline, which did not significantly differ between the two groups before radiotherapy.

One of the drawbacks of the current study is that the patient population was not well balanced with regard to a number of pre-treatment variables and that the varying radiation doses have been analyzed retrospectively. However, the multivariate logistic regression analysis revealed that the differences between IMRT and 3D-CRT became even larger as expressed by the corrected OR. Therefore, it is unlikely that the unequal distribution between the treatment groups account for the differences observed in the reported outcome measures.

In conclusion, IMRT results in a significant reduction of both observer-rated and patient-rated xerostomia, as well as other head and neck symptoms compared to standard 3D-CRT. Eventually, these differences translate into a significant improvement of the more general dimensions of HRQoL.

# References


1 Bjordal K, Kaasa S, Mastekaasa A. Quality of life in patients treated for head and neck cancer: a follow-up study 7 to 11 years after radiotherapy. Int J Radiat Oncol Biol Phys 1994;28:847-856.

2 Xia P, Fu KK, Wong GW, *et al.* Comparison of treatment plans involving intensity-modulated radiotherapy for nasopharyngeal carcinoma, *Int J Radiat Oncol Biol Phys* 2000; 48:329-337.

3 Roesink JM, Moerland MA, Battermann JJ, Hordijk GJ, Terhaard CH. Quantitative dose-volume response analysis of changes in parotid gland function after radiotherapy in the head-and-neck region. Int J Radiat Oncol Biol Phys 2001;51:938-946.

4 Eisbruch A, Ten Haken RK, Kim HM, Marsh LH, Ship JA. Dose, volume, and function relationships in parotid salivary glands following conformal and intensity-modulated irradiation of head and neck cancer. Int J Radiat Oncol Biol Phys 1999;45:577-587.

5 Eisbruch A, Ship JA, Dawson LA, *et al*. Salivary gland sparing and improved target irradiation by conformal and intensity modulated irradiation of head and neck cancer. World J Surg 2003;27:832-837.

6 de Arruda FF, Puri DR, Zhung J, *et al*. Intensity-modulated radiation therapy for the treatment of oropharyngeal carcinoma: the Memorial Sloan-Kettering Cancer Center experience. Int J Radiat Oncol Biol Phys 2006;64:363-373.

7 Chao KS, Majhail N, Huang CJ, *et al*. Intensity-modulated radiation therapy reduces late salivary toxicity without compromising tumor control in patients with oropharyngeal carcinoma: a comparison with conventional techniques. Radiother Oncol 2001;61:275-280.

8 Pow EH, Kwong DL, McMillan AS, *et al*. Xerostomia and quality of life after intensity-modulated radiotherapy vs. conventional radiotherapy for early-stage nasopharyngeal carcinoma: initial report on a randomized controlled clinical trial. Int J Radiat Oncol Biol Phys 2006;66:981-991.

9 Parliament MB, Scrimger RA, Anderson SG, *et al*. Preservation of oral health-related quality of life and salivary flow rates after inverse-planned intensity- modulated radiotherapy (IMRT) for head-and-neck cancer. Int J Radiat Oncol Biol Phys 2004;58:663-673.

10 Jabbari S, Kim HM, Feng M, *et al*. Matched case-control study of quality of life and xerostomia after intensity-modulated radiotherapy or standard radiotherapy for head-and-neck cancer: initial report. Int J Radiat Oncol Biol Phys 2005;63:725-731.

11 Cox JD, Stetz J, Pajak TF: Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys 1995;31:1341-1346.

12 Aaronson NK, Ahmedzai S, Bergman B, *et al.* The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85:365-376.

13 Bjordal K, hlner-Elmqvist M, Tollesson E, *et al.* Development of a European Organization for Research and Treatment of Cancer (EORTC) questionnaire module to be used in quality of life assessments in head and neck cancer patients. EORTC Quality of Life Study Group. Acta Oncol 1994;33:879-885.

14 Gregoire V, Coche E, Cosnard G, Hamoir M, Reychler H. Selection and delineation of lymph node target volumes in head and neck conformal radiotherapy. Proposal for standardizing terminology and procedure based on the surgical experience. Radiother Oncol 2000;56:135-150.

15 Fogliata A, Cozzi L, Bieri S, Bernier J. Critical appraisal of a conformal head and neck cancer irradiation avoiding electron beams and field matching. Int J Radiat Oncol Biol Phys 1999;45:1331-1338.

16 Jellema AP, Slotman BJ, Doornaert P, Leemans CR, Langendijk JA. Impact of radiation-induced xerostomia on quality of life after primary radiotherapy among patients with head and neck cancer. Int J Radiat Oncol Biol Phys 2007;69:751-760.

17 Graff P, Lapeyre M, Desandes E, *et al*. Impact of intensity-modulated radiotherapy on health-related quality of life for head and neck cancer patients: matched-pair comparison with conventional radiotherapy. Int J Radiat Oncol Biol Phys 2007;67:1309-1317.

18 Eisbruch A, Kim HM, Terrell JE, *et al*. Xerostomia and its predictors following parotid-sparing irradiation of head-and-neck cancer. Int J Radiat Oncol Biol Phys 2001;50:695-704.

19 Jellema AP, Doornaert P, Slotman BJ, Leemans CR, Langendijk JA. Does radiation dose to the salivary glands and oral cavity predict patient-rated xerostomia and sticky saliva in head and neck cancer patients treated with curative radiotherapy? Radiother Oncol 2005;77:164-171.

20 Meirovitz A, Murdoch-Kinch CA, Schipper M, Pan c, Eisbruch A. Grading xerostomia by physicians or by patients after intensity-modulated radiotherapy of head-and-neck cancer. Int J Radiat Oncol Biol Phys 2006;66:445-453.

21 Vissink A, Burlage FR, Spijkervet FK, Jansma J, Coppes RP. Prevention and treatment of the consequences of head and neck radiotherapy. Crit Rev Oral Biol Med 2003;14:213-225.

22 Levendag PC, Teguh DN, Voet P, *et al*. Dysphagia disorders in patients with cancer of the oropharynx are significantly affected by the radiation therapy dose to the superior and middle constrictor muscle: A dose-effect relationship. Radiother Oncol 2007;85:64-73.

23 Eisbruch A, Schwartz M, Rasch C, *et al*. Dysphagia and aspiration after chemoradiotherapy for head-and-neck cancer: which anatomic structures are affected and can they be spared by IMRT? Int J Radiat Oncol Biol Phys 2004;60(5:1425-1439.

24 Rosenthal DI, Chambers MS, Fuller CD, *et al.* Beam path toxicities to non-target structures during intensity-modulated radiation therapy for head and neck cancer. Int J Radiat Oncol Biol Phys 2008;May 1 [Epub ahead of print].

25 Cannon DM, Lee NY. Recurrence in region of spared parotid gland after definitive intensity-modulated radiotherapy for head and neck cancer. Int J Radiat Oncol Biol Phys 2008;70:657-659.

26 Schoenfeld GO, Amdur RJ, Morris CG, *et al.* Patterns of failure and toxicity after intensity-modulated radiotherapy for head and neck cancer. Int J radiat Oncol Biol Phys 2008;71:377-385.