Clin Oral Invest (2013) 17:1619–1625
DOI 10.1007/s00784-012-0854-6

ORIGINAL ARTICLE

The influence of parotid gland sparing on radiation damages of dental hard tissues

Jeremias Hey · Johannes Seidel · Ramona Schweyen · Yvonne Paelecke-Habermann · Dirk Vordermark · Christian Gernhardt · Thomas Kuhnt

Received: 5 October 2011 / Accepted: 25 September 2012 / Published online: 5 October 2012

Abstract
Objective The aim of the present study was to evaluate whether radiation damage on dental hard tissue depends on the mean irradiation dose the spared parotid gland is subjected to or on stimulated whole salivary flow rate.
Material and methods Between June 2002 and October 2008, 70 patients with neck and cancer curatively irradiated were included in this study. All patients underwent dental treatment referring to the guidelines and recommendations of the German Society of Dental, Oral and Craniomandibular Sciences prior, during, and after radiotherapy (RT). During the follow-up period of 24 months, damages on dental hard tissues were classified according to the RTOG/EORTC guidelines. The mean doses (D_{mean}) during spared parotid gland RT were determined. Stimulated whole saliva secretion flow rates (SFR) were measured before RT and 1, 6, 12, 24 months after RT.
Results Thirty patients showed no carious lesions (group A), 18 patients developed sporadic carious lesions (group B), and 22 patients developed general carious lesions (group C). Group A patients received a D_{mean} of 21.2±11.04 Gy. Group B patients received a D_{mean} of 26.5±11.59 Gy and group C patients received a D_{mean} of 33.9±9.93 Gy, respectively. The D_{mean} of group A was significantly lower than the D_{mean} of group C ($p<0.001$). Additionally, the mean SFR 6 months after RT of group A was significantly higher than the mean SFR of group C ($p<0.01$).
Conclusions Irradiation damage on dental hard tissue correlates with increased mean irradiation doses as well as decreased salivary flow rates.
Clinical relevance Parotid gland sparing resulting in a dose below 20 Gy reduces radiation damage on dental hard tissues, and therefore, the dose may act as a predictor for the damage to be expected.

Keywords Head and neck irradiation · Parotid gland sparing · Salivary flow rate · Radiation caries

J. Hey (✉) · J. Seidel · R. Schweyen
Department of Prosthetic Dentistry, University School of Dental Medicine, Martin-Luther-University Halle-Wittenberg,
Große Steinstraße 19,
06108 Halle, Germany
e-mail: jeremias.hey@medizin.uni-halle.de

Y. Paelecke-Habermann
Department of Psychology,
Julius-Maximilians-University Würzburg,
Marcusstraße 9-11,
97070 Würzburg, Germany

D. Vordermark
Department of Radiotherapy, University Clinic,
Martin-Luther-University Halle-Wittenberg,
Dryanderstraße 4,
06110 Halle, Germany

C. Gernhardt
Department of Operative Dentistry and Periodontology,
University School of Dental Medicine,
Martin-Luther-University Halle-Wittenberg,
Große Steinstraße 19,
06108 Halle, Germany

T. Kuhnt
Department of Radiotherapy, University Clinic,
Südring 75,
18059 Rostock, Germany

Introduction

Radiation damage on dental hard tissue (radiation-related caries) is the most threatening dental complication in patients who undergo head and neck radiotherapy. It causes generalized dental destruction and impairs quality of life in cancer patients. Radiation damage on dental hard tissue is expected to be a multifactorial disease [1]. Reduced salivary flow rate due to radiotherapy is generally accepted as one

critical factor [2]. Due to the anatomical position, salivary glands are frequently involved in the irradiated area. According to the applied dose, cellular decrease and interstitial fibrosis occur and lead to impaired saliva quality and quantity [3, 4].

Intensity-modulated radiotherapy (IMRT) and 3D conformal radiotherapy (3D-CRT) offer the possibility to reduce the radiation-induced damage to the salivary gland tissue [5]. Particularly, parotid gland sparing preserves salivary flow rates and improves quality of life after radiotherapy [6]. In a recent study, Gomez et al. examined the correlation between irradiation on salivary gland and damage on dental hard tissue. They found that low dose irradiation of salivary glands is correlated with less severe damage to dental hard tissues [7]. However, their findings are questionable for the following reasons: (1) salivary flow rate as the known critical factor was not determined and (2) contrary to scientific knowledge, they took the non-spared parotid gland into account for statistical calculation, although the less irradiated gland is responsible for the main part of saliva production. Thus, the abovementioned correlation cannot be validated.

In two former prospective studies, we demonstrated that parotid gland sparing in radiotherapy for head and neck cancer preserves the salivary flow rate [8, 9]. As an expansion to our previous studies, we performed an analysis of post-radiation damage dental hard tissue. Based on these data, in this study we assess whether the extent of radiation damage on dental hard tissue depends on the irradiation the spared parotid gland is subjected to and on the salivary flow rate. We hypothesize that the extent of radiation damage on dental hard tissue depends neither on the irradiation dose nor on the salivary flow rate.

Methods

Recruitment of patients

Between June 2003 and September 2008, all patients with head and neck cancer receiving a curative radiotherapy were prospectively evaluated in two studies granted by German Cancer Aid association (grant no. 106386 and 108429). One hundred seventeen patients participated in these studies. The protocols were approved by the medical faculty's ethics committee at the Martin-Luther-University Halle-Wittenberg. The studies comprised a strict dental care management and documentation of effects on dental hard tissue. Only patients with at least three or more teeth remaining after dental treatment prior to radiotherapy were included in the present study. Edentulous patients, patients with insufficient lip closure, and patients who refused dental treatment prior to radiotherapy were excluded. Thus, data of 70 patients could be used for statistical evaluation. All described therapeutical radiotherapies were performed according to the official NCCN guidelines.

Treatment planning, definition of target volumes, and irradiation dose

Patients received 3D-CRT (2003–2006) or IMRT (2006–2008). No randomization was done. For all patients, the treatment of the bilateral neck was indicated, ensuring that the primary tumor regions were irradiated. Additionally, regional and supraclavicular lymph nodes were irradiated.

Patients were immobilized using a custom-made thermoplastic head–neck–shoulder mask. A computer tomography (CT) scan (Lightspeed; General Electric, Fairfield, USA) with slice thickness 5 mm of the head and neck region was performed for treatment planning.

Two planning systems (Helax TMS version 6.1 and Oncentra Masterplan version 1.5/3.0; Nucletron, Veenendaal, Netherlands) were used for the 3D treatment planning. The 3D-CRT was performed by standardized six to seven portal arrangements as described in a previous investigation [10]. Patients receiving 3D-CRT were treated with 6 and 10-MV photons of a linear accelerator (Primus and Oncor; Siemens Medical Solutions, Erlangen, Germany). IMRT was based on the step-and-shoot approach with seven or nine equidistant 6-MV beams. The treatment technique was similar to the one described by Georg et al. [11]. The planning strategy was to cover 95 % of the planning target volumes (PTVs) with 95 % of the prescribed dose. The mean dose given to at least one parotid gland was limited to 26 Gy without compromising PTV. The maximum dose to the spinal cord was 45 Gy.

Two different clinical target volumes (CTVs) were delineated. The primary CTV included the region of the primary tumor or postoperative tumor bed and pathological lymph nodes. The low dose volume was named secondary CTV. The secondary CTV included the adjuvant treated regions of the neck without a histological or clinical proof of pathological changed lymph nodes. The primary PTV was defined like the primary CTV with an adequate safety margin of 5 mm. The secondary PTV included the primary PTV and different lymph node chains of the neck (secondary CTV) with a safety margin of 5–8 mm; smaller margins were chosen close to an organ at risk.

The secondary PTV was irradiated 5 days a week, each time with a single dose of 2 Gy, until a cumulative dose of 50 Gy was reached. Afterwards, primary PTV was irradiated in the same way until the total dose reached 64–70 Gy. Dose specifications are related to a reference point in target volume as described in the ICRU report 62 for IMRT [12, 13].

Determination of the parotid gland doses

The PTVs and both parotid glands, the mandibular, and the oral mucous membrane were outlined on the transversal

slices of the planning CT scans. The goal was to minimize the mean dose in the contralateral parotid while maintaining a homogeneous dose distribution in the target volumes. No effort was made to spare the submandibular or minor salivary glands.

The mean dose and the partial volumes receiving specified doses were determined for each gland from a dose–volume histogram (DVH). Based on an algorithm initially proposed by Lyman, the DVHs were transformed [14]. Afterwards, mean doses in Gray of the ipsilateral and contralateral parotid glands were calculated for every patient.

Determination of the stimulated whole salivary flow rate

All patients underwent saliva collection at six different time points: within 1 week before radiotherapy and 1, 6, 12, and 24 months after radiotherapy. All saliva samples were collected at least 1 h after a meal in the morning (9:00 to 11:00 am). First, patients were asked to rinse the mouth and swallow any residual saliva. Then, the patients were instructed to chew on a paraffin pellet (Ivoclar Vivadent; Ellwangen, Germany) for 5 min and to collect the produced saliva into cups during this time. Saliva was drawn up into one-way syringes, and the stimulated whole salivary flow rates (SFR) were calculated in milliliters per minute [15, 16].

Oral treatment prior to radiotherapy

Referring to the guidelines and recommendations of the German Society of Dental, Oral and Craniomandibular Sciences

Teeth

- with periodontal probing depth equal to or greater than 5 mm
- with furcation involvement
- with carious lesions reaching the pulp
- which were impacted and retained
- with large fillings, fractures, or significant occlusal wear
- which were positioned in a high dose region of >55 Gy
- which were non-vital and without sufficient root canal filling
- which were painful, sensitive to percussion, or revealed apical radiolucency

were extracted prior to radiotherapy. In addition, teeth, which were predestinated to be severely affected by compromised mouth hygiene due to radiogenic trismus, were also removed.

To avoid complications of molar teeth extractions after radiotherapy, the situation of shortened dental arch was intended [17]. If a shortened dental arch was not possible, the canines were preserved for later prosthodontic treatment if possible. Initial caries and medium carious lesions were treated conventionally [18]. All patients received a professional tooth cleaning before radiotherapy.

Oral treatment during radiotherapy

During treatment course of radiotherapy, the oral cavity was inspected weekly by a radiation oncologist. At each appointment, oral hygiene instructions were reinforced. Patients who were adversely affected by mucositis up to level 1 received dexpanthenol-containing mouthwash solutions. All patients received custom-made fluoride carriers of 5 mm-thick ethylene vinyl acetate. Patients were instructed to use the carriers without fluoride gel during radiation to keep cheek and tongue in distance to locally increased radiation doses caused by scattered radiation from metallic crowns. In addition, patients were instructed to use fluoride gel on their carriers for 10 min at least once a day after toothbrushing.

Oral treatment after radiotherapy

All patients were advised to take part in a special dental follow-up treatment. Quarterly, patients were offered free professional tooth cleaning. In addition, a dental check-up was made during these appointments. In case of carious lesions, teeth were treated following the recommendations of Kielbassa et al. and Grotz et al. [18, 19].

Classification of radiation damage on dental hard tissue

Radiation damages on dental hard tissues were classified according to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) guidelines as proposed by Grotz et al. [19]. The classification is described in Table 1. Due to the therapeutic consequence and the difficulty to discriminate between the different grades in clinical practice, the RTOG/EORTC guidelines were modified. Classification grade 1 and 2 as well as classification grade 3 and 4 were pooled.

Statistics

Descriptive statistics were used to characterize the patient population. The statistical analyses were performed using SPSS 17.0 for Windows. Differences in the mean irradiation dose to the spared parotid gland and in the mean stimulated whole salivary flow rate among groups based on radiation damages on dental hard tissues were analyzed by using one-factor analysis of variance with Bonferroni correction. Level of significance was set to 5 % ($p<0.05$).

Table 1 Range-scaled rating of development of characteristic of late radiation damage on dental hard tissue equivalent to RTOG/EORTC score (RTOG 0=no change in comparison with starting point) [19]

Grade	Findings	Measures taken
Grade 0	No pathological finding	Prophylaxis continuation. No therapeutic measures taken
Grade 1	Chalky-white spots. Loss of shine and translucency of the enamel. Initial caries at predilection site tooth cervix, incisal edge, and cusp tips as well	Intensification of oral hygiene, fluoridation. If necessary, urgent filling therapy or crowning as prophylaxis
Grade 2	Caries undermining the enamel attended by loss of laminar parts of enamel. Dentin core is directly exposed, usually in the cervical area	Urgent crowning of the tooth. In case of trepanation of the pulp cavity indication for tooth extraction
Grade 3	Subtotal to total loss of the enamel. Dentin seems to be softened, so that a dental probe can penetrate	Extraction of the tooth under particular conditions
Grade 4	Subtotal or total destruction of the tooth's crown	Urgent indication for operative extraction of the tooth. Potentially beginning of an infected osteoradionecrosis, if necessary local periradicular revision

Results

Classification of radiation damage on dental hard tissue

Forty-seven patients were excluded from the evaluation due to exclusion criteria or medical conditions. Twelve of them died during the observation period. Thus, data of 70 patients were analyzed. The observation period ranged from 24 to 54 months with a mean of 34 months. Clinical teeth status data at the 24-month follow-up were taken into account for statistical analyses. During the period of observation, 30 patients were found to be grade 0. No effects on dental hard tissue were determined in these patients. They shall be further classified as group A. Eighteen patients were found to be grade 1 and grade 2. They developed sporadic carious lesions. Conventional restorative and prosthodontic treatment was necessary due to the damage to dental hard tissue. No teeth had to be removed. These patients shall be further classified as group B. Another 22 patients were found to be grade 3 and grade 4. They developed general carious lesions. A conventional treatment was not possible due to the rampant tooth decay. Several teeth had to be removed. These patients shall be further classified as group C. The patients and tumor characteristics of each group are shown in Table 2.

Mean irradiation dose in the spared parotid gland

The spared parotid gland of group A patients was exposed to a mean irradiation dose of 21.2±11.04 Gy, group B patients 26.5±11.59 Gy, and group C patients 33.9±9.93 Gy, respectively. The mean irradiation dose of group A was significantly lower than the mean irradiation dose of group C ($p<0.001$). The distributions of the mean irradiation doses of the spared parotid glands are shown in Fig. 1.

Salivary flow rates

The SFR decreased in all groups after radiotherapy. Six months after radiotherapy, the SFR reached its minimum in group A and C. At 12 and 24 months after radiotherapy, the mean SFR slightly increases in all groups, but did not reach initial values.

Six months after radiotherapy, in group A the mean SFR decreased by 50 % from 6 ml/5 min to 3 ml/5 min., in group B by 60 % from 6.1 ml/5 min to 2.4 ml/5 min, and in group C by 80 % from 5.8 ml/5 min to 1.1 ml/5 min. Mean SFR at 6 months after radiotherapy in group A was significantly higher than the mean SFR in group C ($p<0.01$). The mean SFRs are listed in Table 3.

Table 2 Patient and tumor characteristics

Study population	Group A	Group B	Group C
Patient number	30	18	22
Male/female	21/9	12/6	18/4
Median age in years (range)	57 (26–77)	59 (36–71)	58 (46–73)
3D-CRT/IMRT	15/15	13/5	20/2
Tumor sites			
Oral cavity	10	6	8
Oropharynx/nasopharynx	10	8	9
Larynx/hypopharynx	6	4	5
Unknown primary (CUP)	1		
Other (myeloma, lymphoma, nasal cavity, paranasal sinus)	3		

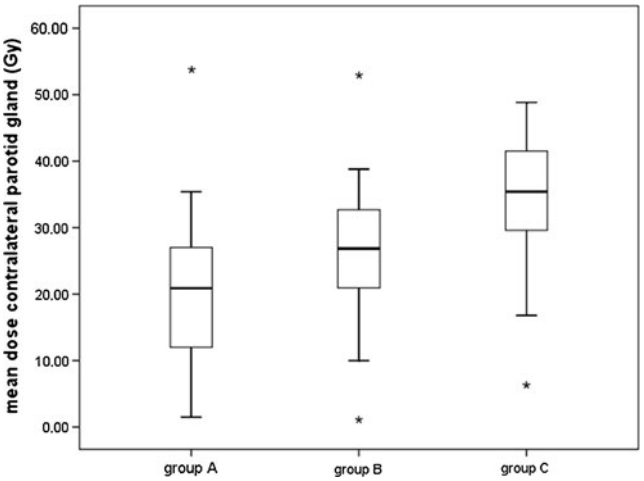

Fig. 1 Boxplot mean dose in Gray

Discussion

A common side effect of radiotherapy for head and neck cancer is radiation damage on dental hard tissue. There are several theories and publications attempting to explain whether the primary cause of radiation damage on dental hard tissue is from irradiation of the surrounding tissue or direct irradiation of the teeth [1]. The direct damage to dental hard tissues is thought to occur in the direct field of x-rays. Franzel et al. detected in vivo that the mechanical properties of teeth are clearly changed by irradiation of 60 Gy [20]. They concluded that enamel and also dentine are strongly affected by irradiation. Particularly, the mechanical properties of the enamel are completely decreased. Therefore, the direct irradiation damage should be the main effect of the radiation damage to dental hard tissue and the accompanying loss of saliva.

Table 3 Mean and standard deviation of whole stimulated salivary flow rate (SFR) prior to radiotherapy and at 1, 6, 12, and 24 months after radiotherapy

Group	Time Point	Patients (*n*)	Mean SFR (ml/5 min)	SD (ml/5 min)
A	Prior to RT	27	6.00	3.13
	1 month after RT	25	3.23	2.27
	6 months after RT	26	3.03	2.09
	12 months after RT	26	3.53	2.36
	24 months after RT	23	3.92	2.31
B	Prior to RT	17	6.10	3.51
	1 month after RT	16	1.79	1.69
	6 months after RT	17	2.43	2.54
	12 months after RT	17	2.51	1.86
	24 months after RT	14	2.28	1.96
C	Prior to RT	21	5.76	3.39
	1 month after RT	20	1.95	2.85
	6 months after RT	20	1.12	1.62
	12 months after RT	18	2.49	3.14
	24 months after RT	20	2.85	2.87

This hypothesis is supported by Walker et al. [21]. They retrospectively analyzed data from 93 head and neck radiotherapy patients. In their study, the individual tooth radiation dose was calculated and then correlated with post-radiation tooth damage. The results suggest three tiers of dose–response: minimal tooth damage below 30 Gy, a two to three times increased dose–tooth damage relationship between 30 and 60 Gy, followed by a critical threshold of 60 Gy above which tooth damage occurs at a ten times higher rate.

Kielbassa et al. negate the importance of the direct radiation damage of dental hard tissues. They demonstrated in vitro that irradiated dental hard tissue is not more susceptible to caries than non-irradiated ones [22, 23]. Therefore, radiation damage on dental hard tissue cannot be explained by the direct radiation damage. In 2011, Gomez et al. determined in a retrospective review that the incidence of dental caries is related to the dose to the salivary glands [7]. They inferred from their results that radiation damage on dental hard tissue is a result of an indirect effect on the oral cavity rather than a direct irradiation effect to the dentition. However, salivary gland function was not measured in this study. Furthermore, the non-spared parotid gland was taken into account for statistical calculation. Most of the studies regarding changes in salivary gland function after radiotherapy focused on the spared parotid gland because less irradiated gland produces larger amount of saliva. Therefore, the effects on the teeth cannot be validated by the reduced function of the salivary gland that is most affected by the irradiation.

However, we found that the extent of radiation damage on dental hard tissue depends on spared parotid gland dose parameters as well as on salivary flow rate. Hence, our initial hypothesis proved to be wrong.

In previous investigations, we have shown that parotid gland sparing preserves salivary flow rates [8, 9]. Now we observed that patients having received a treatment with a D_{mean} of 33.9 Gy suffered from destructive radiation-related damage of their dental hard tissue, while patients having received a treatment with a D_{mean} of 21.2 Gy had no changes of their dental hard tissues ($p<0.001$; ANOVA).

Besides, there was a significant relationship between the mean SFR and the changes of the dental hard tissues at 6 months after radiotherapy, too ($p<0.01$; ANOVA). Such significant differences were not detected at any other time point.

In a recently published study by Karbach et al., no significance was found between the unstimulated salivary flow rate and radiation damage on dental hard tissue [24]. A few points may explain their results. First, they used the unstimulated salivary flow rate as a parameter, which is less predictable for radiation damage on dental hard tissue [2]. Second, their time of follow-up examinations varied in a range from 6 to 110 months. Therefore, the recovery of the

irradiated glands was not taken into account. Third, only 40 patients were investigated making a statistical evaluation questionable. Therefore, this study cannot be used to contradict our findings.

However, similar factors limited the results of our study. The measurement of the salivary flow rate is an established but flawed method for the functional state of salivary glands after radiotherapy. First of all, the salivary flow rate varies up to 44 % within healthy individuals over time [25]. Moreover, it is known that the method of measuring the whole salivary flow rate results in a higher salivary flow rate compared to the more detailed examination techniques of parotid gland alone using custom-made collection devices like Lashley cups [26]. Thus, the whole salivary flow rate obtained in this study does not represent the remaining flow rate of the parotid glands alone after radiotherapy.

Additionally, a few patients were not able to participate timely to all follow-up examinations. Due to the aspect that parotid glands recover after radiotherapy, only measurements within the correct time line were taken into account for this evaluation [9]. These missing data led to a lack of power in analysis.

Furthermore, the quality of saliva might be of higher importance for the preservation of dental hard tissue than the salivary flow rate. In case of a lack of basic buffer ions, saliva is not able to remineralize the teeth adequately. The result is a steady tooth demineralization despite good oral hygiene. Unfortunately, the quality of saliva was not determined constantly in our evaluation. Likewise, other aspects associated with the quantity and quality of the saliva like radiation mucositis or changes in the oral microbiology were not determined as well [27]. The results suggest that the mean radiation dose on the spared parotid gland may take these aspects into account, therefore functioning as a reference parameter. Therefore, it may be an appropriate indicator for the functional state of the salivary glands in describing the oral environment and thus an evaluation criterion for the development of radiation damage on dental hard tissues as well. Besides, the mean radiation dose on the spared parotid gland is available prior to the radiotherapy. Hence, it may act as a predictor for damage on dental hard tissue and may influence extraction decisions prior to radiotherapy. In cases where the contralateral parotid gland can be spared with doses below 20 Gy, just a minimal invasive restoration protocol prior to radiotherapy may be needed.

In a previous investigation, we suggested that parotid gland sparing from a radiation dose below 26 Gy maintains an adequate salivary flow rate [9]. Referring to the present results, it is recommended to surpass this reference for patients with teeth and to strive for a dose below 20 Gy.

Like Karbach et al., we used the RTOG/EORTC guidelines as proposed by Grotz et al. to classify radiation damage on dental hard tissue [19, 25]. Despite the fact that in regard to therapeutic consequences, classification grade 1 and 2 as well as classification grade 3 and 4 can be united, the guidelines are a useful tool. In our experience, very detailed caries indices are not appropriate in dental management regarding radiotherapy for head and neck cancer. On the one hand, tumor fatigue and radiation-related trismus aggravate dental treatment for the patients. On the other hand, time-consuming dental treatment without a noticeable benefit for the patient on its own reduces compliance. In our evaluation, a lot of time in dental follow-up treatment had to be spent to reinforce oral hygiene.

Considering these results, further investigations should be undertaken to determine the relation between the incidences of radiation damage on dental hard tissue and the radiation dose in the spared parotid gland. In these studies, patients should be observed years after the end of therapy to investigate an increase of radiation damage on dental hard tissue incidence which might just be timely shifted compared to other patients. In addition, the quality of saliva after radiotherapy should be observed more closely to explain radiation damage dental hard tissue more precisely. In context with preservation of salivary gland function, not only the quantity but also the quality of saliva might be of particular importance.

Summary

The mean dose in the spared parotid gland as well as the stimulated whole salivary flow rate affects the extent of radiation damage on dental hard tissue. Parotid gland sparing after radiotherapy reduces radiation damage on dental hard tissue. Therefore, guidelines regarding dental treatment in advance of any radiotherapy in the head and neck region should implement the mean radiation doses of the spared parotid gland as a reference parameter. Referring to the presented results, it could be recommended to strive for an irradiation dose in the spared parotid gland below 20 Gy. The results suggest that in cases of doses below 20 Gy in the spared parotid gland, just a minimal invasive restoration protocol prior to radiotherapy would be needed. Certainly, clinical long-term results have to prove these findings.

Conflict of interest The authors declare no conflict of interest.

References

1. Schweyen R, Hey J, Fränzel W, Vordermark D, Hildebrandt G, Kuhnt T (2012) Radiation-related caries: etiology and possible preventive strategies. What should the radiotherapist know? Strahlenther Onkol 188:21–28
2. Spak CJ, Johnson G, Ekstrand J (1994) Caries incidence, salivary flow rate and efficacy of fluoride gel treatment in irradiated patients. Caries Res 28:388–393

3. Chao KS, Majhail N, Huang CJ, Simpson JR, Perez CA, Haughey B, Spector G (2001) Intensity-modulated radiation therapy reduces late salivary toxicity without compromising tumor control in patients with oropharyngeal carcinoma: a comparison with conventional techniques. Radiother Oncol 61:275–280
4. Jensen SB, Pedersen AM, Reibel J, Nauntofte B (2003) Xerostomia and hypofunction of the salivary glands in cancer therapy. Support Care Cancer 11:207–225
5. Chao KS, Deasy JO, Markman J, Haynie J, Perez CA, Purdy JA, Low DA (2001) A prospective study of salivary function sparing in patients with head-and-neck cancers receiving intensity-modulated or three-dimensional radiation therapy: initial results. Int J Radiat Oncol Biol Phys 49:907–916
6. Parliament MB, Scrimger RA, Anderson SG, Kurien EC, Thompson HK, Field GC, Hanson J (2004) 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 58:663–673
7. Gomez DR, Estilo CL, Wolden SL, Zelefsky MJ, Kraus DH, Wong RJ, Shaha AR, Shah JP, Mechalakos JG, Lee NY (2011) Correlation of osteoradionecrosis and dental events with dosimetric parameters in intensity-modulated radiation therapy for head-and-neck cancer. Int J Radiat Oncol Biol Phys 81:e207–e213
8. Hey J, Setz J, Gerlach R, Janich M, Sehlleier S, Schaller HG, Gernhardt CR, Kuhnt T (2009) Parotid-gland sparing 3D conformal radiotherapy in patients with bilateral radiotherapy of the head and neck region—results in clinical practice. Oral Oncol 45:e11–e17
9. Hey J, Setz J, Gerlach R, Janich M, Hildebrandt G, Vordermark D, Gernhardt CR, Kuhnt T (2011) Parotid gland-recovery after radiotherapy in the head and neck region—36 months follow-up of a prospective clinical study. Radiat Oncol 6:125
10. Kuhnt T, Janich M, Gotz U, Gerlach R, Chiricuta IC, Hansgen G (2006) Presentation of a 3D conformal radiotherapy technique for head-and-neck tumors resulting in substantial protection of the parotid glands. Strahlenther Onkol 182:325–330
11. Georg D, Kroupa B, Georg P, Winkler P, Bogner J, Dieckmann K, Pötter R (2006) Inverse planning—a comparative intersystem and interpatient constraint study. Strahlenther Onkol 182:473–480
12. International Commission on Radiation Units and Measurements (1993) ICRU 50: prescribing and reporting photon beam therapy. Inc ICRU News 1:1–72
13. International Commission on Radiation Units and Measurements (1999) ICRU 62: prescribing, recording and reporting photon beam therapy (supplement to ICRU Report 50). Inc ICRU News 1:1–8
14. Lyman JT, Wolbarst AB (1989) Optimization of radiation therapy, IV: a dose-volume histogram reduction algorithm. Int J Radiat Oncol Biol Phys 17:433–436
15. Burlage FR, Coppes RP, Meertens H, Stokman MA, Vissink A (2001) Parotid and submandibular/sublingual salivary flow during high dose radiotherapy. Radiother Oncol 61:271–274
16. Dawes C (1987) Physiological factors affecting salivary flow rate, oral sugar clearance, and the sensation of dry mouth in man. J Dent Res 66:648–653
17. Witter DJ, van Palenstein Helderman WH, Creugers NH, Kayser AF (1999) The shortened dental arch concept and its implications for oral health care. Community Dent Oral Epidemiol 27:249–258
18. Kielbassa AM, Hinkelbein W, Hellwig E, Meyer-Luckel H (2006) Radiation-related damage to dentition. Lancet Oncol 7:326–335
19. Grotz KA, Riesenbeck D, Brahm R, Seegenschmiedt MH, Al-Nawas B, Dorr W, Kutzner J, Willich N, Thelen M, Wagner W (2001) Chronic radiation effects on dental hard tissue (radiation caries). Classification and therapeutic strategies. Strahlenther Onkol 177:96–104
20. Franzel W, Gerlach R, Hein HJ, Schaller HG (2006) Effect of tumor therapeutic irradiation on the mechanical properties of teeth tissue. Z Med Phys 16:148–154
21. Walker MP, Wichman B, Cheng AL, Coster J, Williams KB (2011) Impact of radiotherapy dose on dentition breakdown in head and neck cancer patients. Pract Radiat Oncol 1:142–148
22. Kielbassa AM (2000) In situ induced demineralization in irradiated and non-irradiated human dentin. Eur J Oral Sci 108:214–221
23. Kielbassa AM, Hellwig E, Meyer-Lueckel H (2006) Effects of irradiation on in situ remineralization of human and bovine enamel demineralized in vitro. Caries Res 40:130–135
24. Karbach J, Walter C, Al-Nawas B (2012) Evaluation of saliva flow rates, *Candida* colonization and susceptibility of *Candida* strains after head and neck radiation. Clin Oral Investig 16:1305–1312
25. Ghezzi EM, Lange LA, Ship JA (2000) Determination of variation of stimulated salivary flow rates. J Dent Res 79:1874–1878
26. Veerman EC, van den Keybus PA, Vissink A, Nieuw Amerongen AV (1996) Human glandular salivas: their separate collection and analysis. Eur J Oral Sci 104:346–352
27. Beer KT, Zehnder D, Lussi A, Greiner RH (2002) Sparing of contralateral major salivary glands has a significant effect on oral health in patients treated with radical radiotherapy of head and neck tumors. Strahlenther Onkol 178:722–726