Journal of Dentistry and Oral Biology

Review Article
Published: 14 Jun, 2019

Radiation-Related Caries-An Update for Dental Clinicians

Ana Lúcia Antunes[1], Rúbia Teodoro Stuepp[2], Mariah Luz Lisboa[3], Beatriz Álvares Cabral de Barros[2], Renata Gondo Machado[2] and Alessandra Rodrigues de Camargo[2]*

[1]Federal University of Santa Catarina, Brazil

[2]Department of Dentistry, Federal University of Santa Catarina, Brazil

[3]Hospital Professor Polydoro Ernani de São Thiago, Federal University of Santa Catarina, Brazil

Abstract

Radiation-related caries is a late consequence of head and neck radiotherapy for the treatment of head and neck cancer. The aim of this study is to present a literature review on the clinical characteristics, classifications systems, etiopathogeny and restorative management of radiation-related caries.

Introduction

Head and Neck Cancer (HNC) is the sixth malignant neoplasm most commonly found worldwide and approximately 400,000 new cases are diagnosed annually [1,2]. The management of cancers of the oral cavity is complex due to the functional and aesthetic implications of treatment of tumours in this region. In most cases, treatment includes Head and Neck Radiotherapy (HNRT), which is often combined with surgery and sometimes with chemotherapy [3].

Radiation dosimetry (measurement of the dose of radiation supplied to the tumor) is expressed by the standard unit Gray (Gy), which represents J/kg. The therapeutic dose of radiation for HNC generally reaches a total of 64 Gy at 70 Gy. In HNC treatment, numerous radiation-induced complications may occur, such as dysgeusia, dysphagia, mucositis, trismus, hyposalivation, osteoradionecrosis and Radiation-Related Caries (RRC), leading to a significant compromising quality of life [2,4,5]. These complications are dose dependent of total radiation and the field of irradiation (anatomical sites involved). In general, serious adverse effects are caused when the total dose administered is <45 Gy, being more serious when the oral cavity is involved bilaterally [6].

Then, the aim of this review is to provide an update on radiation-related caries.

Radiation-Related Caries

Radiation-related caries, also known as radiation caries, is a late consequence of HNRT for the treatment of HNC [3], affecting approximately 25% of the patients and with the onset between 6 and 12 months after the conclusion of the treatment [3,7]. Usually, RRC has no acute pain, mostly affects the cervical surface of premolars and molars, has rapid progression [3] and is associated with persistent infection and increased risk for the development of osteoradionecrosis [3,7].

The evolution of RRC differs in clinical appearance, development and progression from the conventional caries. Usually, RRC begins as discreet enamel cracks and fractures and progress to a brown/blackish discoloration of the enamel. If not treated, RRC develop as incisal/cuspal wear in association with widespread cervical (amelocemental junction) caries, wich leads to enamel delamination, destruction of the underlying dentin, and, finally, amputation of the dental crown. In contrast, the conventional caries usually occur especially in pits, fissures and teeth proximal regions [7].

Because of this different pattern, some authors seeks to develop a system to detect, asses and manage RRC. In this context, the International Caries Detection and Assessment System (ICDAS), a well-recognized tool to assess and standardize clinical diagnosis of caries, classifies lesions of conventional caries on the basis of their clinical visual appearance. For this, the lesion receive a code between 1 to 6 according to the stage. In code 1 there is a visual carious change in enamel seen clinically only when the tooth is dry; Code 2: visual carious change in enamel seen clinically wet or dry; Code 3: clinically detectable enamel lesions with "intact" surfaces; Code 4 and 5: clinically detectable lesions in dentine; Code 6: lesion in to pulp [8].

In 2008, Walker affirms that the traditional caries measures may not be valid for assess the pattern and extent of tooth destruction in RRC since this lesions differs from conventional caries

OPEN ACCESS

***Correspondence:**
Rúbia Teodoro Stuepp, Department of Dentistry, University Federal de Santa Catarina, Campus Reitor João David Ferreira Lima, Trindade, Florianopolis, 88040-900, Santa Catarina, Brazil, Tel: +55 3721-9079;
E-mail: rubia_ts@hotmail.com

Received Date: 04 May 2019
Accepted Date: *12 Jun 2019*
Published Date: *14 Jun 2019*

Citation:
Antunes AL, Stuepp RT, Lisboa ML, Cabral de Barros BÁ, Machado RG, de Camargo AR. Radiation-Related Caries-An Update for Dental Clinicians. J Dent Oral Biol. 2019; 4(1): 1151.
ISSN: 2475-5680

em development and progress. Then, the author proposed Post-Radiation Dental Index (PRDI) based on clinical apperance. Walker proposed a Surface Score ranging 0 to 5 to the buccal, lingual and oclusal surface of the clinical crown for unrestored tooth. In score 0 there is no change in tooth surface; Score 1: White line and/or brown stain; enamel is intact and most of the surface is smooth and shiny; Score 2: single focal área of enamel/tooth structure loss (<2 mm diameter); Score 3: single enamel/tooth structure loss focal área (>2 mm diameter) OR more than 1 focal área of enamel/tooth structure loss. Total área of tooth loss <1/3 surface área; Score 4: Enamel/tooth structure loss >1/3 but 2/3 of surface área. Score 5: extensive enamel/tooth structure loss >2/3 of surface área. These finds should may cross check with the index score of restored teeth, when necessary, also proposed by the author [9].

A study evaluated, through standardized photographs, 883 teeth of patients who received HNRT and classified each dental element according to ICDAS and PRD in order to adopt some classification method that contributed to the analysis of disease progression. After analysis, the authors concluded that of the 814 teeth clinically diagnosed with RRC, 69.7% of the teeth presented code 5 and 6 for ICDAS, and 56.7% presented scores 4 and 5 for PRDI, which affirms the aggressive character of RRC. In conclusion, the author affirms that the ICDAS and PRDI has limited applicability in the assessment of RRC and therefore ideally should not be used for clinical decisions in this scenario [7].

With reggard to etiopathogeny, thefactors linked with the RRC remains incertain [10]. The development of RRC has been associated with hyposalivation, since saliva has essential functions in maintaining tooth structure due to control of pH, remineralization, antimicrobial and tooth cleansing effects [4]. Beyond that, recently studies show that radiation induces direct modifications in mineralized dental tissue and, consequently, its mechanical properties (Figure 1) [11].

Indirect Effects of Radiation on Dental Tissue

Salivary glands are the major oral tissues affected by ionizing radiation during HNRT. Some studies show that glandular fibrosis begins immediately after irradiation and intensifies until the end of treatment, causing rapid reduction of salivary flow and increased viscosity of saliva. About 80% of the salivary function is lost after irradiation with doses of 20 Gy, and irreversible damage of the salivary gland can occur when the dose of 30 Gy is reached [12].

Therefore, irradiation of the salivary glands can result in changes in saliva composition, production and quality. The salivary flow may be related to the alterations of the mineralized tissues of the tooth and, consequently, to the process of cariogenesis. Patients receiving mean doses of radiation of 33.9 Gy exhibited damage to dental tissues, while those receiving a mean dose of 21.2 Gy did not show any changes. Therefore, the extent of damage to hard dental tissues depends on the dose of radiation received by the salivary gland as well as the salivary flow rate. In addition, the lack of control of the salivary pH difficults the process of remineralization of hard dental tissue, resulting in an increased risk of caries [13].

Direct Effects of Radiation on Dental Tissue

The rapid progression of RRC indicates that changes in the degree of mineralization of dental tissues may influence the developmental process of the disease [2].

Recently, studies have shown that irradiation changes the prismatic structure of the enamel, leading to microcracks in the minerals of hydroxyapatite and decreasing the hardness and elasticity of enamel and dentin, as well as altering the enamel demineralization pattern. In addition, degeneration of the odontoblastic process and obliteration of dentinal tubules occurs as a consequence of direct irradiation due to vascularization and metabolism, which severely weakens the dentin [4]. Also, it was observed the reduction of hardness of the cervical enamel and alterations in the enamel prisms, which became shorter and rounded, but no significant difference in the levels of Ca and Pwas observed in teeth irradiated with doses of 20 Gy, 40 Gy and 70 Gy [12].

In studies conduct with irradiated teeth (60 Gy) posterior submitted to the nanoscrati test, it was observed that the higher the load used in the test, the greater the deformation in the irradiated enamel, the enamel delamination, the formation of debris and radial cracks in the tracing. X-Ray diffraction spectrum analysis indicated that irradiation decreased crystallinity and increased crystal size of the enamel. The irradiation also resulted in an increase in the carbonate/mineral ratio, altering the chemical composition of the enamel, and statistically reducing the superficial microhardness of this tissue. In addition, the dentine showed increased deformations-groove depth, debris accumulation, dentin delamination, cracking and cleavage in high loads. The irradiated dentin resulted in a higher coefficient of friction than the non-irradiated dentin. X-Ray Diffraction spectrum analysis indicated that irradiation decreased crystallinity and increased the size of dentin crystals. In addition, the spectroscopy test showed changes in the chemical composition of the dentin. As a result, the researchers found that dentin showed similar behavior to irradiation when compared to irradiated dental enamel, with decreased crystallinity, decreased mineral content (chemical composition) and decreased surface microhardnes [11].

In another study, teeth were submitted to radiation doses of 50 Gy to 70 Gy to analysis under polarized light microscopy.The cervical surface of the irradiated enamel presented shades ranging from black to grayish, demonstrating a qualitative reduction of birefringence of the enamel of this region. In MEV, the cervical surface of enamel showed the prisms with altered morphology, once the interprismatic spaces were increased after the radiation when compared to the control group [14].

Regarding the dental pulp, one study analyzed 23 extracted teeth from patients who received doses of 50 Gy to 70 Gy of radiation. It was observed in 20 teeth clinical and radiographic changes characteristic of RRC. The histological analysis revelead similarities in the morphology of dental pulp between irradiated e non-irradiated teeth. Were observed a central region with presence of blood vessels, fibroblasts and nerve bundles, an external region with greater density of fibroblasts and an area characterized by low cellularity (Weil zone) in the subodontoblastic region. The results of the immunohistochemical analysis indicated the preservation of the activities of the microvasculature, the neural components and the components of the extracellular matrix of the dental pulp of the irradiated teeth. This findings indicate that radiotherapy was not able to cause detectable micromorphological changes in pulp tissues of irradiated teeth [15].

Influence of Radiotherapy on Restorations of Irradiated Teeth

In order to reduce the damage of radiation in healthy tissues of

Figure 1: A case of RRC showing the classical signs: cervical carie with brown/blackish discoloration of the enamel.

patients with HNC, dental surgeons should prioritize the care of the mouth before radiotherapy [16].

Studies about the influence of radiation on restorative materials have been carried out with the objective of assisting the elaboration of recommendations for adequate dental management of RRC [17].

One study analyzed the effect of 60 Gy of radiation on the microtraction of the composite resin. Scanning electron and scanning electron microscopy showed that defects in the adhesiveness of the restoration were present in control group (non-irradiated teeth) and on group of teeth restored before irradiation, however, greater adhesion defects in enamel and dentin were verified with statistical difference when the restoration protocol was performed after irradiation. In conclusion, radiotherapy has a negative influence on enamel and dentin union strength when the restorative protocol is performed after radiotherapy [18].

Another research verified the adhesion of two adhesive systems in enamel and dentin of non-irradiated (control group) and irradiated teeth with 20, 40 and 70 Gy. After the micro-shear test, it was concluded that when compared to the control group, the enamel had no significant difference in the bond strength of any of the adhesive types used, regardless of the radiation dose. For the dentin, the Universal Single Bond adhesive (Group 2) had greater bond strength when compared to Adper Single Bond 2 (Group 1) adhesive, but did not have a statistically significant result, regardless the radiation dose. The authors concluded that irradiation does not influence the adhesion of restorative material to enamel and dentin, despite the radiation dose [19].

One study compared the clinical behavior of the following restorative materials: conventional glass ionomer cement (KetacFil-3M/ESPE) KF, resin modified glass ionomer cement PF (PhotacFil-3M/ESPE) and HX composite resin (Herculite XRV) with adhesive (Optibond FL). Restorations were performed on cervical caries lesions in irradiated patients. After 24 months of follow-up, was observed significant differences between the different types of materials for marginal adaptation and long-term structural integrity of the restorations when using composite resin and resin-modified glass ionomer compared to the conventional glass ionomer. Significant differences were also found when restoration failure was assessed due to marginal caries in restored teeth, with conventional glass ionomer cement showing better protection than the other materials. In addition, patients who used the fluoride gel showed better protection against secondary caries. It was concluded that the conventional glass ionomer cement is associated with protection against secondary caries, however, the composite resin and the modified glass ionomer has a greater marginal adaptation [20].

Discussion

On the last few years, HNRT has undergone major advances in order to increase therapeutic efficacy and preserve healthy oral tissues surrounding the tumor, thereby reducing the side effects of therapy and improving the quality of life of patients undergoing to this treatment [4,7].

RRC is recognized as one of the adverse effects of HNRT. However, the etiology, diagnosis, prevention and treatment remains uncertain [7]. Researchs has shown that radiotherapy directly affects hard dental tissue, with a direct effect on mineralization, microhardness and/or enamel and dentin structure [11,14]. Others studies affirm that the synergistic effect of damage to the salivary glands and to the mineralized tissue are responsible for the occurrence of RRC [21].

The onset mean time of RRC is the first year after radiotherapy, with rapid progression. The diagnosis of RRC is usually late, probably due to the discontinuation of the dental treatment of patients submitted to HNRT, which negatively impacts the prognosis of these lesions [7].

Until now, there isn't an adequate index to assess and determine RRC. Although the ICADS method can be used to classify such lesions, its original proposal is the qualitative assessment of conventional caries, considering the amount of dentine involvement, focusing on the width and depth of the cavity and the amount of dentine exposure as a parameter for advanced lesions, therefore it may have a limit use and interpretation in the context of RRC. The PRDI is, up to date, the only developed method of assessment of caries, in irradiated tooth. The assessment considers only the amount of dental structure loss as a parameter of severity, which is not compatible with RRC progression patterns, making this clinical applicability limited [7]. Then, it's evidente the necessity of the development of methods of assessment and diagnosis to guide the dental clinician on the management of RRC.

The main purpose of this study was to perform an up-date on RRC, discussing the different structural changes that occur in dental tissues after HNRT, correlating with the different radiation doses.

Based on the literature studied, important changes in enamel and dentin structure were verified. In addition, it was found that the extent of damage to dental tissue is dose-dependent to salivary gland irradiation [21]. Negative changes in the behavior of restorative materials after irradiation were also verified [18-20].

Dental caries is a chronic and multifactorial infectious disease. The cariogenic microorganisms present in the dental biofilm produce acids, such as lactic, formic, acetic and propionic acids, which are products of the metabolism of dietary substrates. These acids decrease the pH of the region (pH<5.0), causing a dental demineralization, therefore, loss of structure. Usually, the factors related to dental caries are the presence of acidogenic microorganisms, a diet rich in carbohydrates and poor hygiene conditions of the oral cavity [22]. The most affected regions are the surfaces where the accumulation of bacterial plaque is facilitated and with difficult hygiene.However, in cases of RRC, the irradiation is a determining factor for the appearance of the lesion. When the dose of dental radiation is less than 30 Gy (salivary gland threshold), damage to the mineralized structures of the tooth is minimal. In contrast, when the mean irradiation dose is between 30 Gy and 60 Gy the damage to dental tissue increases fromtwo to three times, the critical threshold being at doses greater than 60 Gy [9,11,12,14].

After receiving total doses of 70 Gy, the enamel prisms look shorter and rounded [11,12,14]. Consequently, the tissue shows changes in the microhardness and alteration of the composition with mineral reduction, which, together, contribute to the rapid progression and aggressiveness of RRC [2,11,12,14].

The presence of chemical changes in irradiated enamel are still controversial. Some studies indicates that there is no difference in the process of mineralization of the irradiated enamel compared to the non-irradiated enamel, even when 70 Gy of radiation is administered [12]. On the other hand, some studies suggest a decrease of the enamel mineral, altering the carbonate/mineral ratio and consequently, the chemical composition of the enamel [11].

In this review, only one study that evaluated the changes in dentin due to irradiation was found. This research indicated that the changes observed in dentin are similar to those observed in enamel, and a dose of 60 Gy was sufficient to generate tissue demineralization with alteration of chemical composition and morphology, decrease of microhardness and surface resistance [11]. We suggested the performance of a new search to this end, with a larger period of publications beyond that used in this study, in order to find more substantial results.

It was not the objective of this study to verify the alterations of HNRT on dental pulp. Nevertheless, a study found revealed that doses of radiation between 50 Gy and 70Gy are not able to cause alterations in the architecture (histopathology) of this tissue [15]. Again, we suggest the performance of a new search to this end, in order to find more concrete results.

It is unanimous among the authors that the most comitted region of the teeth by RRC is cervical surface. Among the causes, it is mentioned the increase in the interprismatic spaces of enamel, morphological alterations in the prismatic structure and reduction of microhardness [12,14].

Conventional caries usually affects surfaces of pits,fissures and proximal region of the teeth, areas where there is greater accumulation of bacterial plaque. In this sense, adequate and regular oral hygiene can modulate the appearance of new lesions more effectively when compared to RRC [22].

Was also an objective of this study to describe the influence of qualitative and quantitative changes in saliva after HNRT in the development of RRC. It was found that the first changes in the amount of saliva are already present at the end of the first week HNRT. Decline in salivary flow remains until total doses for treatment of the neoplasm are reached [12,23]. In addition, it was verified that the decrease of the salivary flow leads to the decrease of the pH and the buffer capacity of the saliva, wich contribute to the aggressive character and rapid progression of RRC [21,23]. Besides, colonization by Streptococcus mutans in the oral cavity tends to increase when salivary glands are present on irradiation field. However, when the contralateral salivary gland is spared from radiation, changes in the quantity and quality of saliva can be minimized [23].

Regarding the RRC management, an important finding of this research revealed that radiation has a negative influence on the restorative procedure, especially when it is performed after radiotherapy. Adhesive defects were found in restorations executedbefore and after RT, but the change was significantly greater when the restorative procedure was performed after radiotherapy [18]. Differing results were found by Da Cunha, who revealed that, in teeth restored after radiotherapy, regardeless the dose of radiation, the bonding strength between the restoration adhesive and the enamel or dentin was not influenced [19].

When used as a restorative material, conventional glass ionomer cement demonstrated better marginal sealing to secondary caries when compared to composite resin and resin modified glass ionomer. However, the structural integrity of glass ionomer cements, both conventional and resin-modified, is compromised by a dehydrated buccal environment common in patients receiving radiation to treat HNC. In this regard, the composite resin presents better marginal adaptation and long-term integrity, especially when the material is used previously to radiotherapy. As an alternative, it is suggested to maintain a glass ionomer cement base covered by composite resin in search of a lower disintegration of the material and improvement of the marginal adaptation [20].

The dental management of patients with HNC should include pre/trans and post-radiotherapy treatment stages. Radiotherapy sequelae can be minimized when assessment and management of oral needs are performed prior to antineoplastic therapy [16].

In conclusion, the results show an amount of damages of the hard dental tissues, ennamel and dentin, as a result of direct effects of radiation. This findings corroborate with the idea of agressive and atypical patterns of dental caries in irradiated teeth with a combination of indirect effects of radiation as hyposalivation. Add information about restoratively treatment suggests that dental materials as resin composites are the best treatment option before irradiation therapy. Further studies of dental alterations may provide a better understanding of the pathogenesis of relatated radiation-caries with an adequate plan of dental materials.

Author Contributions

All authors equally contributed to this paper with conception and design of the study, literature review, data collection and analysis, drafting, critical revision and editing, and final approval of the final version.

References

1. Fregnani ER, Parahyba CJ, Morais-Faria K, Fonseca FP, Ramos PA, de Moraes FY, et al. IMRT delivers lower radiation doses to dental structures than 3DRT in head and neck cancer patients. Radiat Oncol. 2016;11(1):116.
2. Morais-Faria K, Neves-Silva R, Lopes MA, Ribeiro AC, de Castro G Jr, da Conceição-Vasconcelos KG, et al. The wolf in sheep's clothing: Microtomographic aspects of clinically incipient radiation-related caries. Med Oral Patol Oral Cir Bucal. 2016;21(3):e299-304.
3. Dobroś K, Hajto-Bryk J, Wróblewska M, Zarzecka J. Radiation-induced caries as the late effect of radiation therapy in the head and neck region. Contemp Oncol (Pozn). 2016;20(4):287-90.
4. Lieshout HF, Bots CP. The effect of radiotherapy on dental hard tissue--a systematic review. Clin Oral Investig. 2014;18(1):17-24.
5. Gomes-Silva W, Prado-Ribeiro AC, Brandão TB, Morais-Faria K, de Castro Junior G, Mak MP, et al. Postradiation Matrix Metalloproteinase-20 Expression and Its Impact on Dental Micromorphology and Radiation-Related Caries. Caries Res. 2017;51(3):216-24.
6. Devi S, Singh N. Dental care during and after radiotherapy in head and

neck cancer. Natl J Maxillofac Surg. 2014;5(2):117-25.

7. Palmier NR, Ribeiro ACP, Fonsêca JM, Salvajoli JV, Vargas PA, Lopes MA, et al. Radiation-related caries assessment through the International Caries Detection and Assessment System and the Post-Radiation Dental Index. Oral Surg Oral Med Oral Pathol Oral Radiol. 2017;124(6):542-7.
8. Pitts NB, Ekstrand KR; ICDAS Foundation. International Caries Detection and Assessment System (ICDAS) and its International Caries Classification and Management System (ICCMS)-methods for staging of the caries process and enabling dentists to manage caries. Community Dent Oral Epidemiol. 2013;41(1):e41-52.
9. Walker MP, Wichman B, Cheng AL, Coster J, Williams KB. Impact of Radiotherapy Dose on Dentition Breakdown in Head and Neck Cancer Patients. Pract Radiat Oncol. 2011;1(3):142-8.
10. Galvão-Moreira LV, da Cruz MC. Dental demineralization, radiation caries and oral microbiota in patients with head and neck cancer. Oral Oncol. 2015;51(12):e89-90.
11. Qing P, Huang S, Gao S, Qian L, Yu H. Effect of gamma irradiation on the wear behaviour of human tooth enamel. Sci Rep. 2015;5:11568.
12. De Barros Da Cunha SR, Ramos PA, Nesrallah AC, Parahyba CJ, Fregnani ER, Aranha AC. The Effects of Ionizing Radiation on the Oral Cavity. J Contemp Dent Pract. 2015;16(8):679-87.
13. Gupta N, Pal M, Rawat S, Grewal MS, Garg H, Chauhan D, et al. Radiation-induced dental caries, prevention and treatment - A systematic review. Natl J Maxillofac Surg. 2015;6(2):160-6.
14. Madrid CC, de Pauli Paglioni M, Line SR, Vasconcelos KG, Brandão TB, Lopes MA, et al. Structural Analysis of Enamel in Teeth from Head-and-Neck Cancer Patients Who Underwent Radiotherapy. Caries Res. 2017;51(2):119-28.
15. Faria KM, Brandão TB, Ribeiro AC, Vasconcellos AF, de Carvalho IT, de Arruda FF, et al. Micromorphology of the dental pulp is highly preserved in cancer patients who underwent head and neck radiotherapy. J Endod. 2014;40(10):1553-9.
16. Villa A, Akintoye SO. Dental Management of Patients Who Have Undergone Oral Cancer Therapy. Dent Clin North Am. 2018;62(1):131-42.
17. Madrid Troconis CC, Santos-Silva AR, Brandão TB, Lopes MA, de Goes MF. Impact of head and neck radiotherapy on the mechanical behavior of composite resins and adhesive systems: A systematic review. Dent Mater. 2017;33(11):1229-43.
18. Naves LZ, Novais VR, Armstrong SR, Correr-Sobrinho L, Soares CJ. Effect of gamma radiation on bonding to human enamel and dentin. Support Care Cancer. 2012;20(11):2873-8.
19. da Cunha SR, Ramos PA, Haddad CM, da Silva JL, Fregnani ER, Aranha AC. Effects of Different Radiation Doses on the Bond Strengths of Two Different Adhesive Systems to Enamel and Dentin. J Adhes Dent. 2016;18(2):151-6.
20. De Moor RJ, Stassen IG, van 't Veldt Y, Torbeyns D, Hommez GM. Two-year clinical performance of glass ionomer and resin composite restorations in xerostomic head- and neck-irradiated cancer patients. Clin Oral Investig. 2011;15(1):31-8.
21. Hey J, Seidel J, Schweyen R, Paelecke-Habermann Y, Vordermark D, Gernhardt C, et al. The influence of parotid gland sparing on radiation damages of dental hard tissues. Clin Oral Investig. 2013;17(6):1619-25.
22. Struzycka I. The oral microbiome in dental caries. Pol J Microbiol. 2014;63(2):127-35.
23. Beer KT, Zehnder D, Lussi A, Greiner RH. 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. 2002;178(12):722-6.