Oral and Craniofacial Diseases & Disorders

Chapter 2

Oral Complications Following Radiation Therapy for Head and Neck Malignancy

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Abstract

Each year, head and neck cancer comprises more than 550,000 cases and contributes to 380,000 deaths, worldwide. Radiation Therapy (RT) is used for head and neck cancers as definitive, adjuvant, or palliative treatment. The most important advantage of RT, compared with surgery, is function preservation; however, normal tissue complications occur during (acute complications) or after (subacute and chronic complications) RT in some cases. Late adverse effects of RT cause serious oral complications, such as xerostomia and hyposalivation, trismus, dental caries, and osteonecrosis, resulting in decreased quality of life. The aim of this chapter is to review the aetiology and pathogenesis of oral complications (with particular focus on dental demineralization and osteoradionecrosis) through previous literature and our clinical experience. This chapter also discusses prevention and treatment of those oral complications.

Keywords: head and neck cancer; radiation therapy; oral complication; osteoradionecrosis of the jaw; radiation-induced dental caries; dental management.

1. Introduction

1.1. Epidemiology of head and neck cancers

Head and Neck Cancer (HNC) is a heterogeneous disease originating from different anatomic sites of the upper aero digestive tract (oral cavity, larynx, hypopharynx, oropharynx, nasopharynx, paranasal sinuses, and nasal cavity). Each year, it comprises more than 550,000 cases and contributes to 380,000 deaths, worldwide [1]. Most cases (approximately 90%) are squamous cell carcinoma (SCC) [2]. Risk factors for HNC include tobacco smoking, alcohol consumption, viral infection (Human papilloma virus [HPV], Epstein Barr virus, and Human Immunodeficiency virus), occupational exposure, prior radiation, and dietary factors [3].

1.2. Radiation therapy in the treatment of head and neck cancers

Radiation therapy (RT) is a primary method of HNC treatment that is potentially curative. RT is offered in approximately 75% of cases of HNC as definitive, adjuvant, or palliative treatment. For early tumours (T1–2, N0), RT can be used as a single treatment modality and alternative to surgical resection. For loco regionally advanced HNC (T3–4, N+), RT can be used with or without chemotherapy as definitive or adjuvant treatment after surgical resection. Moreover, RT is the only potentially curative option for surgically inoperable tumours, such as nasopharyngeal cancers, or for patients who are medically inoperable [4].

The most important advantage of RT, relative to surgery, is function preservation; thus, it is preferred by many HNC patients [5]. However, normal tissue complications that occur during (acute complications) or after (subacute and chronic complications) make this treatment method challenging [6], as it may be difficult to achieve maximum tumour control with minimal normal tissue complication (therapeutic ratio).

The most commonly used RT technique in HNC treatment is external beam radiation therapy, including photon, electron and proton beam therapy; rarely brachytherapy is performed with interstitial implants or intracavitary applicators.

The advent of modern technologies over recent decades in both imaging and radiation treatment modalities has dramatically improved the outcome of radiation therapy treatment.

1.3 Organ-sparing radiation therapy for head and neck malignancy

In the past, radiation oncologists used two-dimensional radiation therapy, involving one beam from one to four directions, to irradiate the tumour. Recently, a variety of techniques have emerged: computed tomographic simulation, magnetic resonance imaging simulation, functional imaging (e.g., positron emission tomography), and image fusion techniques which allow the radiation oncologist to obtain a three-dimensional (3D) image of the patient's

tumour and anatomy, and 3D conformal radiation therapy (3D-CRT) with corresponding target definitions (GTV: gross target volume, CTV: clinical target volume, PTV: planning target volume). These techniques allow radiation oncologists to precisely contour the targets and avoid surrounding normal tissues, thus increasing the therapeutic ratio. For improved conformity of dose distribution, forward-planning 3D-CRT led to inverse-planning intensity-modulated radiation therapy (IMRT) with simultaneous integrated boost technique, in which the intensities of individual beamlets forming each beam are manipulated by using more advanced calculation algorithms to determine the optimum dose distribution, which confirms targets and spares nearby normal tissues [7, 8]. 3D-CRT and IMRT induce different dose distributions for the same disease **(Figure 1)**.

More advanced technologies have subsequently emerged, including image-guided radiation therapy, volumetric modulated arc therapy, stereotactic body radiation therapy, tomotherapy, and proton therapy. These techniques enable precise delivery of radiation dose by using on-board imaging, cone beam computed tomography, and tumour tracking systems [9]. The above modern technologies have improved quality of life for HNC patients by reducing the incidence of late effects of radiation [10].

2. Aetiology and Pathogenesis of Oral Complications Following Head and Neck Malignancy

There have been two noteworthy paradigm shifts in HNC treatment strategy [11]. The first involves mortality of adjuvant concurrent Chemoradiotherapy (CRT) in patients with advanced HNC. A literature review published in 2016 reported that postoperative concurrent CRT not only improves locoregional control of advanced HNC, but also improves overall survival, compared with postoperative RT alone [12]. A second major paradigm shift has resulted from the epidemic of HPV-associated HNC [11]. Most cases of head and neck SCC comprise oropharyngeal SCC, which can be stratified according to infection with HPV [13,14]. A meta-analysis of several retrospective case series and a prospective clinical trial showed that HPV-positive oropharyngeal SCC exhibits a better prognosis than HPV-negative SCC [15,16]. A favourable outcome of HPV-positive oropharyngeal SCC may be attributed to an increased sensitivity to RT [17]. Cellular, molecular, and genetic theories have been proposed to explain differential sensitivities to therapeutic radiation between HPV-positive and HPV-negative oropharyngeal SCC [18-21]. Patients with HPV-positive oropharyngeal SCC are younger, thus their comparatively longer survival is more likely to enable late effects of RT to become evident [11]. These late adverse effects of RT result in serious oral complications, such as xerostomia and hyposalivation, trismus, dental caries, and osteonecrosis [11,22,23].

2.1. Radiation induced dental caries

Teeth are composed of enamel, pulp-dentine complex, and cementum [24]. Enamel is

mainly composed of the phosphate-based mineral hydroxyapatite. Dentine forms the largest portion of the tooth, and collagen is the primary component of the dentine [24]. Tooth integrity is maintained through the demineralization-remineralization process, in which calcium, phosphate, and fluoride ions play important roles [24]. Demineralization is the process of removing mineral ions from hydroxyapatite crystals in enamel, dentine, and cementum; remineralization is restoration of these mineral ions to the hydroxyapatite crystals [24].

The first signs of deterioration of dental hard tissues are visible within 3 months after RT for head and neck malignancy [25]. Decay rapidly increases, typically without pain [26]. Brown discoloration of enamel or dentine is sometimes visible, and is mostly situated on the cervical and incisal edges of the occlusal surface [27]. Interestingly, radiation caries begin on the labial surface in the cervical areas of the teeth **(Figure 2)**; subsequently, affected smooth surfaces include mandibular anterior teeth, which are resistant to caries in non-irradiated individuals because they are mechanically cleaned by the continuous flow of saliva from the sublingual caruncle [23].

Although it is controversial whether the incidence of radiation caries is a direct or indirect effect of irradiation on teeth [25], some previous studies have suggested that radiation caries occur primarily as a result of salivary gland damage (loss of saliva), which leads to hyposalivation [25,28,29]. Saliva is the major source for calcium and phosphate in the oral cavity, which serve numerous functions, such as maintenance of the mucous membrane, cleaning, buffering capacity, and antimicrobial action [11]. Reduced salivary flow results in an alteration of oral microflora that favours cariogenic bacteria [11]; additionally, there are no microscopic differences between initial radiation caries lesions and healthy incipient lesions [23]. Kielbassa et al. have published numerous studies regarding radiation-related damage to dentition [23,30,31], where they evaluated the microhardness in each layer of teeth (i.e., enamel or dentine). There were no significant differences in microhardness or transverse micrographic data for *in situ* caries lesions between 60-Gy irradiated and nonirradiated human dental enamel [30]. There was also no significant difference in transverse micrographical data between *in situ* 60-Gy irradiated and nonirradiated human dental enamel [31].

However, identification of saliva-based mechanisms in the development of radiation-induced dental caries remains challenging [32]. Comparison between radiation caries-free patients and those with radiation caries following RT for nasopharyngeal carcinoma showed no significant difference in saliva PH and buffering capacity; however, stimulated saliva flow rate significantly decreased in the radiation caries group [33].

Some studies have reported a direct destructive effect on dental hard tissues, especially at the dentinoenamel junction. Springer et al. [34] reported that irradiation did not measurably affect the extent of collagen destruction of mineralized dental tissue *in vitro*, but radiogenic

destruction of collagen in pulp tissue was observed. Radiogenic destruction of dental pulp collagen as an additional component of direct irradiation-induced damage has synergistic effects with hyposalivation in the development of dental caries [34]. In a histopathological study with a rat model, 12 and 18-Gy irradiation had no significant effect on inflammation, necrosis, and hyalinization in rat dental pulp; vascular congestion was significantly different [35]. Regarding pulp viability of patients assessed by pulse oximetry, oxygenation levels in pulp tissue decreased in a time-dependent manner up to 30 Gy, then remained unchanged up to 70 Gy, and recovered at 4 to 5 months after the initiation of RT [36]. In an immunohistochemical study of the direct effects of radiation on microvasculature, innervation, and extracellular matrix in the dental pulp of patients, no morphologic changes were found in terms of microvascular activity, neural components, or extracellular matrix fibroblasts [37]. However, those studies involved limitations, such as restriction to animal models, short study duration, and small number of samples.

A recent systematic review by Lieshout andBots [27] regarding the effect of RT on dental hard tissue concluded that radiation caries occur due to a combination of both hyposalivation and direct effects on the hard tissue of teeth. They reported differences in outcomes between *in vitro* and *in vivo* irradiated teeth, where *in vitro* irradiation showed fewer negative effects than *in vivo* irradiation [27]. Radiogenic cell damage, with impeded vascularization and metabolism, results in the degeneration of odontoblasts and obliteration of dentine tubules [27]. The weakened microhardness of the supporting dentin causes enamel ablation at the dentinoenamel junction, resulting in microcrack formation in enamel at cervical, incisal, or occlusal areas [27]. Additional and extreme bacterial colonization may increase the risk of radiation caries [27]; however, a recent *in vivo* study showed no statistical difference in microbial diversity in relation to the presence and absence of radiation caries [23]. Some recent *in vitro* studies have revealed direct effects of irradiation on dentition. The nanoscratch test revealed that the main damage to human tooth dentine upon exposure to 60 Gy gamma irradiation is due to delamination and cracks in dentine [38]. The latest scanning electron microscopy analysis reported that irradiation induced dehydration of the dentine and decreased the Ca/P weight ratio, and that surface hardness loss increased in an irradiation dose-dependent manner [39].

Irradiation decreases vascularity and cellularity of the periodontal membrane [23]. A recent radiological study reported that IMRT widened the periodontal ligament space [40]. The pathological significance of a wide periodontal ligament space remains elusive, but inflammatory changes may cause enlargement of the periodontal ligament space through resorption of adjacent bone [40]. Chronic inflammation causes fibrosis, which represents replacement of injured tissue by collagen [40]. Progressive fibrosis within bone is caused by radiation injury to bone vasculature and surrounding tissues [23]. We consider that radiation-induced dental caries are probably not strictly a result of direct damage to dentition and hyposalivation, but

may also be a result of damage to the surrounding tissue. Thus, irradiation-induced damage to the jawbone can cause osteoradionecrosis.

2.2. Osteoradionecrosis

Osteoradionecrosis (ORN) of the jaws is a rare but the most serious complication of RT for head and neck malignancies. ORN of the jaw is defined as exposed bone persisting for >6 months [41]. Patients with ORN suffer from trismus, intractable pain, and chronic drainage, resulting in severely reduced quality of life **(Figure 3)**. When ORN worsens, lesions may cause full-thickness devitalization of bone, resorption of the inferior border of the mandible, an orocutaneous fistula, or a pathological fracture [42]. Although the incidence of ORN of the jaw is progressively declining [43], recent large-scale studies have reported post-IMRT incidences of ORN at 4.3% [44] and 6.2% [45], indicating that ORN is not eradicated.

There have been several reported classifications to facilitate the diagnosis of ORN [46–54]. Jacobson et al. classified ORN into stages I–III and proposed a treatment strategy for each stage: Stage I (early stage), exhibiting minimal soft tissue ulcerationand limited exposure of cortical bone, should be treated conservatively; Stage II (intermediate stage), exhibiting pathologic changes localized to the mandibular cortex and underlying medullary bone, commonly resolves with conservative treatment or minimal surgical intervention; Stage III (advanced stage), showing full-thickness involvement of the bone, including the inferior border (e.g., pathologic fracture may be present), should be treated with surgical intervention (i.e., bone and/or soft tissue replacement) [47].

A histopathological study of bone specimens from segmental mandibulectomy for advanced ORN revealed the heterogeneity of bone viability between cortical and cancellous bone in ORN lesions [55]. Histopathologically necrotic changes that involve the absence of blood vessels within Haversian canals are more prevalent in cortical bone than cancellous bone in mandibular ORN, likely due to reduced periosteal blood supply from previous RT damage [55]. Saka et al. conducted an excellent experimental study in minipigs and humans; they classified the mandible into three anatomical zones as follows: Zone I - mandibular body, beginning inthe symphysis and ending at the connecting linebetween the retromolar area and the mandibular angle; Zone II - the caudal portion of the mandibularramus, located dorsally and cranially to Zone I, extending to the condylar base; and Zone III - the condyle (i.e., the condylar processwith the mandibular head, located cranial to Zone II) [56]. The most common site of ORN is the mandibular body (i.e., Zone I), in which the dominant blood supply to the cortical bones is periosteal, deriving from the mental, submental, and sublingual arteries. Collateral supply is endosteal and periosteal, deriving from the inferior alveolar and mental arteries [56]. Therefore, necrotic changes of cortical bones in mandibular ORN are likely caused by damage to the microcirculation throughout the entire periosteum.

This underlying aetiology (i.e., decreased periosteal blood supply) may relate to treatment outcome for ORN. Minimal surgical debridement alone often results in poor outcome in ORN [57] **(Figure 3)**. The refractoriness of ORN to minimal debridement may be related to necrotic changes in cortical bone. Repeated minimal debridement in ORN risks advancing fragility of the residual bone because necrotic changes are dominant in cortices near the inferior border of the mandible [55]. This aetiology may be why advanced ORN requires surgical management with wide extirpation of disease and simultaneous free flap reconstruction [47,58].

3. Dental Management in Patients Undergoing Radiation Therapy

3.1. Prevention of osteoradionecrosis

Prevention of ORN is an important issue for dental oncologists. Ben-David et al. reported that meticulous prophylactic dental care and dosimetric advantages offered by IMRT, are likely to be key factors in reducing the incidence of ORN [59]. They found that the use of a strict prophylactic dental care policy and IMRT resulted in no cases of clinical ORN. A systematic review by Nabil and Samman reported that the incidence of ORN after dental extraction in irradiated patients was 7%; no ORN occurred in any patients who received a radiation dose of <60 Gy [60]. Another retrospective study of 830 cases reported that the interval between RT and the occurrence of ORN was highly variable (range, 2–122 months), indicating the time-independence of ORN occurrence [61].

Considering the above factors, the following issue is important in prophylactic dental care before RT for head and neck malignancy, as well as in post-therapeutic dental management: should unrestorable teeth be prophylactically removed? Although ORN sometimes occurs spontaneously as a result of odontogenic diseases (e.g., apical or marginal periodontitis and pericoronitis) [60],tooth extraction is considered to be the most common aetiologic cause of ORN. However, prophylactic dental extraction remains controversial because studies have shown that tooth extraction before RT did not reduce the risk of ORN [62]. Some studies reported a low prevalence of ORN associated with tooth extraction after RT (2.14% [63] and 1.7% [64]), and found no apparent benefit of pre-RT extractions to reduce the risk of ORN, indicating that pre-RT extractions may cause ORN [41,45]. Moreover, a large retrospective cohort study reported that tooth extraction after RT was not an independent risk factor for ORN [45]. However, the importance of a complete pre-RT dental evaluation by an experienced practitioner has been noted; it has been also suggested that all unrestorable teeth and teeth with periodontal problems should be extracted to reduce post-RT extractions that contribute to ORN [45,65].

Radiation dose-volume for the jaw plays a significant role in ORN development. Particular consideration should be given to teeth in parts of the jaw expected to receive a radiation dose >50 Gy [59,66]. The range between 50 Gy and 60 Gy showed the most significant

differences between patients with and without ORN, suggesting that minimizing the proportion of mandibular volume exposed to 50 Gy could reduce ORN risk [67].

The relation between primary lesion and ORN site should be considered for the prevention of ORN. A previous study showed that ORN occurred in both the maxilla and mandible after RT of the oral cavity and hypopharynx [66]. Because irradiation fields for oropharyngeal and nasopharyngeal cancers often involve both the maxilla and mandible, severe radiation-induced salivary gland damage frequently occurs in these patients [66]. Particular attention, including prophylactic extraction of unrestorable teeth, may be necessary in case of patients who are scheduled for RT of oral, nasopharyngeal, oropharyngeal, and hypopharyngeal cancer [66].

3.2. Treatment of radiation-induced dental caries

Although restoration should be kept simple for the maintenance of acceptable aesthetics and function [23], treatment of radiation-induced dental caries is often extremely difficult [68]. Adhesive dentistry is not impeded by irradiation [23,69]. According to a previous *in vitro* study, demineralization of the root surface after irradiation may be hampered by application of the dentine adhesive system [70].

However, restoration in cases of radiation caries often fails due to difficult access to cervical carious lesions and incomplete removal of soft dental caries, frequently leading to recurrence of caries and amputation of the crown [68,71]. A study involving polarized light microscopy and scanning microscopy showed that residual and secondary caries in irradiated patients occur due to the difficulty in performing appropriate removal of soft dental caries and providing proper anatomical shape to cavities [71,72]. Siliva et al. concluded that restoration failure seems to be similar to ordinary dental restoration failure, and that direct radiogenic damage to dentition is not essential to early restoration failure in radiation-induced caries [71].

For the prevention of radiation-induced dental caries, fluoride prophylaxis with custom-made carriers and high fluoride concentrations (5000 ppm) is recommended [23]. Chlorhexidine mouthwashes after normal daily tooth brushing are also advocated [68]. Deng et al. indicated the importance of decreasing demineralization or increasing remineralization [11]. Although fluoride use can enhance remineralization [72], the efficacy of fluoride may be limited in HNC patients because of the lack of calcium and phosphate due to hyposalivation and low patient compliance [73]. A previous study reported no significant difference in caries incidence between groups with and without daily fluoride application [73]. Dental trays designed to enhance the contact time of fluoride-containing liquid or gel on the teeth are expensive and uncomfortable, resulting in limited patient adherence [11]. A recent study by Sim et al. aimed to determine the effect of casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) on caries progression in irradiated nasopharyngeal carcinoma patients [74]. CPP-ACP delivers

vesicles to colocalize and stabilize bioavailable calcium, phosphate, and fluoride ions at the tooth surface, and has a synergistic effect with fluoride in promoting remineralization *in situ* [74,75] and in healthy subjects, such as orthodontic patients [76,77]. However, Sim et al. reported that CPP-ACP did not significantly reduce caries progression in irradiated nasopharyngeal carcinoma patients in the first 3 months after RT, compared with controls [74].

4. Conclusions

The current chapter reviewed the literature regarding underlying aetiology, prevention, and treatment of radiation-induced dental caries and osteoradionecrosis, and found discrepancies between *in vitro* and *in vivo* studies. *In vitro* studies showed that irradiation does not directly damage dentition, and that agents for remineralization are effective. In contrast, the occurrence of radiation-induced dental caries is frequently inevitable, and applications to enhance remineralization are limited in clinical practice. As a matter of course, the aetiologies of radiation caries are complex, including hyposalivation, hypovascularity in the periosteum, degeneration of dentine, and reduction of dental pulp viability. Moreover, necrosis of the oral mucosa leading to exposure of the jawbone inevitably occurs following irradiation of carcinoma in certain patients. Clinicians should consider the likelihood of oral complications following RT for head and neck malignancy. Nonetheless, it is necessary to continue investigating effective prevention approaches for those complications.

5. Figures

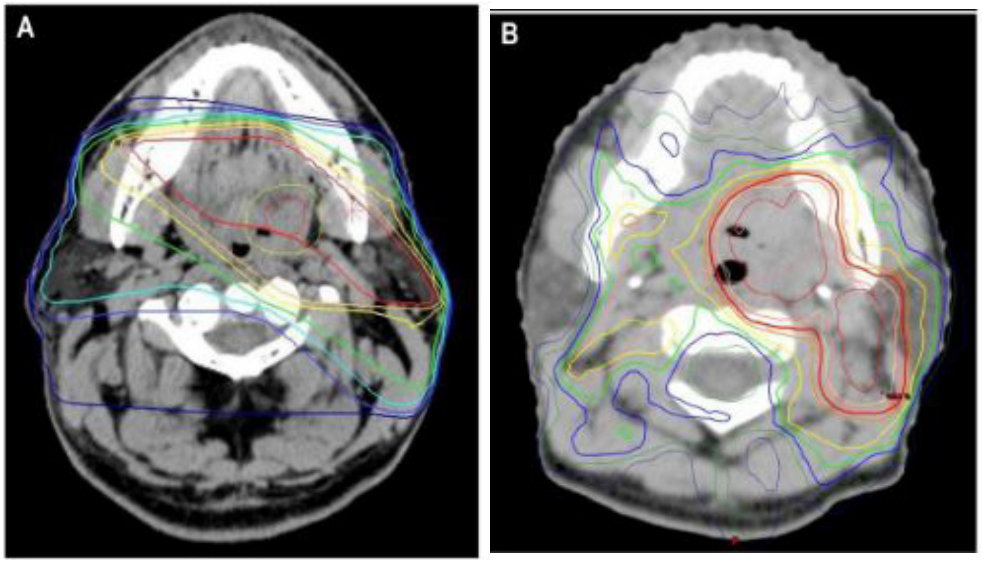

Figure 1: Planning computed tomographic images of three-dimensional conformal radiation therapy **(A)** and intensity-modulated radiation therapy (IMRT) **(B)**. The right parotid gland is spared by IMRT **(B)**.

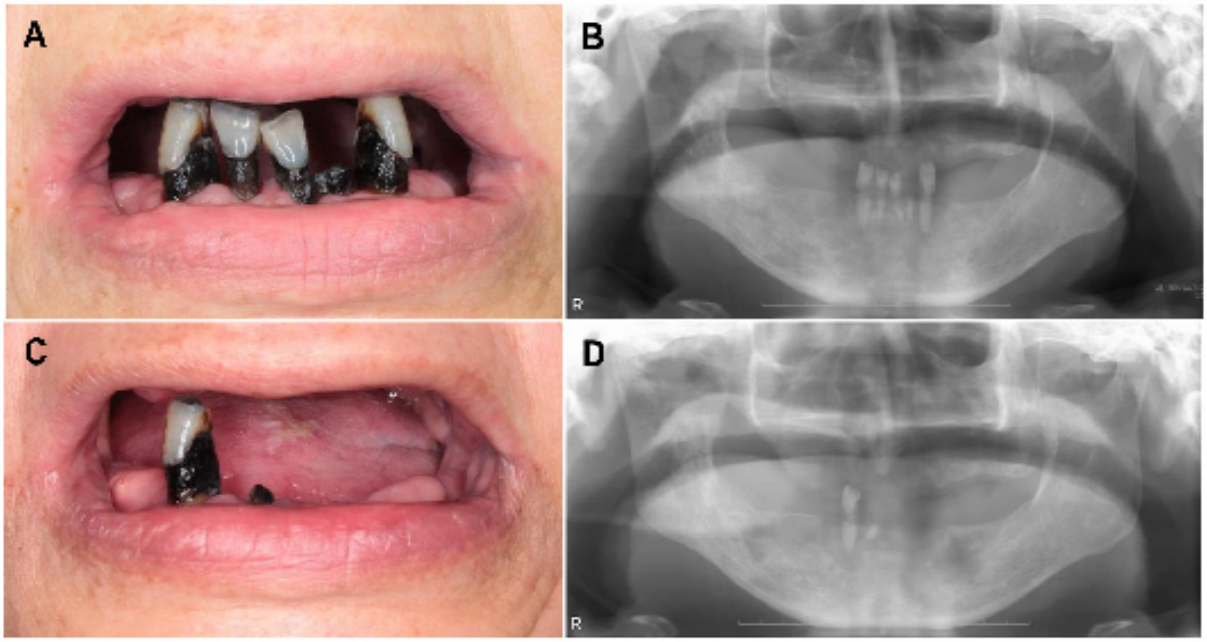

Figure 2: Clinical images of radiation-induced dental caries. This patient received concurrent chemoradiotherapy (CCRT) (70 Gy/35 fractions and cisplatin) for right maxillary carcinoma (squamous cell carcinoma, cT4bN2cM0). Intraoral image **(A)** and panoramic radiography **(B)** at 4 years after completion of CCRT. Radiation caries is evident at cervical areas of mandibular anterior teeth. Intraoral image **(C)** and panoramic radiography **(D)** at 6 years after completion of CCRT. Anterior teeth with radiation caries are lost.

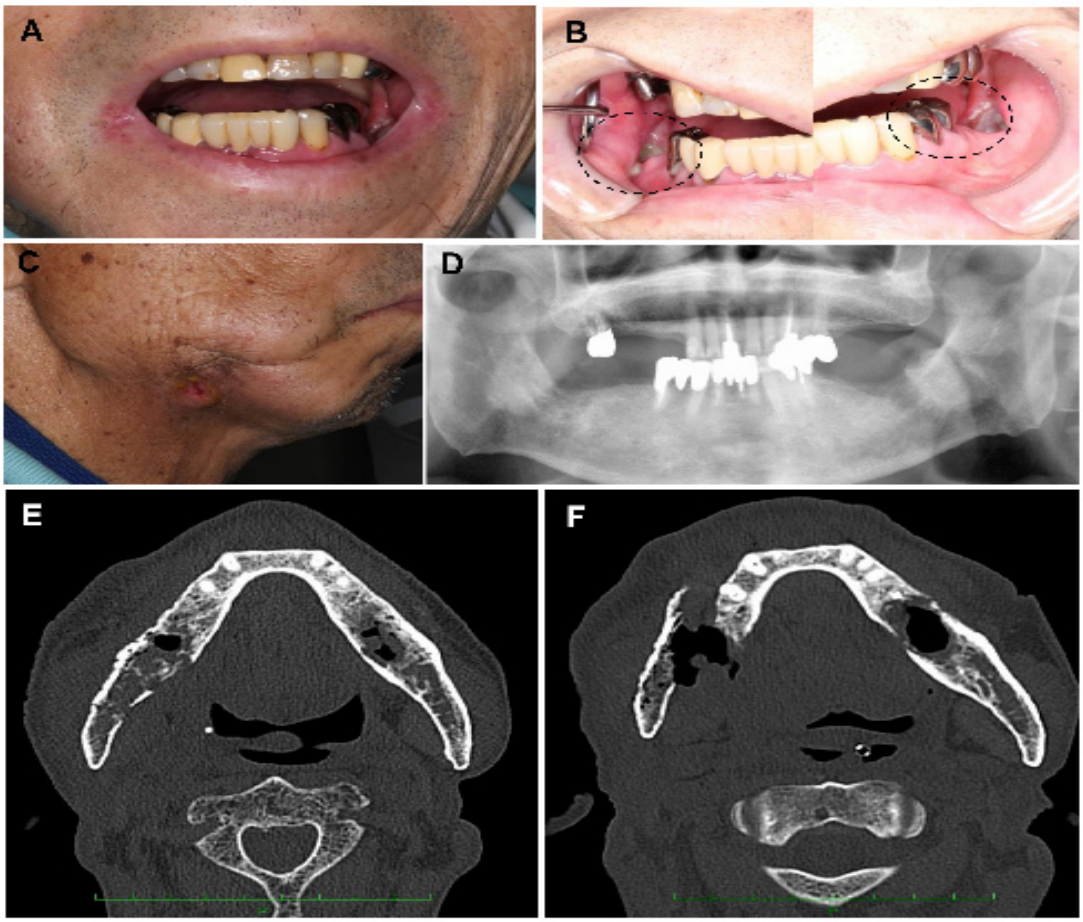

Figure 3: Clinical images of mandibular osteoradionecrosis. This patient received concurrent chemoradiotherapy (CCRT) (70 Gy/35 fractions and cisplatin) for left oropharyngeal carcinoma (squamous cell carcinoma, cT2N0M0). Intraoral **(A, B)**, facial images **(C)**, and panoramic radiography **(D)** at 3 years and 8 months after completion of CCRT. Note the presence of trismus **(A)**, bilateral bone exposure in mandibular molar regions **(B)**, and orocutaneous fistula **(C)**. Osteolysis is more evident in computed tomography **(E)** than in panoramic radiography **(D)**. The patient received repeated minimal debridement for bilateral bone exposure in the previous hospital. At 4 years after completion of CCRT, pathological fracture occurred in the right mandible **(F)**.

5. References

1. Global Burden of Disease Cancer Collaboration, Fitzmaurice C, Allen C, Barber RM, Barregard L, Bhutta ZA, et al. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease Study. JAMA Oncol. 2017; 3:524-8.

2. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA: A Cancer Journal for Clinicians. 2011;61:69-90.

3. Sankaranarayanan R, Masuyer E, Swaminathan R, Ferlay J, Whelan S. Head and neck cancer: a global perspective on epidemiology and prognosis. Anticancer Res. 1998; 18:4779-86.

4. Vokes EE, Kies MS, Haraf DJ, Stenson K, List M, Humerickhouse R, et al. Concomitant chemoradiotherapy as primary therapy for locoregionally advanced head and neck cancer. J Clin Oncol. 2000;18:1652-61.

5. Forastiere AA, Goepfert H, Maor M, Pajak TF, Weber R, Morrison W, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. N Engl J Med. 2003;349:2091-8.

6. Yeh SA.Radiotherapy for head and neck cancer.Semin Plast Surg. 2010;24:127-36.

7. Purdy JA. Advances in the planning and delivery of radiotherapy: new expectations, new standards of care. In: Meyer JL, ed. IMRT, IGRT, SBRT, 2nd ed. Basel: Karger; 2011:1-28.

8. Lauve A, Morris M, Schmidt-Ullrich R, Wu Q, Mohan R, Abayomi O, et al. Simultaneous integrated boost intensity modulated radiotherapy for locally advanced head-and-neck squamous cell carcinomas: II–clinical results. Int J Radiat Oncol Biol Phys. 2004;60:374-87.

9. Parvathaneni U, Laramore GE, Liao JJ. Technical Advances and pitfalls in Head and Neck Radiotherapy. J Oncol. 2012;2012:597467.

10. Chao KS, Majhail N, Huang CJ, Simpson JR, Perez CA, Haughey B, 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;61:275-80.

11. Deng J, Jackson L, Epstein JB, Migliorati CA, Murphy BA. Dental demineralization and caries in patients with head and neck cancer. Oral Oncol. 2015;51:824-31.

12. Lin SS, Massa ST, Varvares MA. Improved overall survival and mortality in head and neck cancer with adjuvant concurrent chemoradiotherapy in national databases. Head Neck. 2016;38:208-15.

13. Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tân PF, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med.2010;363:24-35.

14. Gillison ML, D'Souza G, Westra W, Sugar E, Xiao W, Begum S, et al.Distinct risk factor profiles for human papillomavirus type 16-positive and human papillomavirus type 16-negative head and neck cancers. J Natl Cancer Inst. 2008;100:407-20.

15. Fakhry C, Westra WH, Li S, Cmelak A, Ridge JA, Pinto H, et al. Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. J Natl Cancer Inst. 2008;100:261-9.

16. Ragin CC, Taioli E.Survival of squamous cell carcinoma of the head and neck in relation to human papillomavirus infection: review and meta-analysis. Int J Cancer. 2007;121:1813-20.

17. Lindel K, Beer KT, Laissue J, Greiner RH, Aebersold DM.Human papillomavirus positive squamous cell carcinoma of the oropharynx: a radiosensitive subgroup of head and neck carcinoma. Cancer. 2001;92:805-13.

18. Chen AM, Felix C, Wang PC, Hsu S, Basehart V, Garst J, et al. Reduced-dose radiotherapy for human papillomavirus-associated squamous-cell carcinoma of the oropharynx: a single-arm, phase 2 study. Lancet Oncol. 2017;18:803-811.

19. Seiwert TY, Zuo Z, Keck MK, Khattri A, Pedamallu CS, Stricker T, et al.Integrativeandcomparative genomic analysis of HPV-positiveandHPV-negativehead and necksquamous cell carcinomas. Clin Cancer Res. 2015;21:632-41.

20. Spanos WC, Nowicki P, Lee DW, Hoover A, Hostager B, Gupta A, et al.Immune response during therapy with cisplatin or radiation for human papillomavirus-related head and neck cancer. Arch Otolaryngol Head Neck Surg.2009;135:1137-46.

21. Wansom D, Light E, Worden F, Prince M, Urba S, Chepeha DB, et al. Correlation of cellular immunity with human papillomavirus 16 status and outcome in patients with advanced oropharyngeal cancer. Arch Otolaryngol Head Neck Surg. 2010;136:1267-73.

22. Lieshout HF, Bots CP. The effect of radiotherapy on dental hard tissue--a systematic review. Clin Oral Investig. 2014;18:17-24.

23. Kielbassa AM, Hinkelbein W, Hellwig E, Meyer-Lückel H. Radiation-relateddamage to dentition.Lancet Oncol. 2006;7:326-35.

24. Abou Neel EA, Aljabo A, Strange A, Ibrahim S, Coathup M, Young AM, et al. Demineralization-remineralizationdynamics in teeth and bone.Int J Nanomedicine. 2016;11:4743-63.

25. Vissink A, Jansma J, Spijkervet FK, Burlage FR, Coppes RP. Oralsequelae of head and neck radiotherapy.Crit Rev Oral Biol Med. 2003;14:199-212.

26. Walker MP, Wichman B, Cheng AL, Coster J, Williams KB.Impact of RadiotherapyDose on DentitionBreakdown in Head and NeckCancerPatients.Pract Radiat Oncol. 2011;1:142-8.

27. Lieshout HF, Bots CP.The effect of radiotherapy on dentalhard tissue--a systematicreview.Clin Oral Investig. 2014;18:17-24.

28. al-Nawas B, Grötz KA, Rose E, Duschner H, Kann P, Wagner W.Using ultrasoundtransmissionvelocity to analyse the mechanicalproperties of teethafter in vitro, in situ, and in vivoirradiation.Clin Oral Investig. 2000;4:168-72.

29. Kielbassa AM, Shohadai SP, Schulte-Mönting J. Effect of saliva substitutes on mineralcontent of demineralized and sounddental enamel.Support Care Cancer. 2001;9:40-7.

30. Kielbassa AM. In situ induced demineralization in irradiated and non-irradiated human dentin.Eur J Oral Sci. 2000;108:214-21.

31. Kielbassa AM, Wrbas KT, Schulte-Mönting J, Hellwig E.Correlation of transversal microradiography and microhardness on in situ-induced demineralization in irradiated and nonirradiated human dental enamel. Arch Oral Biol. 1999;44:243-51.

32. Galvão-Moreira LV, da Cruz MC.Dentaldemineralization, radiation caries and oral microbiota in patients with head and neck cancer.Oral Oncol. 2015;51:e89-90.

33. Zhang J, Liu H, Liang X, Zhang M, Wang R, Peng G, et al. Investigation of salivaryfunction and oralmicrobiota of radiationcaries-freepeople with nasopharyngealcarcinoma.PLoS One. 2015;10:e0123137.

34. Springer IN, Niehoff P, Warnke PH, Böcek G, Kovács G, Suhr M, et al.Radiation caries--radiogenic destruction of dental collagen.Oral Oncol. 2005;41:723-8.

35. Madani ZS, Azarakhsh S, Shakib PA, Karimi M.Histopathologicalchanges in dentalpulp of ratsfollowingradiotherapy. Dent Res J (Isfahan). 2017;14:19-24.

36. Kataoka SH, Setzer FC, Gondim-Junior E, Pessoa OF, Gavini G, Caldeira CL.Pulp vitality in patients with intraoral

and oropharyngeal malignant tumors undergoing radiation therapy assessed by pulse oximetry.J Endod. 2011;37:1197-200.

37. 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;40:1553-9.

38. Qing P, Huang S, Gao S, Qian L, Yu H. Effect of gamma irradiation on the wear behavior of human tooth dentin. Clin Oral Investig. 2016;20:2379-86.

39. Velo MMAC, Farha ALH, da Silva Santos PS, Shiota A, Sansavino SZ, Souza AT, et al.Radiotherapyalters the composition, structural and mechanicalproperties of rootdentin in vitro. Clin Oral Investig. 2018. doi: 10.1007/s00784-018-2373-6.

40. Chan KC, Perschbacher SE, Lam EW, Hope AJ, McNiven A, Atenafu EG, et al. Mandibularchanges on panoramicimagingafterhead and neckradiotherapy.Oral Surg Oral Med Oral Pathol Oral Radiol. 2016;121:666-72.

41. Wahl MJ. Osteoradionecrosis prevention myths. Int J Radiat Oncol Biol Phys. 2006; 64: 661-669.

42. Hiraoka Y, Akashi M, Wanifuchi S, Kusumoto J, Shigeoka M, Hasegawa T, et al. Association between pain severity and clinico-histopathological findings in the mandibular canal and inferior alveolar nerve of patients with advanced mandibular osteoradionecrosis. Oral Surg Oral Med Oral Pathol Oral Radiol. 2018. doi: 10.1016/j.oooo.2018.03.017

43. Maesschalck T, Dulguerov N, Caparrotti F, Scolozzi P, Picardi C, Mach N, et al. Comparison of the incidence of osteoradionecrosis with conventional radiotherapy and intensity-modulated radiotherapy. Head Neck. 2016;38:1695-702.

44. Owosho AA, Tsai CJ, Lee RS, Freymiller H, Kadempour A, Varthis S, et al. The prevalence and risk factors associated with osteoradionecrosis of the jaw in oral and oropharyngeal cancer patients treated with intensity-modulated radiation therapy (IMRT): The MemorialSloanKetteringCancerCenter experience.Oral Oncol. 2017;64:44-51.

45. Chen JA, Wang CC, Wong YK, Wang CP, Jiang RS, Lin JC, et al. Osteoradionecrosis of mandiblebone in patients with oral cancer--associatedfactors and treatment outcomes.Head Neck. 2016;38:762-8.

46. Lyons A, Osher J, Warner E, Kumar R, Brennan PA. Osteoradionecrosis--a review of current concepts in defining the extent of the disease and a new classification proposal.Br J Oral Maxillofac Surg. 2014;52:392–5.

47. Jacobson AS, Buchbinder D, Hu K, Urken ML. Paradigm shifts in the management of osteoradionecrosis of the mandible.Oral Oncol. 2010;46:795–801.

48. He Y, Liu Z, Tian Z, Dai T, Qiu W, Zhang Z. Retrospective analysis of osteoradionecrosis of the mandible: proposing a novel clinical classification and staging system. Int J Oral Maxillofac Surg. 2015;44:1547–57.

49. Notani K, Yamazaki Y, Kitada H, Sakakibara N, Fukuda H, Omori K, et al. Management of mandibular osteoradionecrosis corresponding to the severity of osteoradionecrosis and the method of radiotherapy. Head Neck. 2003;25:181–6.

50. Schwartz HC, Kagan AR. Osteoradionecrosis of the mandible: scientific basis for clinical staging.Am J Clin Oncol. 2002;25:168–71.

51. Støre G, Boysen M. Mandibular osteoradionecrosis: clinical behaviour and diagnostic aspects. Clin Otolaryngol Allied Sci. 2000;25:378–84.

52. Glanzmann C, Grätz KW. Radionecrosis of the mandibula: a retrospective analysis of the incidence and risk factors. Radiother Oncol. 1995;36:94–100.

53. Epstein JB, Wong FL, Stevenson-Moore P. Osteoradionecrosis: clinical experience and a proposal for classification.J Oral Maxillofac Surg. 1987;45:104–10.

54. Marx RE. Osteoradionecrosis: a new concept of its pathophysiology.J Oral Maxillofac Surg. 1983;41:283–8.

55. Akashi M, Hashikawa K, Wanifuchi S, Kusumoto J, Shigeoka M, Furudoi S, et al. Heterogeneity of Necrotic Changes between Cortical and Cancellous Bone in Mandibular Osteoradionecrosis: A Histopathological Analysis of Resection Margin after Segmental Mandibulectomy.Biomed Res Int. 2017;2017:3125842.

56. Saka B, Wree A, Anders L, Gundlach KK. Experimental and comparative study of the blood supply to the mandibular cortex in Göttingen minipigs and in man.J Craniomaxillofac Surg. 2002;30:219-25.

57. D'Souza J, Lowe D, Rogers SN. Changing trends and the role of medical management on the outcome of patients treated for osteoradionecrosis of the mandible: experience from a regional head and neck unit.Br J Oral Maxillofac Surg. 2014;52:356-62.

58. Curi MM, Oliveira dos Santos M, Feher O, Faria JC, Rodrigues ML, Kowalski LP. Management of extensive osteoradionecrosis of the mandible with radical resection and immediate microvascular reconstruction. J Oral Maxillofac Surg. 2007;65:434-8.

59. Ben-David MA, Diamante M, Radawski JD, Vineberg KA, Stroup C, Murdoch-Kinch CA, et al. Lack of osteoradionecrosis of the mandible after intensity-modulated radiotherapy for head and neck cancer: likely contributions of both dental care and improved dose distributions.Int J RadiatOncolBiol Phys. 2007;68:396-402.

60. Nabil S, Samman N. Incidence and prevention of osteoradionecrosis after dental extraction in irradiated patients: a systematic review.Int J Oral Maxillofac Surg. 2011;40: 229-43.

61. Reuther T, Schuster T, Mende U, Kübler A. Osteoradionecrosis of the jaws as a side effect of radiotherapy of head and neck tumour patients--a report of a thirty year retrospective review.Int J Oral Maxillofac Surg. 2003;32:289-95.

62. Chang DT, Sandow PR, Morris CG, Hollander R, Scarborough L, Amdur RJ, et al. Do pre-irradiation dental extractions reduce the risk of osteoradionecrosis of the mandible? Head Neck. 2007;29:528-36.

63. Sulaiman F, Huryn JM, Zlotolow IM. Dental extractions in the irradiated head and neck patient: a retrospective analysis of Memorial Sloan-Kettering Cancer Center protocols, criteria, and end results. J Oral Maxillofac Surg. 2003;61:1123-31.

64. Koga DH, Salvajoli JV, Kowalski LP, Nishimoto IN, Alves FA. Dental extractions related to head and neck radiotherapy: ten-year experience of a single institution. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2008;105:e1-6.

65. Koga DH, Salvajoli JV, Alves FA. Dental extractions and radiotherapy in head and neck oncology: review of the literature. Oral Dis. 2008;14:40-4.

66. Wanifuchi S, Akashi M, Ejima Y, Shinomiya H, Minamikawa T, Furudoi S, et al. Cause and occurrence timing of osteoradionecrosis of the jaw: a retrospective study focusing on prophylactic tooth extraction.Oral Maxillofac Surg. 2016;20:337-42.

67. Tsai CJ, Hofstede TM, Sturgis EM, Garden AS, Lindberg ME, Wei Q, et al. Osteoradionecrosis and radiation dose to the mandible in patients with oropharyngeal cancer.Int J Radiat Oncol Biol Phys. 2013;85:415-20.

68. 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;6:160-6.

69. Gernhardt CR, Kielbassa AM, Hahn P, Schaller HG. Tensile bond strengths of four different dentin adhesives on irradiated and non-irradiated human dentin in vitro. J Oral Rehabil. 2001;28:814-20.

70. Gernhardt CR, Koravu T, Gerlach R, Schaller HG. The influence of dentin adhesives on the demineralization of irradiated and non-irradiated human root dentin.Oper Dent. 2004;29:454-61.

71. Silva AR, Alves FA, Berger SB, Giannini M, Goes MF, et al. Radiation-related caries and early restoration failure

in head and neck cancer patients. A polarized light microscopy and scanning electron microscopy study. Support Care Cancer. 2010;18:83-7.

72. Cochrane NJ, Cai F, Huq NL, Burrow MF, Reynolds EC. New approaches to enhanced remineralization of tooth enamel. J Dent Res. 2010;89:1187-97.

73. Epstein JB, van der Meij EH, Lunn R, Stevenson-Moore P. Effects of compliance with fluoride gel application on caries and caries risk in patients after radiation therapy for head and neck cancer.Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1996;82:268-75.

74. Sim CP, Wee J, Xu Y, Cheung YB, Soong YL, Manton DJ. Anti-caries effect of CPP-ACP in irradiated nasopharyngeal carcinoma patients. Clin Oral Investig. 2015;19:1005-11.

75. Shen P, Manton DJ, Cochrane NJ, Walker GD, Yuan Y, Reynolds C, et al. Effect of addedcalciumphosphate on enamelremineralization by fluoride in a randomizedcontrolled in situtrial. J Dent. 2011;39:518-25.

76. Bailey DL, Adams GG, Tsao CE, Hyslop A, Escobar K, Manton DJ, et al. Regression of post-orthodonticlesions by a remineralizingcream. J Dent Res. 2009;88:1148-53.

77. Morgan MV, Adams GG, Bailey DL, Tsao CE, Fischman SL, Reynolds EC. The anticariogeniceffect of sugar-freegumcontainingCPP-ACPnanocomplexes on approximalcariesdetermined using digitalbitewingradiography.Caries Res. 2008;42:171-84.