Oral Oncology 51 (2015) 824–831

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Review

# Dental demineralization and caries in patients with head and neck cancer

Jie Deng [a,*], Leanne Jackson [b], Joel B. Epstein [c], Cesar A. Migliorati [d], Barbara A. Murphy [b]

[a] School of Nursing, Vanderbilt University, Nashville, TN, United States
[b] Vanderbilt-Ingram Cancer Center, Vanderbilt University, Nashville, TN, United States
[c] Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles Ca and Division of Otolaryngology and Head and Neck Surgery, City of Hope National Medical Center, Duarte, CA, United States
[d] Department of Diagnostic Sciences and Oral Medicine, College of Dentistry, University of Tennessee Health Sciences Center, Memphis, TN, United States

ARTICLE INFO

*Article history:*
Received 16 March 2015
Received in revised form 23 June 2015
Accepted 24 June 2015
Available online 18 July 2015

*Keywords:*
Head and neck cancer
Dental demineralization
Dental caries
Decay
Radiation caries
Radiation therapy
Prevention
Review

SUMMARY

Concurrent chemoradiation (CCR) therapy is a standard treatment for patients with locally advanced head and neck cancer (HNC). It is well documented that CCR causes profound acute and late toxicities. Xerostomia (the symptom of dry mouth) and hyposalivation (decreased salivary flow) are among the most common treatment side effects in this cohort of patients during and following treatment. They are the result of radiation-induced damage to the salivary glands. Patients with chronic hyposalivation are at risk for demineralization and dental cavitation (dental caries), often presenting as a severe form of rapidly developing decay that results in loss of dentition. Usual post-radiation oral care which includes the use of fluoride, may decrease, but does not eliminate dental caries associated with radiation-induced hyposalivation. The authors conducted a narrative literature review regarding dental caries in HNC population based on MEDLINE, PubMed, CLNAHL, Cochrane database, EMBASE, and PsycINFO from 1985 to 2014. Primary search terms included *head and/or neck cancer, dental caries, dental decay, risk factor, physical symptom, physical sequellea, body image, quality of life, measurement, assessment, cost, prevention, and treatment*. The authors also reviewed information from National Institute of Dental and Craniofacial Research (NIDCR), American Dental Association (ADA), and other related healthcare professional association web sites. This literature review focuses on critical issues related to dental caries in patients with HNC: potential mechanisms and contributing factors, clinical assessment, physical sequellea, negative impact on body image and quality of life, potential preventative strategies, and recommendations for practice and research in this area.



## Introduction

Treatment paradigms for head and neck cancer (HNC) have shifted dramatically over the past two decades. Increased use of chemoradiation for patients with locally advanced HNC has improved local disease control and overall survival [1]. Unfortunately, chemoradiation is associated with increased acute and late effects that result in substantial symptom burden and decrements in quality of life (QOL) [2–5]. A second major paradigm shift results from the epidemic of human papillomavirus (HPV)-associated HNCs [6,7]. These tumors are biologically and epidemiologically distinct. Of note, the literature provides evidence of improved survival in patients with HPV-positive HNC [8]. Patients with HPV-associated HNC are younger, thus long-term functional outcomes are of critical importance as these patients are likely to live for protracted periods with the late effects of therapy. The treatment and epidemiologic shifts noted above have resulted in an increased number of HNC survivors. There are more than half a million HNC survivors in the United States [9]. Prevention and treatment of long-term effects of HNC therapy have therefore become a priority issue. Among common but under-addressed long-term effects of radiation therapy are oral complications such as, xerostomia and hyposalivation, dental demineralization and caries, trismus, and osteonecrosis [10] (see Figs. 1 and 2).

## Methods

The authors conducted a narrative literature review regarding dental caries in HNC population based on MEDLINE, PubMed,

* Corresponding author at: Vanderbilt University School of Nursing, 461 21st Ave. South, GH 516, Nashville, TN 37240, United States. Tel.: +1 615 875 7713; fax: +1 615 343 5898.
*E-mail address:* jie.deng@vanderbilt.edu (J. Deng).

http://dx.doi.org/10.1016/j.oraloncology.2015.06.009
1368-8375/

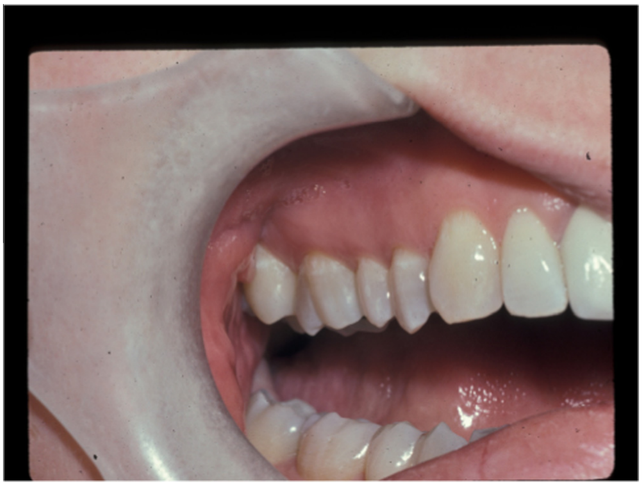

**Fig. 1.** Demineralization with "white lesions" on gum margins.

CLNAHL, Cochrane database, EMBASE, and PsycINFO from 1985 to 2014. Primary search terms included *head and/or neck cancer, dental caries, dental decay, risk factor, physical symptom, physical sequellea, body image, quality of life, measurement, assessment, cost, prevention, and treatment*. The search generated 96 citations that were relevant to the topic and provided the foundation for this review. The authors also reviewed information from National Institute of Dental and Craniofacial Research (NIDCR), American Dental Association (ADA), Healthy People 2020, National Cancer Institute (NCI), American Cancer Society (ACS), and other related healthcare professional association web sites (e.g., Oral Cancer Foundation). This literature review will focus on critical issues related to dental caries in patients with HNC: potential mechanisms and contributing factors, clinical assessment, physical sequelae, negative impact on body image and QOL, potential preventative strategies, and recommendations for practice and research in this area.

## Normal dental physiology

Dental enamel is mainly composed of calcium-phosphate (hydroxyapatite) crystals [11,12]. Other minerals, e.g., fluoride, magnesium, strontium and lead, may be incorporated into the crystalline structure when present at the time of enamel formation. The enamel surface is constantly reforming as a result of two competing processes: demineralization and remineralization [13–16]. If demineralization predominates, mineral loss and damage to hydroxyapatite and matrix breakdown can occur. The mineral loss followed by disintegration of the matrix component leads to cavitation [13]. However, if enamel demineralization is detected sufficiently early, the enamel matrix framework can remineralize with the aggressive use of oral care regimens and dietary modifications [11,17].

**Fig. 2.** Structural loss and staining on cusp tips and gum margins of teeth.

## Saliva: role in dental health

Saliva is secreted by the three major salivary glands and the minor salivary glands found throughout the mucosa of the upper aerodigestive tract. Saliva is a complex fluid which serves numerous functions including: lubrication and maintenance of the mucous membranes (water, electrolytes, mucin, and proline-rich glycoproteins), cleansing (water), buffering capacity and remineralization (bicarbonate, calcium, and phosphate), antimicrobial action (immunoglobulin, defensins, lysozyme, and mucins), digestion (amylase, lipase, and water), taste (water and gustin), and phonation (water and mucin) [18–20]. Several of these functions impact dental health as described below.

### *Buffering*

Between meals and after brushing, oral pH is generally between 6.5 and 7.5. Tooth enamel is prone to demineralization when oral pH drops to 5.5 or below [11]. Most commonly ingested foods result in a dramatic drop of the oral pH into an acidic range which is permissive of demineralization. After a meal, bicarbonate which is contained in saliva acts as a buffer to return the oral pH to a neutral range. Loss of salivary buffering capacity results in increased risk for caries.

### *Enamel substrate*

Remineralization requires two essential substrates: calcium and phosphate [11,12]. Saliva is the primary source for both. Thus, any insult that results in decreased salivary flow may lead to impaired remineralization. Of note, the highest mineral content is present in submandibular saliva.

### *Cariogenic bacteria*

A number of bacteria associated with increased dental caries have been identified. These include streptococcus and lactobacillus species [17,21]. Decreased saliva results in an alteration of oral microflora which favours cariogenic bacteria.

## Xerostomia and hyposalivation

It is important to distinguish the symptom of oral dryness (xerostomia) from hyposalivation (a decrease in measured salivary flow). Measurement of salivary flow does not always correlate well with subjective symptoms. This may be due to changes in salivary composition [22]. Both the symptom (xerostomia) and the functional loss (hyposalivation) can be clinically meaningful. Xerostomia results in patient discomfort and decreased quality of life [23–25]. Hyposalivation may result in functional limitations (e.g., impacting voice, swallowing or sleep) and oral complications (e.g., dental caries) [26–30]. Damage to major and minor salivary glands may results in reduction in the quantity saliva (stimulated or unstimulated) or salivary content.

## Causes of dental caries in head and neck cancer patients undergoing radiation therapy

Although factors such as chemotherapy agents, opioid analgesics, and anti-depressants can contribute to hyposalivation [15], the overwhelming etiology is radiation-induced damage to the salivary glands [31]. The severity and frequency of xerostomia and hyposalivation is related to the radiation dose and volume of radiated salivary tissue [32]. Salivary glands are sensitive to radiation, and even low doses result in a rapid decrease in function [32,33]. In healthy people, the average salivary flow rate is approximately 1.0 ml/min [33]. Within one to two weeks of initiating radiation therapy there is a dramatic decrease in salivary flow rates to well less than 0.5 ml/min [33]. Damage to salivary tissue may be permanent if cumulative doses exceed 30 Gy [32].

Several approaches have been evaluated to prevent radiation hyposalivation. Intensity modulated radiation therapy (IMRT) allows for tumor targeting with relative sparing of normal tissue. Although IMRT can clearly decrease xerostomia, many HNC patients continue to have long-term hyposalivation [34–36]. One study reported that almost 90% HNC patients post IMRT-based therapy experienced some degree of xerostomia with 66% with moderate to severe symptoms [37]. Thus, xerostomia/hyposalivation remains a significant problem despite use of IMRT techniques. Xerostomia/hyposalivation can contribute to dental caries [28–31,37]. Salivary gland transfer, although effective, has not been widely accepted in the era of IMRT [38]. The tissue protectant Ethyol has demonstrated modest efficacy in preventing late xerostomia; however, due to costs, side effects and inconvenience of administration this agent is not widely utilized [39].

Once patients have developed hyposalivation, cholinergic stimulatory agents particularly muscarinic agonists may be used to increase residual salivary function. If stimulation of residual salivary gland function is not possible, the treatment options are limited [16]. Symptom palliation becomes the primary concern and strategies to prevent potential oral and dental complications are required [31,40].

Diet changes contribute to risk of dental caries formation in HNC population. During treatment when weight loss is an issue, HNC patients are often advised to eat frequent small meals with emphasis on high calorie foods. The frequency of meals may make it difficult to brush between feedings. In addition, patients often use liquid supplements containing refined carbohydrates which favor adhesion to dental surface and predispose to caries [21].

HNC patients face challenges in plaque control. Pain from mucositis can inhibit effective oral hygiene which impacts mechanical removal of plaque [21]. Thick and tenacious secretions may pool in the oral cavity inhibiting effective brushing. Busy treatment schedules may result in long delays between oral intake and dental cleaning.

Increased cariogenic oral bacteria (i.e., streptococcus and lactobacillus species) were identified in patients with severe radiation induced dental caries [17,21]. These bacteria produce acid and result in increased risk of dental caries. The microbial shift to cariogenic organisms has been clearly documented in HNC patients during and following radiation therapy [41].

Although the direct effects of radiation on the dentition in human beings are still unknown, studies conducted primarily *in vitro* indicated that radiation therapy may exert direct effects on the dental structure, including changes in microhardness and/or alterations in micro-morphological structures of both enamel and dentin [42–44] as well as chemical composition of enamel and dentin [45]. However, more research is warranted to understand direct radiation effects on dental caries and enamel demineralization.

## Incidence and prevalence of dental caries in head and neck cancer patients

Radiation-associated dental caries may progress rapidly in HNC patients who do not follow an appropriate oral care regimen [17]. Incidence data regarding the dental caries in post-radiation HNC patients are surprisingly poor [46]. In a literature review conducted by the Oral Care Study Group of the Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology (MASCC/ISOO) which included 37 HNC trials, the prevalence of dental caries in HNC patients treated with radiation was 24% (4 studies) and 21% respectively (9 studies) for those treated with chemoradiation [47,48]. Of note, the prevalence of decayed, missing or filled teeth (DMFT), a standard outcome measure of dental health, was 17.01 for HNC patients who had received radiation versus 4.4 for healthy controls. The prevalence of dental disease appears to increase significantly over time as demonstrated by a retrospective study conducted in 314 nasopharyngeal cancer patients. In this study, the prevalence of dental disease escalated from 16% the first year post-radiation to 36%, 55% and 74% at 3, 5 and 7 years post-treatment respectively [49].

## Cost of dental caries treatment

Dental caries remains one of the major health problems affecting human beings in developed and developing countries [50]. Dental caries may lead to local oral pain, dental infection (abscess formation) that can lead to osteonecrosis, and general health complications. In addition, dental caries may result in adverse impact on body image, and negative effect upon QOL and increased health care costs. Although data is unavailable on monetary cost of dental caries treatment in HNC patients, data from general population indicates that treatment of dental caries is costly [51]. The literature reports that dental disease is the fourth most expensive disease to treat in most industrialized countries. Traditional curative dental care is a significant economic burden for many industrialized countries where approximately 10% of public health expenditure relates to oral health [52]. These data have provided insight regarding the importance of prevention and early identification of dental caries. Due to the potential for frequent and rapidly progressive and severe dental caries in HNC patients, better understanding the scope of the problem and negative impact of dental caries, as well as identifying preventive strategies for dental caries, are imperative [52].

## Impact of socioeconomic status (SES) on dental outcomes in HNC patients

Defining SES is challenging due to a lack of consensus regarding critical SES measures [53]. Education, income (person or household), and occupation have been characterized as the dominant, objective indicators of social stratification [53]. Additional indices may be of importance in select settings. In the HNC population, other factors, particularly insurance status, may have a potentially important influence on dental outcomes. In a study conducted at Vanderbilt, 60% of HNC patients did not have dental insurance (data unpublished). For those who do have dental insurance, significant coverage limitations may be present. Before proceeding to radiation-based therapy dental assessment with extraction of non-restorable diseased teeth is mandatory. This would include teeth with (1) advanced periodontal disease, (2) non-restorable and non-viable teeth, and (3) root tips and partly erupted teeth in the high dose field of irradiation. In addition, instituting oral/dental preventive measures is critical. Because pre-treatment dental care is considered medically necessary, sources for care are usually identified. However, long-term dental care to sustain oral health may be sacrificed due to lack of insurance coverage and/or cost. Extrapolating from data in the general population, one would expect to see an inverse relationship between SES (e.g., education, income, and occupation) and prevalence of dental outcomes [54–56]. Research to examine the impact of SES on dental outcomes in HNC patients is critical and warranted.

## Clinical assessment of dental health

Methods used primarily for clinical assessment of dental caries include (1) standardized assessment criteria; and (2) imaging modalities. Several standardized dental assessment criteria are available and widely used to evaluate dental caries through visual–tactile examination, e.g., decayed/missing/filled teeth/surfaces (DMFT/S) [57–60]; the International Caries Detection and Assessment System (ICDAS) core criteria I and II [61–63]; and Nyvad Caries Diagnostic Criteria [64–66]. Imaging modalities include radiographs and digital photography.

### *Standardized assessment criteria*

#### *Decayed, missing or filled teeth/surfaces (DMFT/S) index*

"Dental integrity" is one of the primary outcome measures used for assessment of oral health. It is commonly evaluated using the DMFT/S index. This index may be applied either to each tooth as a whole (DMFT) or to individual surfaces (DMFS). It provides a comprehensive and overarching picture of the severity of the individual's dental caries. *Strengths*: The DMFT/S index allows for comparison across populations, comparison to historical populations, and comparisons of dental status over time. It has therefore been recommended by the World Health Organization to evaluate dentition status since the 1930s (Oral Health Surveys, WHO, 1987) [57] and remains popular in dental caries research. *Limitations*: Limitations to the DMFT/S index include: inability to capture information regarding decay between posterior teeth, lack of information regarding the cause for missing teeth, lack of information regarding the number of teeth at risk, lack of information regarding sealants, and lack of information regarding intra-oral distribution of dental caries [67].

#### *International caries detection and assessment system (ICDAS) core criteria*

The ICDAS core criteria and associated estimates of caries activity are based upon the histological extension of lesions spreading into the tooth tissues. In ICDAS system coronal carious lesions and root caries and lesions accompanied by restorations and sealants have different codes. *Strengths*: The ICDAS-II defines the condition of the tooth, the stages of caries process, and the severity and activity state of the lesion, which are easily detectable by the investigators and clinicians. Thus, there is an increased chance of detecting incipient carious lesions. *Limitations*: The ICDAS-II is a complicated index due to the recording of non-primary caries lesion related conditions, which may lead to an overestimation of seriousness of dental caries experience. The average examination time spent on ICDAS II coding was reported to be twice as long as that for the WHO DMFT/S criteria. This might impact its use for epidemiological purposes [67–71].

#### *Nyvad caries diagnostic criteria*

The Nyvad caries diagnostic system was the first system to clearly define criteria for the activity assessment of both non-cavitated and cavitated lesions. Besides the inclusion of lesions at the noncavitated stage, the assessment of lesion activity is of major importance as this represents demineralization and lesions that may be reversible. *Strengths*: Initial lesions can be diagnosed using Nyvad's caries diagnostic criteria, and interventions can be applied to stop the progression of the lesion, which means that a less invasive treatment can be performed. *Limitation*: It is difficult to make an exact diagnosis of a precavitated active lesion such as a white spot lesion over the occlusal surface. These lesions can be underdiagnosed, progressing to frank cavitation. In addition, due to the physiologic wear of the occlusal surface during mastication, these lesions are not easily identified [70,72,73].

The MASCC/ISOO Oral Study Group recommended the use of clearly defined oral outcomes for future studies. However, each of the above dental assessment systems have strengths and limitations. None of them were sufficiently comprehensive [74]; thus, the MASCC/ISOO did not make specific recommendations regarding tool selection [46]. Based on the identified need, investigators undertook the development and testing of an Oral Health Assessment Form [74]. The tool was designed to standardize the collection and documentation of clinically relevant oral health data specifically for HNC patients with emphasis on monitoring early stages of dental pathology where interventions may be effective [75]. The Oral Health Assessment Form includes: (1) number of remaining teeth; (2) dental status (DMFT/S); (3) visual examination of all teeth surfaces applying the ICDAS-II criteria (codes: 0–6); (4) tactile examination using an explorer to comment on both enamel and dentin surfaces; (5) salivary examination; (6) gingival and periodontal status; (7) trouble with dentures (if applicable); (8) inter-incisal opening (IIO) measurement; (9) oral health findings requiring treatment; and (10) treatment/referral need [74].

### *Imaging modalities*

The clinical visual and tactile examination cannot provide interproximal evaluation of cavities and is limited in assessing the extent of a carious lesion; thus, imaging modalities serve as an important supplement to diligently exercised clinical examinations. Panoramic radiography is a rapid and convenient method to visualize dental status including dental lesions, restorations, and bone lesions such as abscesses or osteonecrosis [76–78]. Bitewing radiographs provide images of the crowns of the top and bottom teeth on a single film and can detect the subtle changes related to dental diseases at sites that are difficult to assess on exam [79,80]. Intraoral digital photography has been frequently reported in the recent literature [81–84]. A recent study has reported excellent inter-rater and intra-rater reliability of intraoral digital photographs in caries detection [83]. Studies have indicated that intraoral digital photography may be an alternative and/or supplementary tool to document dental caries. Imaging studies provide the benefit of archiving, remote scoring, multiple scorings, and enabling longitudinal analysis as well as enabling examiner blinding.

## Physical sequelae

Although there is a paucity of data in the HNC patient population, it is clear from the general dental literature that poor dental health results in substantial adverse health outcomes including: (1) increase in oral infections; (2) dietary adaptations that lead to long-term nutritional deficiencies; (3) pain and/or discomfort; (4) speech alteration; and (5) chronic inflammation with potentially associated systemic symptoms. Of importance, evidence shows that dental caries and other oral complications may be associated with medical conditions such as respiratory disease, cardiovascular disease, and diabetes [85,86]. Given the fact that HPV-associated oropharyngeal cancer is epidemic, the potential impact of dental caries on general health outcomes for HNC survivors is profound [87,88]. This underscores the importance for optimizing preventive dental strategies in HNC survivors.

## Negative impact on body image and quality of life

HNC patients are at high risk for body image disturbances because both cancers and their treatment may result in disfigurement. The face is critical to individual identity, communication and interpersonal relationships. In addition, the face is highly visible and unlike other body parts cannot be inconspicuously hidden from view [89,90]. Impaired body image is associated with depression in HNC patients [90] and may lead to social anxiety and isolation.

Although data is limited, it may be hypothesized that lost, discoloured, cracked or fractured teeth may cause or worsen disturbances in body image in the HNC population. In addition, loss of dentition may lead to decreased oral function. Function loss may also contribute to poor body image. A more thorough understanding of body image disturbance and the relationship with dental outcomes is needed to assist researchers in developing targeted supportive care techniques that can minimize body image disturbance. The impact of dental status on body image may become a more prominent issue as younger patients with HPV-associated cancer experience late oral health complications of treatment. In general, the expectations of younger patients regarding dentition is different from that of older generations [91,92]. Dental caries, dental loss, and the use of dental appliances are less acceptable. Furthermore, there is the general expectation that dentition can be salvaged by contemporary dental techniques. Thus, the loss of dentition may impact body image more strongly in the younger HNC patient population.

Data from the general population have indicated that dental caries and loss are associated with decreased overall QOL as well as oral health-related QOL [93–95]. However, the effect of dental caries on the overall and oral health-related QOL has not been well studied in HNC populations.

## Potential preventative strategies

### *Dental caries prevention in head and neck cancer patients: current practice and gaps*

*Current practice:* National Institute of Dental and Craniofacial Research (NIDCR) recommends oral health maintenance in HNC patients before, during and after chemoradiation. Recommendations include: pre-treatment assessment of dentition with extraction of non-viable teeth, rigorous oral hygiene, diets that minimize risk for dental caries and the use of prescription-strength fluoride to enhance enamel remineralization [96].

*Gaps:* The cornerstone of current preventative dental care is the routine use of prescription-strength fluoride [97], which has been shown to be an effective preventive agent in the HNC population. However, caries remain problematic even for patients who strictly adhere to current guidelines; thus augmentation strategies to further diminish the frequency and severity of dental carries in HNC populations is needed.

### *Microbial management*

Following radiation therapy, colony counts of microorganisms demonstrate a shift in oral microflora with increase in cariogenic bacteria such as Streptococci mutans and Lactobacillus species [98,99]. Thus, management of caries risk should include reduction of colony counts by cariogenic bacteria. Chlorhexidine suspension has been shown to reduce colonization of cariogenic flora in HNC patients. Unfortunately, the effect is not sustained and a rapid recovery in cariogenic bacterial counts is noted. This suggests the need for ongoing therapy to control the oral flora and reducing caries risk.

### *Salivary stimulation*

Stimulation of residual salivary secretion may be possible and should be addressed in patient management. Prior to prescription, assessment of saliva production is recommended [100,101]. Sialagogues are seldom effective in patients with near total salivary dysfunction and cannot increase salivary glands function if glands are completely destroyed, but they can enhance the function when there is residual glandular tissue. Sialogogues available include pilocarpine, cevimeline and bethanechol [102,103].

### *Approaches for enhancing enamel remineralisation and preventing enamel demineralization*

In the general and HNC patient populations with xerostomia, a number of agents have been investigated to determine whether they enhance dental outcomes by either decreasing demineralization or increasing remineralization [104]. Data clearly support the use of fluoride to enhance remineralization, thus, the use of fluoride has become a mainstay of preventive dental care in the HNC population [105]. Fluoride may be administered in a number of ways. Patients may be fitted with dental trays designed to enhance contact time of fluoride containing liquid or gel on the teeth. The trays are worn for a specified period of time, typically recommended for 5 minutes per day. Although these devices result in increased contact with the enamel surface, trays are expensive and uncomfortable, thus compliance may be limited. Alternatives include brush on gel, pastes and rinses with concentrations of fluoride that require a prescription. Finally, fluoride varnish or lacquers may be applied by dental health professionals in addition to daily applications at home.

Unfortunately, the efficacy of fluoride may be limited in the HNC population due to the lack of calcium and phosphate secondary to hyposalivation [104] and patient adherence [105,106]. Remineralization cannot occur if the degree of saturation of calcium and phosphate in saliva related to tooth mineral is low. Exogenous calcium and phosphate may hypothetically improve dental outcomes by allowing remineralization of dental surfaces. A number of studies using calcium-phosphate supplements have reported positive results (e.g., preventing dental caries). A study reported the use of Caphosol (calcium-phosphate solution) in dental health in 126 patients with xerostomia due to Sjögren syndrome, radiation therapy to the head and neck and medication induced symptoms [107]. A significant difference was seen between "compliant" (used Caphosol® at least once a day) and "non-compliant" (used Caphosol® less than once a day) patients, i.e., the surface increments in both root ($p = .04$) and coronal surfaces ($p = .004$), and the number of decayed surfaces in the compliant group actually decreased. Although the cost of this agent prohibits its current use as a long-term preventive agent, the study demonstrates that Caphosol® rinse used at least once per day may prevent caries. In another study,[108] 57 patients between 0 and 15 years post-radiation participated in a randomized controlled trial (RCT) comparing standard of care with fluoride versus standard of care, fluoride and Enamelon® (calcium-phosphate paste). The number of root caries per subject was 0.04 for the intervention arm versus 1.65 for those with standard of care ($p = 0.03$). Although Enamelon® is no longer being produced, the study findings support the conduct of clinical trials using calcium-phosphate systems for the prevention of dental caries in post-radiation HNC patients.

Calcium and phosphate tend to precipitate, thus, delivery systems have been developed to optimize administration [104,109–111]. The remineralizing system with the most extensively researched technology uses casein phosphopeptide from milk to stabilize calcium and phosphate ions forming CPP-ACP complexes – Minimal intervention (MI) paste. MI paste received FDA 510K Clearance to sell and market as a Class I medical device on October 20, 2004 (K042200) [110]. When applied to a dental surface, CPP-ACP interacts with hydrogen ion forming calcium hydrogen phosphate ($CaHPO_4$). Under a diffusion gradient, the $CaHPO_4$ will enter into the porosities of the enamel subsurface of the tooth and release the calcium and phosphate producing enamel mineral. Of note, CPP-ACP is activated in an acidic milieu similar to that experienced by patients with hyposalivation. MI paste is currently used for treating hypersensitivity [112]. A number of studies, including several randomized controlled clinical trials have shown the effectiveness of CPP-ACP in reducing caries progression and causing regression of white spots in orthodontic patients [113,114]. Three quasi-experimental [115–117] and two RCTs [118,119] conducted in different study populations (i.e., six-year-old children, adults with dental occlusal white spot lesions, and orthodontic patients) demonstrated that CPP-ACP with fluoride was superior to fluoride alone in remineralizing carious lesions. Studies in the HNC population are limited. In one recent small RCT conducted in patients with nasopharyngeal carcinoma [120], 24 participants were recruited pre-radiation therapy and randomized into using either CPP-ACP with fluoride or fluoride alone. The study followed patients for only three months post treatment; none-the-less, subjects using CPP-ACP with fluoride showed a trend toward lower caries progression than the controls using fluoride alone. In summary, most of the studies were flawed (e.g., non-RCTs, insufficient sample size, and inadequate follow-up) or were conducted in non-oncologic patient populations; however, data from the literature support the potential and promising results of calcium and phosphate on remineralization of early dental caries in HNC patients with post-radiation therapy.

In recent years, other remineralizing agents containing different calcium-phosphate formulas and fluoride have been reported in the literature, such as functionalized β-tricalcium phosphate (fTCP)-containing toothpaste (Clinpro™ Tooth Crème) and Colgate Sensitive Pro-Relief Toothpaste®. Although the literature has indicated that these agents have increased remineralization potential compared to artificial saliva, the effectiveness of different calcium-phosphate formulas on prevention and long-term management of dental caries in HNC patient populations have not been systematically compared through rigorous designed RCT projects.

## Recommendations for practice and research

Radiation caries is a frequent complication and may generate significant impact on HNC patients' long-term and overall QOL. To enable optimal dental care for HNC patients before, during and after radiation therapy, close interdisciplinary communication and cooperation among radiation oncologists, dentists, medical oncologists, and oral surgeons is absolutely essential. Clinicians should be equipped with knowledge about signs and symptoms of any incipient dental decay so that appropriate clinical assessment and timely treatment referral can be made. Clinicians need to inform and educate HNC patients about (1) potential risk of dental caries after radiation-based therapy; and (2) preventative strategies, e.g., treatment of xerostomia-related complaints, meticulous oral hygiene, diet adaptation, control of cariogenic flora, and use of prescription-strength fluoride. Compliance with preventative strategies must be reinforced by the health care team. Although approaches to management of caries risk are available, dental caries is still a significantly and frequently clinical long-term effect experienced by HNC patients after radiation therapy. All components of the caries process should be addressed in these high-risk patients, this includes: salivation, diet instructions, oral hygiene, microbial flora, and mineralization of tooth structure. Thus, well-designed randomized controlled trials are needed to identify the most effective approaches to prevent and manage dental caries in HNC patients.

## Funding

The work was supported by Vanderbilt Office of Clinical and Translational Scientist Development.

## Conflict of interest statement

None declared.

## References

[1] 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 2014. 2014 Sept 16.
[2] Murphy BA, Gilbert J, Cmelak A, Ridner SH. Symptom control issues and supportive care of patients with head and neck cancers. Clin Adv Hematol Oncol 2007;5(10):807–22.
[3] Murphy BA, Gilbert J, Ridner SH. Systemic and global toxicities of head and neck treatment. Expert Rev Anticanc 2007;7(7):1043–53.
[4] Murphy BA. Clinical and economic consequences of mucositis induced by chemotherapy and/or radiation therapy. J Support Oncol 2007;5(9 Suppl 4):13–21.
[5] Murphy BA, Ridner S, Wells N, Dietrich M. Quality of life research in head and neck cancer: a review of the current state of the science. Crit Rev Oncol Hematol 2007;62(3):251–67.
[6] Chaturvedi AK, Engels EA, Anderson WF, Gillison ML. Incidence trends for human papillomavirus-related and -unrelated oral squamous cell carcinomas in the United States. J Clin Oncol 2008;26(4):612–9.
[7] Cmelak AJ, Li S, Goldwasser MA, Murphy B, Cannon M, Pinto H, et al. Phase II trial of chemoradiation for organ preservation in resectable stage III or IV squamous cell carcinomas of the larynx or oropharynx: results of Eastern Cooperative Oncology Group Study E2399. J Clin Oncol 2007;25(25):3971–7.
[8] The Oral Cancer Foundation. HPV Connection, the human papilloma virus, 2012. <http://oralcancerfoundation.org/hpv/index.htm> [accessed 7.15.12].
[9] Swierzewski SJ. Head and neck cancer overview, 2014. <http://www.healthcommunities.com/head-and-neck-cancer/overview-of-head-and-neck-cancer.shtml> [accessed 1.8.15].
[10] National institute of dental and craniofacial research, national institutes of health. Oral complications of cancer treatment: what the dental team can do, 2009. Access method: <http://www.nidcr.nih.gov/oralhealth/Topics/CancerTreatment/OralComplicationsCancerOral.htm#top> [accessed 11.8.14].
[11] Robinson C, Shore RC, Brookes SJ, Strafford S, Wood SR, Kirkham J. The chemistry of enamel caries. Crit Rev Oral Biol Med 2000;11(4):481–95.
[12] Walsh LJ. Contemporary technologies for remineralisation therapies: a review. International Dentistry SA 2009;11(6):6–16.
[13] Da Silva JD, Mitchell DA, Mitchell L. Oxford American Handbook of Clinical Dentistry (Oxford American Handbooks of Medicine). New York: Oxford University Press; 2007.
[14] Featherstone JD. Dental caries: a dynamic disease process. Aust Dent J 2008 Sep;53(3):286–91.
[15] Epstein JB, Scully C. The role of saliva in oral health and the causes and effects of xerostomia. J Can Dent Assoc 1992;58(3):217–21.
[16] Brosky ME. The role of saliva in oral health: strategies for prevention and management of xerostomia. J Support Oncol 2007;5(5):215–25.
[17] Epstein JB, Thariat J, Bensadoun RJ, Barasch A, Murphy BA, Kolnick L, et al. Oral complications of cancer and cancer therapy: from cancer treatment to survivorship. CA Cancer J Clin 2012;62(6):400–22.
[18] Hand AR. Salivary glands. In: Nanci A, editor. Ten Cate's oral histology: development, structure and function. Montreal: Mosby Elsevier; 2008. p. 290–1.
[19] Mandel ID. The role of saliva in maintaining oral homeostasis. J Am Dent Assoc 1989;119(2):298–304.
[20] Liena-Puy C. The role of saliva in maintaining oral health and as an aid to diagnosis. Med Oral Patol Oral Cir Bucal 2006;11(5):E449–55.
[21] McCaul LK. Oral and dental management for head and neck cancer patients treated by chemotherapy and radiotherapy. Dent Update 2012;39(2):135–8. 40.
[22] Kolnick L, Deng J, Epstein JB, Migliorati CA, Rezk J, Dietrich MS, et al. Associations of oral health items of the Vanderbilt Head and Neck Symptom Survey with a dental health assessment. Oral Oncol 2014;50(2):135–40.

[23] Duncan GG, Epstein JB, Tu D, El Sayed S, Bezjak A, Ottaway J, et al. Quality of life, mucositis, and xerostomia from radiotherapy for head and neck cancers: a report from the NCIC CTG HN2 randomized trial of an antimicrobial lozenge to prevent mucositis. Head Neck 2005;27(5):421–8.
[24] Henson BS, Inglehart MR, Eisbruch A, Ship JA. Preserved salivary output and xerostomia-related quality of life in head and neck cancer patients receiving parotid-sparing radiotherapy. Oral Oncol 2001;37(1):84–93.
[25] Lin A, Kim HM, Terrell JE, Dawson LA, Ship JA, Eisbruch A. Quality of life after parotid-sparing IMRT for head-and-neck cancer: a prospective longitudinal study. Int J Radiat Oncol Biol Phys 2003;57(1):61–70.
[26] Backstrom I, Funegard U, Andersson I, Franzen L, Johansson I. Dietary intake in head and neck irradiated patients with permanent dry mouth symptoms. Eur J Cancer B Oral Oncol 1995;31B(4):253–7.
[27] Rhodus NL, Moller K, Colby S, Bereuter J. Articulatory speech performance in patients with salivary gland dysfunction: a pilot study. Quintessence Int 1995;26(11):805–10.
[28] Logemann JA, Smith CH, Pauloski BR, Rademaker AW, Lazarus CL, Colangelo LA, et al. Effects of xerostomia on perception and performance of swallow function. Head Neck 2001;23(4):317–21.
[29] Hamlet S, Faull J, Klein B, Aref A, Fontanesi J, Stachler R, et al. Mastication and swallowing in patients with postirradiation xerostomia. Int J Radiat Oncol Biol Phys 1997;37(4):789–96.
[30] Flink H. Studies on the prevalence of reduced salivary flow rate in relation to general health and dental caries, and effect of iron supplementation. Swed Dent J Suppl 2007(192):3–50. 2p.
[31] Furness S, Bryan G, McMillan R, Worthington HV. Interventions for the management of dry mouth: non-pharmacological interventions. Cochrane Database Syst Rev 2013. 8CD009603.
[32] Cassolato SF, Turnbull RS. Xerostomia: clinical aspects and treatment. Gerodontology 2003;20(2):64–77.
[33] Franzen L, Funegard U, Ericson T, Henriksson R. Parotid gland function during and following radiotherapy of malignancies in the head and neck. A consecutive study of salivary flow and patient discomfort. Eur J Cancer 1992;28(2–3):457–62.
[34] 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(3): 275–80.
[35] Daly ME, Lieskovsky Y, Pawlicki T, Yau J, Pinto H, Kaplan M, et al. Evaluation of patterns of failure and subjective salivary function in patients treated with intensity modulated radiotherapy for head and neck squamous cell carcinoma. Head Neck 2007;29(3):211–20.
[36] Saarilahti K, Kouri M, Collan J, Kangasmaki A, Atula T, Joensuu H, et al. Sparing of the submandibular glands by intensity modulated radiotherapy in the treatment of head and neck cancer. Radiother Oncol 2006;78(3):270–5.
[37] Cooperstein E, Gilbert J, Epstein JB, Dietrich MS, Bond SM, Ridner SH, et al. Vanderbilt Head and Neck Symptom Survey version 2.0: report of the development and initial testing of a subscale for assessment of oral health. Head Neck 2012;34(6):797–804.
[38] Jha N, Seikaly H, Harris J, Williams D, Liu R, McGaw T, et al. Prevention of radiation induced xerostomia by surgical transfer of submandibular salivary gland into the submental space. Radiother Oncol 2003;66(3):283–9.
[39] Sasse AD, Clark LG, Sasse EC, Clark OA. Amifostine reduces side effects and improves complete response rate during radiotherapy: results of a meta-analysis. Int J Radiat Oncol Biol Phys 2006;64(3):784–91.
[40] Furness S, Worthington HV, Bryan G, Birchenough S, McMillan R. Interventions for the management of dry mouth: topical therapies. Cochrane Database Syst Rev 2011(12):Cd008934.
[41] Hae-Soon L, Kyung-Yi C, Ae-Ok K, Mi-Ran K, Youn-Shin K, Mi-Sun K, et al. Cariogenic activity in saliva of Korean head and neck cancer patients. Int J Oral Biol 2014;39(2):57–63.
[42] de Siqueira Mellara T, Palma-Dibb RG, de Oliveira HF, Garcia Paula-Silva FW, Nelson-Filho P, da Silva RA, et al. The effect of radiation therapy on the mechanical and morphological properties of the enamel and dentin of deciduous teeth – an in vitro study. Radiat Oncol 2014;9:30. Jan 22.
[43] Gonçalves LM, Palma-Dibb RG, Paula-Silva FW, Oliveira HF, Nelson-Filho P, Silva LA, et al. Radiation therapy alters microhardness and microstructure of enamel and dentin of permanent human teeth. J Dent 2014;42(8): 986–92.
[44] Kielbassa AM, Hinkelbein W, Hellwig E, Meyer-Lückel H. Radiation-related damage to dentition. Lancet Oncol 2006;7(4):326–35.
[45] Reed R, Xu C, Liu Y, Gorski JP, Wang Y, Walker MP. Radiotherapy effect on nano-mechanical properties and chemical composition of enamel and dentine. Arch Oral Biol 2015;60(5):690–7.
[46] Brennan MT, Spijkervet FK, Elting LS. Systematic reviews and guidelines for oral complications of cancer therapies: current challenges and future opportunities. Support Care Cancer 2010;18(8):977–8.
[47] Hong CH, Napeñas JJ, Hodgson BD, Stokman MA, Mathers-Stauffer V, Elting LS, et al. A systematic review of dental disease in patients undergoing cancer therapy. Support Care Cancer 2010;18(8):1007–21.
[48] National Cancer Institute, National Institutes of Health. Oral complications of chemotherapy and head/neck radiation (PDQ®). 2014. Access method: http://www.cancer.gov/cancertopics/pdq/supportivecare/oralcomplications/HealthProfessional/page1 [accessed 11.8.14].
[49] Siala W, Mnejja W, Elloumi F, Ghorbel A, Mnif J, Frikha M, et al. Late toxicities after conventional radiotherapy for nasopharyngeal carcinoma: incidence and risk factors. J Radiother 2014;2014(Article ID 268340):8 pages.
[50] Elkassas D, Arafa A. Remineralizing efficacy of different calcium-phosphate and fluoride based delivery vehicles on artificial caries like enamel lesions. J Dent 2014;42(4):466–74.
[51] Thompson B, Cooney P, Lawrence H, Ravaghi V, Quinonez C. Cost as a barrier to accessing dental care: findings from a Canadian population-based study. J Public Health Dent 2014;74(3):210–8.
[52] Kandelman D, Arpin S, Baez RJ, Baehni PC, Petersen PE. Oral health care systems in developing and developed countries. Periodontol 2000;60(1): 98–109.
[53] American Psychological Association, Task Force on Socioeconomic Status. Report of the APA Task Force on socioeconomic status. Washington, DC: American Psychological Association; 2007.
[54] Reisine ST, Psoter W. Socioeconomic status and selected behavioral determinants as risk factors for dental caries. J Dent Educ 2001;65(10): 1009–16.
[55] Tanaka K, Miyake Y, Sasaki S, Hirota Y. Socioeconomic status and risk of dental caries in Japanese preschool children: the Osaka Maternal and child health study. J Public Health Dent 2013;73(3):217–23.
[56] Tickle M, Williams M, Jenner T, Blinkhorn A. The effects of socioeconomic status and dental attendance on dental caries' experience, and treatment patterns in 5-year-old children. Br Dent J 1999;186(3):135–7.
[57] World Health Organization. Oral health surveys: basic methods. Geneva: WHO; 1987.
[58] National institute of dental and craniofacial research, national institutes of health. Dental caries (tooth decay) in adults (age 20 to 64), 2014. Access method: <http://www.nidcr.nih.gov/DataStatistics/FindDataByTopic/DentalCaries/DentalCariesAdults20to64.htm> [accessed 12.15.14].
[59] Michelet M. Caries and periodontal disease in cancer survivors. Evid Based Dent 2012;13(3):70–3.
[60] Schwendicke F, Dorfer CE, Schlattmann P, Page LF, Thomson WM, Paris S. Socioeconomic inequality and caries: a systematic review and meta-analysis. J Dent Res 2015;94(1):10–8. Ebub 2014 Nov 15.
[61] Ismail AI, Sohn W, Tellez M, Amaya A, Sen A, Hasson H, et al. The International Caries Detection and Assessment System (ICDAS): an integrated system for measuring dental caries. Community Dent Oral Epidemiol 2007;35(3):170–8.
[62] Iranzo-Cortes JE, Montiel-Company JM, Almerich-Silla JM. Caries diagnosis: agreement between WHO and ICDAS II criteria in epidemiological surveys. Community Dent Health 2013;30(2):108–11.
[63] Clara J, Bourgeois D, Muller-Bolla M. DMF from WHO basic methods to ICDAS II advanced methods: a systematic review of literature. Odontostomatol Trop 2012;35(139):5–11.
[64] Nyvad B, Machiulskiene V, Baelum V. Reliability of a new caries diagnostic system differentiating between active and inactive caries lesions. Caries Res 1999;33(4):252–60.
[65] Nyvad B, Machiulskiene V, Baelum V. Construct and predictive validity of clinical caries diagnostic criteria assessing lesion activity. J Dent Res 2003;82(2):117–22.
[66] Shankar S, Naveen N, Kruthika M, Vinay S, Shaikh H. Comparison of def index with Nyvad's new caries diagnostic criteria among three to six years old children in a school at Bangalore city. Indian J Dent Res 2012;23(2):135–9.
[67] Mehta A. Comprehensive review of caries assessment systems developed over the last decade. RSBO 2012;9(3):316–21.
[68] Banava S, Fattah M, Mj Kharrazifard, Safaie T, Askarzadeh S, Safaie Yazdi M, et al. Clinical comparison of dental caries by DMFT and ICDAS systems. JIDA 2012;24(2):176–83.
[69] 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.
[70] Braga MM, Mendes FM, Ekstrand KR. Detection activity assessment and diagnosis of dental caries lesions. Dent Clin North Am 2010;54(3):479–93.
[71] Chng T. GLUT2 and TAS1R2 genotype and risk of dental caries. Toronto, Ontario Canada: University of Toronto; 2012.
[72] de Amorim RG, Figueiredo MJ, Leal SC, Mulder J, Frencken JE. Caries experience in a child population in a deprived area of Brazil, using ICDAS II. Clin Oral Investig 2012;16(2):513–20.
[73] Gonzalez MC, Ruiz JA, Fajardo MC, Gomez AD, Moreno CS, Ochoa MJ, et al. Comparison of the def index with Nyvad's caries diagnostic criteria in 3- and 4-year-old Colombian children. Pediatr Dent 2003;25(2):132–6.
[74] Jackson LK, Epstein JB, Migliorati CA, Rezk J, Shintaku WH, Noujeim ME, et al. Development of tools for the oral health and panoramic radiograph evaluation of head and neck cancer patients: a methodologic study. Spec Care Dentist 2015;7:1–8.
[75] Ekstrand KR, Martignon S, Ricketts DJ, Qvist V. Detection and activity assessment of primary coronal caries lesions: a methodologic study. Oper Dent 2007;32(3):225–35.
[76] Farman AG, Panoramic Corporation. Panoramic radiology: seminars on maxillofacial imaging and interpretation. Berlin; New York: Springer; 2007.
[77] Moll MA, Seuthe M, von See C, Zapf A, Hornecker E, Mausberg RF, et al. Comparison of clinical and dental panoramic findings: a practice-based crossover study. BMC Oral Health 2013;13:48.

[78] Choi JW. Assessment of panoramic radiography as a national oral examination tool: review of the literature. Imaging Sci Dent 2011;41(1):1–6.
[79] Tantradi P, Sreenivasan V, Kadaganche H. Role of bitewing in enhancing the assessment of DMFS index in a group of Indian adolescents. Indian J Dent Res 2010;21(2):266–9.
[80] Kamburoglu K, Kolsuz E, Murat S, Yuksel S, Ozen T. Proximal caries detection accuracy using intraoral bitewing radiography, extraoral bitewing radiography and panoramic radiography. Dentomaxillofac Radiol 2012;41(6):450–9.
[81] Manjunath S, Ragavendra RT, Setty SK, Jayalakshmi K. Photography in clinical dentistry-a review. Int J Dent Clin 2011;3(2):40–3.
[82] Kopycka-Kedzierawski DT, Billings RJ. Comparative effectiveness study to assess two examination modalities used to detect dental caries in preschool urban children. Telemed J E Health 2013;19(11):834–40.
[83] Boye U, Pretty IA, Tickle M, Walsh T. Comparison of caries detection methods using varying numbers of intra-oral digital photographs with visual examination for epidemiology in children. BMC Oral Health 2013;13:6.
[84] Sharland M. Improving your image... then and now. Digital photography in dentistry. Dent Update 2013;40(4):333–4. 6.
[85] Institute of Medicine. Advancing oral health in America. Washington, DC: National Academy of Sciences; 2011.
[86] Healthy People 2020, Office of Disease Prevention and Health Promotion, U.S. Department of Health and Human Services. Oral Health: overview, 2009. Access method: <http://www.healthypeople.gov/2020/topics-objectives/topic/oral-health> [accessed 11.2.14].
[87] Udeabor SE, Rana M, Wegener G, Gellrich NC, Eckardt AM. Squamous cell carcinoma of the oral cavity and the oropharynx in patients less than 40 years of age: a 20-year analysis. Head Neck Oncol 2012;4:28.
[88] Benson E, Li R, Eisele D, Fakhry C. The clinical impact of HPV tumor status upon head and neck squamous cell carcinomas. Oral Oncol 2014;50(6):565–74.
[89] Bronheim H, Strain JJ, Biller HF. Psychiatric aspects of head and neck surgery. Part II: Body image and psychiatric intervention. Gen Hosp Psychiatry 1991;13(4):225–32.
[90] Rhoten BA, Deng J, Dietrich MS, Murphy B, Ridner SH. Body image and depressive symptoms in patients with head and neck cancer: an important relationship. Support Care Cancer 2014;22(11):3053–60.
[91] Cunha-Cruz J, Hujoel PP, Nadanovsky P. Secular trends in socio-economic disparities in edentulism: USA, 1972–2001. J Dent Res 2007;86(2):131–6.
[92] Marinelli RD, Sreebny LM, Kamen S. Perception of dental needs by the well elderly. Spec Care Dentist 1982;2(4):161–4.
[93] Slade GD. Derivation and validation of a short-form oral health impact profile. Community Dent Oral Epidemiol 1997;25(4):284–90.
[94] Lawrence HP, Thomson WM, Broadbent JM, Poulton R. Oral health-related quality of life in a birth cohort of 32-year olds. Community Dent Oral Epidemiol 2008;36(4):305–16.
[95] Stenman U, Ahlqwist M, Bjorkelund C, Hakeberg M. Oral health-related quality of life–associations with oral health and conditions in Swedish 70-year-old individuals. Gerodontology 2012;29(2):e440–6.
[96] National institute of dental and craniofacial research, national institutes of health. Oral complications of cancer treatment: what the oncology team can do, 2009. Access method: <http://www.nidcr.nih.gov/oralhealth/topics/cancertreatment/oralcomplicationscanceroncology.htm> [accessed 11.2.14]
[97] Weyant RJ, Tracy SL, Anselmo TT, Beltran-Aguilar ED, Donly KJ, Frese WA, et al. Topical fluoride for caries prevention: executive summary of the updated clinical recommendations and supporting systematic review. J Am Dent Assoc 2013;144(11):1279–91.
[98] Epstein JB, McBride BC, Stevenson-Moore P, Merilees H, Spinelli J. The efficacy of chlorhexidine gel in reduction of Streptococcus mutans and Lactobacillus species in patients treated with radiation therapy. Oral Surg Oral Med Oral Pathol 1991;71(2):172–8.
[99] Epstein JB, Loh R, Stevenson-Moore P, McBride BC, Spinelli J. Chlorhexidine rinse in prevention of dental caries in patients following radiation therapy. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1989;68(4):401–5.
[100] Gorsky M, Epstein JB, Parry J, Epstein MS, Le ND, Silverman Jr S. The efficacy of pilocarpine and bethanechol upon saliva production in cancer patients with hyposalivation following radiation therapy. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2004;97(2):190–5.
[101] Chainani-Wu N, Gorsky M, Mayer P, Bostrom A, Epstein JB, Silverman Jr S. Assessment of the use of sialogogues in the clinical management of patients with xerostomia. Spec Care Dentist 2006;26(4):164–70.
[102] Han P, Suarez-Durall P, Mulligan R. Dry mouth: a critical topic for older adult patients. J Prosthodont Res 2015;59(1):6–19. Epub 2014 Dec 9.
[103] Saleh J, Figueiredo MA, Cherubini K, Salum FG. Salivary hypofunction: an update on aetiology, diagnosis and therapeutics. Arch Oral Biol 2015;60(2):242–55. Epub 2014 Nov 4.
[104] Cochrane NJ, Cai F, Huq NL, Burrow MF, Reynolds EC. New approaches to enhanced remineralization of tooth enamel. J Dent Res 2010;89(11):1187–97.
[105] 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(3):268–75.
[106] Epstein JB, van der Meij EH, Emerton SM, Le ND, Stevenson-Moore P. Compliance with fluoride gel use in irradiated patients. Spec Care Dentist 1995;15(6):218–22.
[107] Singh ML, Papas AS. Long-term clinical observation of dental caries in salivary hypofunction patients using a supersaturated calcium-phosphate remineralizing rinse. J Clin Dent 2009;20(3):87–92.
[108] Papas A, Russell D, Singh M, Kent R, Triol C, Winston A. Caries clinical trial of a remineralising toothpaste in radiation patients. Gerodontology 2008;25(2):76–88.
[109] Reynolds EC. Remineralization of enamel subsurface lesions by casein phosphopeptide-stabilized calcium phosphate solutions. J Dent Res 1997;76(9):1587–95.
[110] Tung MS, Eichmiller FC. Amorphous calcium phosphates for tooth mineralization. Compend Contin Educ Dent 2004;25(9 Suppl 1):9–13.
[111] Charig A, Winston A, Flickinger M. Enamel mineralization by calcium-containing-bicarbonate toothpastes: assessment by various techniques. Compend Contin Educ Dent 2004;25(9 Suppl 1):14–24.
[112] GC America Inc. About MI Paste™ & MI Paste Plus™, 2014. Access method: <http://www.mi-paste.com/about.php> [accessed 12.12.14].
[113] Morgan MV, Adams GG, Bailey DL, Tsao CE, Fischman SL, Reynolds EC. The anticariogenic effect of sugar-free gum containing CPP-ACP nanocomplexes on approximal caries determined using digital bitewing radiography. Caries Res 2008;42(3):171–84.
[114] Bailey DL, Adams GG, Tsao CE, Hyslop A, Escobar K, Manton DJ, et al. Regression of post-orthodontic lesions by a remineralizing cream. J Dent Res 2009;88(12):1148–53.
[115] Juárez-López ML, Hernández-Palacios RD, Hernández-Guerrero JC, Jiménez-Farfán D, Molina-Frechero N. Preventive and remineralization effect over incipient lesions of caries decay by phosphopeptic phosphate of calcium amorfous. Rev Invest Clin 2014;66(2):144–51.
[116] Krithikadatta J, Fredrick C, Abarajithan M, Kandaswamy D. Remineralisation of occlusal white spot lesion with a combination of 10% CPP-ACP and 0.2% sodium fluoride evaluated using Diagnodent: a pilot study. Oral Health Prev Dent 2013;11(2):191–6.
[117] Wang JX, Yan Y, Wang XJ. Clinical evaluation of remineralization potential of casein phosphopeptide amorphous calcium phosphate nanocomplexes for enamel decalcification in orthodontics. Chin Med J (Engl) 2012;125(22):4018–21.
[118] Robertson MA, Kau CH, English JD, Lee RP, Powers J, Nguyen JT. MI Paste Plus to prevent demineralization in orthodontic patients: a prospective randomized controlled trial. Am J Orthod Dentofacial Orthop 2011;140(5):660–8.
[119] Vashisht R, Indira R, Ramachandran S, Kumar A, Srinivasan MR. Role of casein phosphopeptide amorphous calcium phosphate in remineralization of white spot lesions and inhibition of Streptococcus mutans? J Conserv Dent 2013;16(4):342–6.
[120] 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 2014 [Epub 2014 Sep 27].