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

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.

© 2015 Elsevier Ltd. All rights reserved.

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,
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 sequella, 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].

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 irradiated 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 Ethylol 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 (DMF) or to individual surfaces (DFMS). 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 dental 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 and stage 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 caries 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. Sialagogues 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 = 0.04) and coronal surfaces (p = 0.004), 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 (CaHPO4). Under a diffusion gradient, the CaHPO4 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 hyposalinization. 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**


