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Oral Complications in Cancer Patients: A Review of Practical Interventions in the Dental Setting

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Oral Complications in Cancer Patients: A Review of Practical Interventions in the Dental Setting

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In the United States, approximately 40% of the population will develop cancer during their lifetime. For the year 2020, an estimated 1,806,590 new U.S. cancer cases will be diagnosed, including an estimated 53,260 oral and oropharyngeal malignancies.[1]

In 2014, a survey by the American Dental Association revealed that 32.3% of the general population does not visit their dentist at least annually.[2] Beyond the financial, social, and physical barriers to routine dental visits, dentists often encounter patients with cancer who present not only with routine dental and periodontal needs, but with the complications of their malignancy and/or its treatments. In addition, it is well-recognized that dental practitioners play a critical role in optimizing treatment-planning and management of cancer patients.

Despite this, most U.S. dental school curricula do not include these topics or provide the basic principles of dental care in the cancer patient population. With rapid advances in newer targeted therapies, surgery, radiation therapy, and chemotherapy, it is challenging for dental professionals to be knowledgeable and comfortable in managing their patients with cancer. Overall, these patients may present with a variety of recognized adverse effects including oral mucositis, infections, salivary gland hypofunction, dental caries, taste disturbances, trismus, and osteonecrosis (medication and/or radiation-related). A common concern among dentists is providing appropriate, cost-effective, evidence-based treatment that is also feasible in the general dental practice setting.

This review will address the most common side effects related to cancer and cancer therapy as well the evidence-based management options. Due to space limitations, the topics of medication- or radiation-induced osteonecrosis (MRONJ, ONJ) and trismus will not be covered.

Table 1 — WHO Oral Toxicity Scale

WHO Grade	Clinical Findings and Symptoms
Grade 1	Mucosal erythema and soreness
Grade 2	Mucosal erythema, ulcerations Patient cannot swallow solid foods
Grade 3	Mucosal erythema, ulcerations Patient cannot swallow food
Grade 4	Extensive mucositis making alimentation impossible

Oral mucositis

Mucositis is defined as erythema with or without ulceration of the oral mucosa. This condition can be painful and hinder the ability to eat. The World Health Organization (WHO) has developed the Oral Toxicity Scale to grade the severity of oral mucositis.[3] This tool is commonly used in research to standardize categorization of the intensity of this condition and to formulate appropriate recommendations. Oral mucositis (OM) affects almost all patients undergoing head and neck radiation therapy, 75-100% of patients receiving high-dose chemotherapy as conditioning for hematopoietic stem cell transplantation (HSCT), and 20-40% of people being administered conventional chemotherapy.[4,5]

OM is initiated by direct cell damage, although the pathogenesis of this complication is highly complex. As the lining epithelial cells of the oral mucosa turn over rapidly (7-14 days), they are especially sensitive to cytotoxic cancer therapies.[6] Not surprisingly, OM can develop as soon as one week after treatment is initiated.[6] While the risk and/or severity of mucositis is difficult to predict in a given patient, influencing factors include drug type, duration, and dose for chemotherapy; type, mucosal field volume, fractionation, and total dose for radiation therapy; and use of concurrent radiation and chemotherapy.[6] In

addition, the severity of OM can require modulation of doses and ultimately may affect prognosis.[5]

Once cancer therapy has ceased, the healing phase occurs over the subsequent 2-4 weeks, and patient management is predominantly palliative in nature. A 2% viscous lidocaine solution or sucking on ice chips can provide temporary relief. In severe cases, the Multinational Association for Supportive Care in Cancer (MASCC/ISOO) guidelines support the use of 0.2% morphine or 0.5% doxepin (tricyclic antidepressant) mouth rinses for pain relief.[7] Nonetheless, these preparations have side effects, which include stinging or burning (doxepin) as well as significant drowsiness. In addition, traditional opioids are frequently less

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Table 2 — Treatment options for oral complications suggested based on current scientific evidence, the authors' experience, as well as management protocols for cancer patients at the James Cancer Hospital Solove Research Institute, Columbus, Ohio.

Drug	Form and Amount	Dosage
Treatment of Oral Candidiasis		
Clotrimazole (Mycelex)	10 mg troche x 50	Dissolve 1 troche slowly in the mouth 5x/day for 10 days without dentures or removable prostheses
Fluconazole	100 mg tablet x 15	Take 1 tablet p.o. Q12H on 1st day, then 1 tablet daily for the next 13 days
Nystatin	*For treatment of oral appliances:*	
	100,000 U/mL oral suspension	Clean and immerse denture or oral appliance in nystatin suspension every night for 10 nights
Mild Bleach Solution	*For treatment of complete acrylic (no metal) dentures:*	
	Household bleach (1 part bleach: 10 parts water)	Clean and immerse denture in diluted bleach solution every night for 10 nights
Pharmaceutical Salivary Stimulants		
Pilocarpine HCL (Salagen)	5 mg tablet x 90	Take 1-2 tablets p.o. Q6-8H Maximum adult daily dose: 30 mg
Cevimeline HCL (Evoxac)	30 mg tablet x 90	Take 1 tablet p.o. Q8H Maximum adult daily dose: 90 mg
HSV and VZV Prophylaxis		
Valacyclovir (Valtrex)	500 mg tablet	Take 1 tablet p.o. BID
Treatment of Oral HSV and VZV Infections		
Valacyclovir (Valtrex)	1000 mg tablets x 20	Take up to 1000 mg p.o. BID (TID for VZV) x 10 days
Treatment of Mild-Moderate Oral Mucositis		
2% Viscous lidocaine oral solution	15, 20 and 100 mL bottles	Rinse with 1 tbsp for 2 minutes and expectorate Q4-6H as needed
Treatment of Severe Oral Mucositis		
Morphine 0.2% oral solution	Not commercially available. Must be compounded at pharmacy.	Rinse with 1 tbsp for 2 minutes and expectorate Q3-6H as needed

Table 3 — Products for caries prevention/arrest and hyposalivation.

	Products for Dry Mouth (OTC and Rx)
Salivea (OTC)	Toothpaste, mouthrinse and mouth sprays Contains salivary enzymes Original Biotene formulation
Biotene (OTC)	Toothpaste, mouthrinse, mouth sprays, gel, lozenges Contains xylitol
Xylimelts (OTC)	Dissolvable oral-adhering discs Contains xylitol
Xerostom (OTC)	Toothpaste, mouthrinse, gel Contains olive oil, betaine and xylitol
Oramoist (OTC)	"Dry mouth relief patch" Contains xylitol
Therabreath (OTC)	Gums, lozenges, mouthrinse. Contains xylitol
Caphosol (Rx)	Artificial saliva
NeutraSal (Rx)	Artificial saliva
SalivaMax (Rx)	Artificial saliva
	Products for Caries Prevention
Colgate PreviDent 5000 Plus (Rx)	1.1% Sodium fluoride toothpaste or gel
3M Clinpro 5000 (Rx)	1.1% Sodium fluoride toothpaste
Duraflor Halo (Rx)	5% Sodium Fluoride Varnish (In-office application)
Advantage Arrest (Rx)	Silver diamine fluoride 38% (In office application) Substantial staining side effect

Non-prescription (Over-the-counter, OTC) products for dry mouth are not supported by current evidence-based scientific literature. The authors do not endorse a particular brand or product listed above.

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effective at controlling mucositis-related pain. Transdermal fentanyl administered through a patch has been suggested by other authors.[6,7] Although "magic mouthwashes" are popular among some practitioners, their formulations are highly variable and there is insufficient evidence to recommend their general use for OM. Similarly, chlorhexidine mouthwashes and other antimicrobial topical solutions may be used to improve oral hygiene in dentate patients, but are not recommended for the sole purpose of preventing OM.[8]

While the true impact on OM is unclear, dental providers should educate patients on basic oral care, as most studies indicate a variety of associated beneficial effects.[8] Basic oral care practices include teeth brushing, daily flossing, and use of one or more mouth rinses (e.g., salt water or 1% sodium bicarbonate, chlorhexidine gluconate 0.12%) to maintain good oral hygiene.[8] Despite the absence of specific guidelines for their use, mouthwashes may help reduce oral discomfort and increase the clearance of oral debris.[8] Cryotherapy is supported by current evidence to prevent OM whereas systemic zinc supplements are no longer endorsed.[6,9] Maintaining ice in the oral cavity (30 minutes) has been recommended in patients receiving bolus doses of 5-fluorouracil (5-FU) and high doses of melphalan for HSCT.[10]

Oral infections

In normal, healthy individuals, the oral microbiobial flora represents a dynamic balance of hundreds of different microorganisms, predominated by bacteria but also containing fungal, viral and protozoal forms.[11] The balanced microbiome is associated with a normal-appearing, asymptomatic mucosa, but even subtle

changes can alter the oral flora sufficiently to cause disease. The substantial and wide-ranging impacts of malignancy and cancer therapy on the oral environment, ranging from mucosal ulceration to salivary hypofunction to immunosuppression, increase the risk for oral infections among all cancer patients. Such increased susceptibility underlies the general recommendation that all sites of active oral infectious disease, including periapical and periodontal disease or secondarily-infected impacted teeth, be treated or removed prior to the initiation of cancer therapy. This section will focus primarily on the infectious complications of candidiasis and herpesvirus infections, particularly herpes simplex virus I and II (HSV/HHV I, II) and varicella zoster (VZV/HHV III).

While several candidal species are associated with oral disease, *Candida albicans* is the most common.[12] This fungus can be found in up to 40-50% of normal, healthy individuals without evidence of disease, and the percentage increases with increasing age. Several patterns of candidiasis are recognized, including acute pseudomembranous (thrush) and erythematous. The latter form is also known as "antibiotic sore mouth" since it often affects patients with upper respiratory infections who are treated by broad-spectrum antibiotics. The subsequent loss of susceptible oral bacteria is thought to permit fungal overgrowth, leading the organisms to consume the keratinized filiform papillae of the tongue. As a result, the dorsal tongue becomes atrophic and erythematous, and patients often describe increasing sensitivity or pain. Acute pseudomembranous candidiasis may be asymptomatic, but patients may complain of a foul, salty, or bitter taste. Oral candidiasis can usually be diagnosed on the basis of clinical features alone; however, oral cytology or tissue biopsy may be needed with some patients.

Among head and neck cancer patients, candidiasis may arise in those receiving chemotherapy alone, but those treated with loco-regional radiation or combined chemoradiotherapy are at particular risk, with rates ranging from 25-67%, likely due to radiation-associated salivary gland injury and xerostomia.[12,13] In another study, oral candidal infection was seen in 37% of patients receiving combined chemoradiation therapy at a mean of 29 days into treatment, and patients with oral candiasis were at significantly greater risk for developing dysphagia.[14] In these settings as well as in strongly immunosuppressed patients, prophylactic use of fluconazole has shown consistent effectiveness in preventing and treating oral candidiasis.[12] In refractory cases, itraconazole has been useful as a second-line agent followed by lipid formulations of amphotericin B. Although topical agents such as clotrimazole or nystatin may be helpful in mild cases of oral candidiasis, they have tended to be less effective in cancer patients compared to systemic agents and their use may not be completely free of untoward drug interactions, particularly in cancer patients using immunosuppressive therapy.[15]

Viral infections, including latent herpesvirus infections, can be difficult to diagnose as well as manage in the setting of immunosuppression. This includes patients with cancer as well as those being treated for cancer with traditional or newer targeted therapies. In the head and neck, this most often involves herpes simplex virus I or II (HSV, HHV I/II) or varicella zoster virus (VZV, HHVIII). In cancer patients, viral activation can also stem from the psychological stress of a cancer diagnosis or the physical stress related to surgery or radiation therapy. A recent report found that among 21 different forms of cancer, VZV infections were most strongly associated with hematological malignancies such as multiple myeloma, lymphoma, and leukemia.[16] Among solid cancers, the relationship was strongest with central nervous system cancer, followed by lung and oral/esophageal cancers. With oral cancer patients, VZV infection was typically identified within three years of initial diagnosis.

Regarding HSV infections, a 2010 manuscript reported a higher prevalence in neutropenic patients compared to head and neck cancer patients treated by adjunctive chemotherapy and radiation (~50% to ~43%) as well as radiotherapy alone (0%).[17] In a 2017 follow-up, this group confirmed the efficacy of antiviral therapy (acyclovir 400 mg 5 x daily, valacyclovir 250 mg x 2 daily to 1 g x 3 daily) in either a treatment or prophylactic strategy.[18] Interestingly, HSV-1 reactivation was shown to be significantly associated with chemotherapy-induced oral mucositis in patients with hematological malignancies or stem cell transplantation; however, culturable *Candida* levels were not.[19]

It should be re-emphasized that immunosuppression in cancer patients can mask the typical diagnostic features of oral herpesvirus infections. While recurrent HSV and VZV in healthy patients commonly presents as multiple small vesicles, limited to bound-down mucosa of the palate or attached gingiva and restricted to one side of the midline, immunosuppression can result in lesions affecting any mucosal surface in any distribution. Vesicle formation is often minimal and lesions may present as non-specific, broad-based ulcerations, occasionally with raised, whitish borders. In these challenging cases, oral cytology can be diagnostically useful in identifying the characteristic epithelial cell alterations (viral cytopathic effects).

Salivary gland hypofunction

Saliva has diverse functions and plays an important role in swallowing,

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digestion, speech, gustation and lubrication of the oral/oropharyngeal mucosa as well as prevention of dental caries and infections. The majority (80-90%) of daily salivary production is provided by the major salivary glands (e.g., parotid, submandibular, and sublingual). Most of the basal saliva flow is derived from the submandibular glands, whereas the bulk of stimulated saliva is provided by the parotid glands. The normal daily production rate of saliva is approximately 1.0-1.5 liters. When the unstimulated (basal) saliva rate is less than 0.1 mL/min and the stimulated rate is less than 0.5-0.7 mL/min, objective hypofunction is confirmed.[20] While the term xerostomia (dry mouth) can encompass both objectively reduced saliva flow and the subjective sensation of reduced or absent salivation, it is often incorrectly used as a synonym for salivary gland hypofunction (SGH).

Normally, saliva production results from parasympathetic stimulation that causes the neurotransmitter acetylcholine to bind to M1 and M3 muscarinic receptors in the salivary glands. A variety of mechanisms can lead to a decrease in salivary flow, but the most common etiology is medication use. A recent systemic review noted that most of the published literature on salivary function does not provide objective measures of SGH.[21] Despite this limitation, the cancer-related medications with the strongest associations with xerostomia/SGH are scopolamine (to prevent nausea and vomiting caused by medications used during surgery) and opioids-analgesics (e.g., buprenorphine, butorphanol).[21] Furthermore, although some medications may not exert a direct xerogenic effect, they may act synergistically with other therapeutic drugs to worsen SGH.

Another relatively frequent cause of SGH is radiation therapy (RT) of the head and neck. Irradiation to the salivary tissue causes atrophy and permanent loss of acinar cells in addition to fibrosis and constriction of the salivary ducts. Possible complications within the oral cavity can vary from an increased risk of dental caries associated with SGH to an increased risk of osteoradionecrosis, particularly in the mandible. Although the advent of intensity-modulated radiotherapy (IMRT) has resulted in better preservation of salivary gland function, many patients are treated with doses greater than the critical limit for retention of submandibular and parotid salivary gland tissues (approximately 40 Gy).

Regardless of the basis for SGH, both over-the-counter (OTC) products and parasympathomimetic drugs have been examined for efficacy in affected patients. As most studies suffer from a moderate to high risk of bias as well as small cohorts of participants, there is insufficient evidence to support the use of topical products.[22,23] The use of chewing gum (preferably sugar-free), however, has been shown to temporarily increase salivary production.[22,24] Oral lubricants and saliva substitutes can also provide temporary relief.[25,26] In practice, the patient should be encouraged to select a specific product based on personal preferences and the cost-benefit ratio of the products. The patient should be aware that relief from these products is relatively brief.

Regarding parasympathomimetic drugs, randomized clinical trial data suggests that pilocarpine (5-10 mg three times daily) is more effective than placebo in increasing salivary flow rate.[23,27] Such benefit is greater in patients who received a cumulative dose less than 50 Gy. Cevimeline HCl (30–45 mg three times daily) has also been shown to improve xerostomia and unstimulated salivary flow rates. The use of these pharmaceutical agents is recommended only after completion of RT.[26] They may also be beneficial with drug-related SGH. Side effects of these medications include sweating (most common), nausea, dyspepsia, vomiting, and flushing.[28] These are more frequent in patients using pilocarpine than cevimeline; however, the latter is more costly (90 tablets: $133 vs. $231). Partial recovery of salivary gland function can be anticipated when the local cumulative dose is ≤ 39 Gy.[25,29] Some authors have suggested that a cumulative dose of < 25–30 Gy to the parotid could allow for complete flow rate recovery.[29] Although a decrease in quality of life and saliva output is expected in the first six months following RT, salivary gland function can improve over 36 months following treatment.[20] Dentists should encourage proper hydration and patient involvement in their management strategy for xerostomia and SGH.

Prevention of dental caries

An increased risk for development of dental caries in patients undergoing cancer therapy is well-documented and primarily attributed to radiotherapy-induced salivary gland hypofunction as well as radiation damage to tooth structure. Patients receiving chemotherapy alone, however, also experience a significantly increased caries rate.

Treatment toxicities, including oral mucositis and dysphagia, often negatively impact oral intake and result in transient or sustained dietary changes. In order to combat treatment or disease-related weight loss, patients may be instructed to use liquid dietary supplements that often contain refined carbohydrates, as well as to eat small, frequent meals.

Together with hyposalivation and a disrupted salivary buffering capacity, this combination can result in enamel demineralization.[30-32]

Oral sensitivity or discomfort may lead to declining oral hygiene measures, and a microbial shift to cariogenic organisms may further contribute to dental caries in this patient population.

Fortunately, the dental team can help reduce the incidence of dental sequelae by initiating preventive measures before, during, and after antineoplastic therapies. Many cancer centers mandate all patients undergo a pre-treatment dental evaluation to identify and remove potential sources of odontogenic and periodontal infection prior to commencing cancer therapy. While even limited pre-treatment protocols have shown to minimize dental complications, preventive strategies during and after cancer treatment are paramount.[33]

Dental caries may arise within the first few months of treatment, and its incidence increases over time. A retrospective study of 314 patients with nasopharyngeal carcinoma reported the prevalence of dental caries escalated from 16% at one-year post-radiotherapy to 37%, 55%, and 74% at three, five, and seven years post-treatment, respectively.[28,34] Significant increase in post-treatment decayed, missing or filled teeth (DMFT) score, a standard measure of dental health, has also been reported in head and neck cancer patients at 9, 12, and 15 months post-radiotherapy.[35] The prevalence of dental caries across all cancer patients is estimated at 28%.[36]

Prevention of dental caries requires a multifaceted approach and generally includes meticulous oral hygiene, once or twice daily use of chlorhexidine mouthwash, and regular dental visits to minimize dental plaque deposits.[33,37] The importance of fluoride supplementation is well-recognized, and all systems of fluoride delivery appear to have equal impact on caries activity. Options include custom trays designed to increase contact time of fluoride product to tooth structures, brush-on gels, pastes, or oral rinses.[31,33,37] In-office application of fluoride varnish by a dental professional may also promote caries resistance. Continual reinforcement of preventive measures is critically important, as compliance has been shown to significantly decrease over time, with as low as 19% of patients continuing to use fluoride trays for more than one year.[33,38] Interestingly, a compliance rate of 86% has been reported with daily use of a 5,000 ppm toothpaste, suggesting substantially better patient acceptance with this mode of delivery.[37]

Poor compliance with any facet of caries prevention, including fluoride use, oral plaque control, and dietary management has been significantly associated with increased post-treatment dental caries, highlighting the importance of a comprehensive approach.[31,37] In addition, secondary benefits to maintaining dental heath include a reduced incidence and severity of oral mucositis.[39] Caries prevention also reduces associated odontogenic infections and dental extractions, minimizing risk for osteoradionecrosis, in patients who have undergone head and neck irradiation, and medication-related osteonecrosis, in patients who have taken anti-resorptive or anti-angiogenic drugs.[32,40,41] While many toxicities of chemoradiation largely resolve over time, problems with the dentition generally remain stable or increase, negatively impacting body image and quality of life.[30] Dental and medical professionals must underscore the importance of maintaining the dentition through conscientious and persistent adherence to a comprehensive caries prevention strategy.

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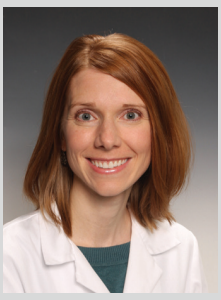
Bissonnette



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Taste disturbances

Patients undergoing systemic chemotherapy or head and neck radiation may report changes in taste and smell perception. Although not life-threatening, they can lead to severe weight loss and subsequent discontinuation of cancer therapy. Taste disturbances may manifest as hypogeusia (reduced ability to taste), ageusia (loss of taste), or dysgeusia (altered taste), and are noted in up to 75% of patients receiving either treatment.[42,43] The most common complaints in patients receiving chemotherapy are a foul taste (45%), taste loss (43%) and a metallic taste (40%).[44] These changes are seen with greatest incidence when the patient's chemotherapy includes docetaxel, carboplatin, anthracycline, or paclitaxel.[44] Head and neck radiation causes damage to the nerves and loss of taste buds. Changes in taste can occur as early as three to four weeks following initiation of RT and at doses as low as 30 Gy, particularly when the anterior (mobile) tongue is irradiated.[42,45]

It is important to reassure patients that these disturbances are usually reversible within one year of completion of therapy.[45] As taste perception can be modulated by the presence of infection (e.g., candidiasis) and xerostomia, the dentist can help alleviate symptoms by treating these other underlying causes if present. A recent study reported a beneficial effect of oral polaprezinc (150 mg daily) in reducing the duration of grade 2 dysgeusia (altered taste causing a change in diet) or preventing it (75 mg daily administered before cancer therapy).[46]

Conclusion

Dentists are positioned to play an important role in the prevention and management of cancer therapy-related toxicities. A wide variety of potentially helpful OTC products and prescription drugs are available. These agents can be costly, however, and it is often difficult to determine which treatment might provide the most favorable improvement in the patient's quality of life.

Unfortunately, the scientific literature regarding dental management for cancer patients is limited by the use of highly variable protocols and inconsistency in the level of data each study provides. Dentists must be cautious in the interventions they recommend and should work in a collaborative approach with the patient's oncologic team. Resources such as the Multinational Association for Supportive Care in Cancer guidelines are available free-of-charge to clinicians. In addition, the *Journal of the National Cancer Institute* (JNCI) has numerous monographs, which offer evidence-based reviews on the subject. ●

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