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After reading the article "Oral Complications of Cancer and Cancer Therapy: From Cancer Treatment to Survivorship," the learner should be able to:
1. Describe the most common and/or serious oral complications and toxicities of treatments used for head and neck cancer, as well as the oral complications and toxicities of systemic treatments used in other types of cancer.
2. Summarize interventions for prevention and/or treatment of oral mucositis, hyposalivation/xerostomia, dental and periodontal infections, and osteonecrosis of the jaw.

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Oral Complications of Cancer and Cancer Therapy

From Cancer Treatment to Survivorship

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Oral complications resulting from cancer and cancer therapies cause acute and late toxicities that may be underreported, underrecognized, and undertreated. Recent advances in cancer treatment have led to changes in the incidence, nature, and severity of oral complications. As the number of survivors increases, it is becoming increasingly recognized that the aggressive management of oral toxicities is needed to ensure optimal long-term oral health and general well-being. Advances in care have had an impact on previously recognized oral complications and are leading to newly recognized adverse effects. Here, the authors briefly review advances in cancer therapy, including recent advances in surgery, oral care, radiation therapy, hematopoietic cell transplantation, and medical oncology; describe how these advances affect oral health; and discuss the frequent and/or severe oral health complications associated with cancer and cancer treatment and their effect upon long-term health. Although some of the acute oral toxicities of cancer therapies may be reduced, they remain essentially unavoidable. The significant impact of long-term complications requires increased awareness and recognition to promote prevention and appropriate intervention. It is therefore important for the primary oncologist to be aware of these complications so that appropriate measures can be implemented in a timely manner. Prevention and management is best provided via multidisciplinary health care teams, which must be integrated and communicate effectively in order to provide the best patient care in a coordinated manner at the appropriate time. **CA Cancer J Clin 2012;62:400-422. ©2012 American Cancer Society.**

Keywords: head and neck neoplasms, oral neoplasms, radiation, chemotherapy, chemoradiation, hematopoietic cell transplantation, mucositis, xerostomia, hyposalivation, osteonecrosis

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Introduction

Oral complications resulting from cancer and cancer therapies cause acute and late toxicities (Table 1) that are underreported, underrecognized, and undertreated. Recent advances in cancer treatment have led to changes in the incidence, nature, and severity of oral complications. Acute oral complications include mucositis, infection, and saliva and neurosensory changes. Complications in survivors include neurosensory changes; saliva, taste, and functional changes; oral and dental infection; and risk of dental disease and necrosis of the jaw. These complications impact quality of life. As the number of survivors increases,[1] it is becoming increasingly recognized that the aggressive management of oral toxicities is needed to ensure optimal long-term oral health and general well-being. Advances in care have had an impact on previously recognized oral complications and are leading to newly recognized side effects. Here, we briefly review advances in cancer therapy, including surgery, chemotherapy, radiation therapy (RT), hematopoietic cell transplantation (HCT), and medical oncology; describe how these advances affect oral health; and discuss the frequent and/or severe oral health complications associated with cancer and cancer treatment.

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TABLE 1. Oral Complications of Cancer Therapy

COMPLICATION	SYMPTOMS
Acute	
Mucosal	Mucositis, pain, dysphagia, limited oral function
Saliva change	Viscosity, volume
Neurosensory	Taste alteration, taste loss, neuropathic pain
Infection	
Dental/periodontal	Acute exacerbation of chronic infection
Mucosal	*Candida*, herpes, other
Limited movement	Opening of the jaw, tongue function
Chronic	
Mucosal pain	Atrophy, neuropathy
Saliva	Viscosity, hyposalivation
Neurosensory	Taste alteration, taste loss, halitosis, mucosal neuropathy, trismus
Limited movement	Lip aperture, mucosa, muscle/TMJ, neck, shoulder, tongue, trismus
Infection	
Mucosal	Pain, halitosis
Dental	Demineralization, caries
Periodontal	Advanced attachment loss, mobility
Risk of mucosal injury	
Necrosis	Soft tissue, bone
Esthetic impact	Social withdrawal, low quality of life, depression
Speech	Social withdrawal, depression
Mastication/dysphagia	Impact on energy and nutrient intake

TMJ indicates temporomandibular joint.

Treatment Advances

Surgery: Head, Neck, and Oral Cancer

Surgery has consistently played an upfront role in the treatment of head, neck, and oral cancers. The choice of surgical treatment depends on tumor location, size, proximity to bone, and depth of infiltration.[2] Tumors that approach or involve the mandible require an understanding of the mechanisms of bone involvement, and necessitate mandible-sparing approaches such as partial thickness mandibular surgery (marginal mandibulectomy and mandibulotomy) for surgical access. In most cases in which bone is involved, a segmental resection of the mandible is necessary with microvascular reconstruction using fibular free flaps to restore mastication and facial contour, and allow for the placement of osteointegrated implants for orofacial and dental rehabilitation.[3] For advanced stage disease, chemoradiation therapy (CRT) offers optimal cancer outcomes and the potential for organ preservation.

Minimally invasive surgery with curative intent for head and neck cancers has increased over the last 3 decades.[4] Transoral robotic surgery and transoral laser microsurgery offer a surgical alternative to CRT-based organ preservation strategies, and several series have shown comparable oncologic outcomes with superior functional results using these surgical approaches.[5] This is because robotic technology provides improved visual access and the ability to manipulate the tissue in a way that cannot be accomplished using nonrobotic transoral techniques.[6,7]

Regardless of the surgical approach, microsurgical reconstructive techniques have evolved to facilitate restoration of form and function in both the primary and salvage setting. In the primary setting, these approaches facilitate surgical removal of more extensive cancers, and complex head and neck defects can be effectively restored and rehabilitated. Soft tissue free flaps such as the radial forearm or lateral thigh allow for the reconstruction of oral and oropharyngeal soft tissue defects. In the salvage setting, these techniques allow for improved healing by providing a vascular supply to the surgical bed and reducing the risk of fistula formation. They also allow coverage and protection for major blood vessels, preventing exposure and vascular catastrophes.

Chemoradiation Therapy

CRT is commonly used as the primary treatment for locally advanced head and neck cancers or as adjuvant therapy for tumors with poor clinical features. Altered RT fractionation and schedules (doses that differ from 1.8 gray [Gy]-2 Gy/day) have been extensively evaluated to improve treatment outcomes. Altered fractionation (AF) plus concurrent CRT improves tumor control and reduces late toxicity; however, it is associated with more severe acute oral toxicities, primarily mucositis.[8-11] Adding chemotherapy to hyperfractionation (2 or more small daily doses or 5 or more weekly fractions) also increases acute toxicities to a level that may limit hyperfractionated RT and CRT to selected patients in clinical trials at large institutions. Concurrent chemotherapy with normofractionated RT (2 Gy/day, 5 days/week, for 5-7 weeks) is the most popular approach in current practice. Concomitant boost RT (supplementary daily dose in addition to 2 Gy on a reduced tumor volume at a given time during RT) has also gained popularity with intensity-modulated RT (IMRT) as a simultaneous integrated boost or as simultaneous modulated accelerated RT. This approach offers improved dose conformation to the tumor volume, superior dose rate, and better treatment time delivery compared with other approaches.[12] Volumetric-modulated arc therapy, a form of rotational IMRT, and stereotactic RT, a form of highly focused irradiation using tridimensional tumor targeting, also offer advantages.[13] Arc therapy reduces IMRT delivery time from 20 minutes to

TABLE 2. Antifungals and Antivirals

ANTIFUNGALS	
ACTION	**TYPE**
Local	Topical polyenes, azoles, chlorhexidine
Systemic	Azoles, caspofungin (micafungin), amphotericin B
ANTIVIRALS	
Prevention/therapy: acyclovir, valacyclovir, famciclovir, foscarnet, ganciclovir, cidofovir	

fewer than 5 minutes, while optimizing dose homogeneity and normal tissue sparing,[14-25] including parotid gland sparing.[26] Stereotactic fractionated RT allows for the generation of x-ray beams from a single electronic source, which can be rotated or moved around a central focus. Linear accelerator-based stereotactic body RT may be used for multisession head and neck irradiation. Stereotactic irradiation generally allows hypofractionation (doses of 2.5 Gy or more) because of the small volume of the treated tumor and the accurate delivery of irradiation. Hypofractionated stereotactic body RT has shown encouraging 2-year overall survival rates of 14% to 41% in the reirradiation setting,[27-35] and this approach is being increasingly investigated as a boost of prophylactic volumes after IMRT. Data for proton therapy in rare radioresistant head and neck cancer has shown high local control rates of 78% to 85% at 5 years with less than 5% severe late toxicity. The role of targeted therapies as novel RT sensitizers has also been investigated.[36] The study by Bonner et al showed improved outcomes with cetuximab plus RT when compared with RT alone, with no significant increase in oral complications noted.[37] Conversely, in a recently reported trial comparing RT plus cisplatin with RT plus cisplatin and cetuximab, the addition of cetuximab did not improve outcomes but did add to toxicity.[38] Thus, the role of targeted agents as part of a combined modality treatment approach for locally advanced head and neck cancer has yet to be clearly defined.

Hematopoietic Cell Transplantation

HCT after myeloablative injury from chemotherapy and/or RT exposure using harvested bone marrow stem cells, autologous or allogeneic peripheral blood stem cells collected by apheresis, or cord blood units is becoming increasingly common, with a growing number of clinical indications and increased access to sources of stem cells.[39] Regimen-related toxicity limited early efforts of transplantation in younger patients. However, the advent of nonmyeloablative or reduced-intensity conditioning regimens generally based on more highly immunosuppressive agents such as fludarabine has expanded the pool of patients who are potentially eligible for HCT. Patients for whom acute toxicities would have been unacceptably high when HCT was first introduced are now able to receive lower intensity regimens that may result in lower regimen-related toxicity.[40,41] In addition, there have been vast improvements in the prevention and treatment of infection (Table 2) and graft-versus-host disease (GVHD) (Table 3), thereby allowing a greater number of patients to undergo this treatment.

Medical Oncology

Some traditional chemotherapy drugs, such as fluorouracil, methotrexate, and doxorubicin, are known to cause acute mucositis.[42,43] Mucositis resulting from targeted therapy may present with isolated ulcerations and mucosal pain (even in the absence of mucosal lesions) and, due to a different presentation, different mechanisms of toxicity appear likely.[44,45] Current treatment and symptom management are based on clinical appearance, and initial reports suggest that topical steroids may be useful in the management of isolated ulcerations associated with targeted therapies.[45] Pain management is discussed below.

Oral toxicities may be severe and protracted, and thus preventive and ongoing oral health care is important.[46,47] A better understanding of the critical pathways involved in the development of certain types of cancers has led to the identification of specific molecular therapeutic targets.[48-50] Targeted strategies are appealing because they can be designed to include patients with a specific molecular abnormality, thus enriching the study population with those patients most likely to respond. This improves the ability to identify effective agents, albeit in select patient populations. Furthermore, patients who are unlikely to benefit are spared unnecessary cost, time delay, and toxicity. The toxicity profile for these agents is also distinct from traditional chemotherapy drugs. In general, targeted agents have a more favorable toxicity profile, with a lower incidence and severity of oral adverse effects.[44,51]

In addition to more traditional systemic therapies and targeted therapies, there is an ever-widening variety of agents that work via distinct mechanisms of action.

TABLE 3. Management of Oral Graft-Versus-Host Disease

TYPE OF MANAGEMENT
Topical: steroids (dexamethasone, budesonide, fluocinonide, and clobetasol); retinoic acid; cyclosporine, tacrolimus, and pimecrolimus; azathioprine
PUVA: psoralen at dose of 10 mg or 20 mg one hour before UV light (0.5 J/cm^2)
Symptom management: mucosa-coating agents, anesthetics, analgesics
Dry mouth management: sialogogues, salivary substitutes
Fibrosis management: physical therapy

PUVA indicates psoralen plus ultraviolet light; UV, ultraviolet; J/cm^2, joules per square centimeter.

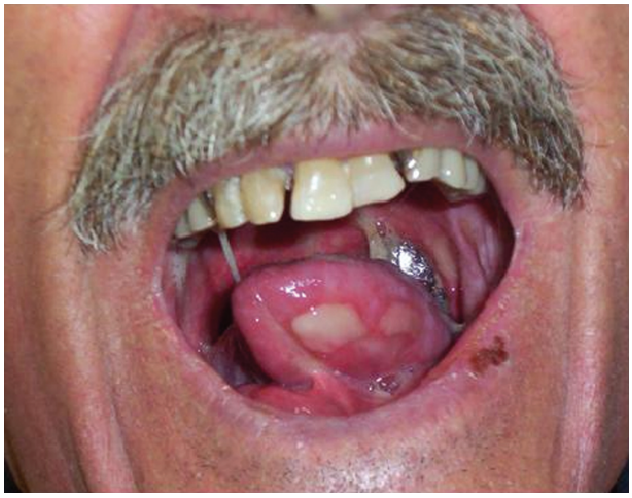

FIGURE 1. Patient With Symptomatic Ulcerative Mucositis Causing Pain and Resulting in Oral Intake Being Limited to Water. Ulcerations are seen on the ventral tongue, but are not visible on the posterior buccal mucosa or the posterior lateral tongue and soft palate. Erythema is noted in the nonkeratinized tissue of the tongue and soft palate. In addition, thick saliva secretions are visible.

Biotherapeutic agents play a role in the therapy of select tumors. Radiopharmaceutical agents have been designed and tested for diagnostic, palliative, and treatment purposes. Photodynamic therapy with or without sensitizing agents may be effective for epithelial skin or mucosal tumors. There are also innumerable areas of active investigation, including the study of vaccine therapy for the treatment and prevention of malignancy and the use of gene therapy for treatment and symptom management.

Mucositis

Biology

Mucositis is an inflammatory process that results from tissue damage due to chemotherapy and/or RT (Fig. 1). Mucositis secondary to RT for head and neck cancer is a locoregional complication; mucositis may involve the entire gastrointestinal (GI) tract when it is secondary to either chemotherapy or total body irradiation (TBI).[52] However, even locoregional inflammation can have systemic impact due to cytokine release, and therefore both locoregional and GI tract mucositis have systemic effects. Sonis et al proposed a theoretical model describing the mechanism of treatment-related mucositis (Table 4).[53,54] This model postulates that during initiation, cells are exposed to an inciting event (chemotherapy or RT), which generates reactive oxygen species leading to direct DNA damage; upregulation of sphingomyelinase and ceramide synthesis; and stimulation of transcription factors, notably nuclear factor-κB (NF-κB). Activated NF-κB upregulates pro-inflammatory cytokines (eg, interleukins 1β and 6 and tumor necrosis factor-α). Upregulation of these cytokines leads to tissue injury, apoptosis, and increased vascular permeability; this enhances the effect of cytotoxic drugs on the mucosa. NF-κB also upregulates adhesion molecules, causing activation of the cyclooxygenase-2 pathway, thus leading to angiogenesis. Prolonged tissue injury occurs from positive feedback loops that are fueled by proinflammatory mediators, causing signaling and amplification. The submucosa and basal epithelium and extracellular matrix are targeted, and therefore injury may not be clinically visible until the ulceration phase. Patients are most symptomatic in this latter phase as epithelial integrity is damaged by a robust inflammatory infiltrate that sensitizes nociceptors. Fungi and bacteria, including anaerobic organisms, are able to colonize the damaged mucosa, a process that may be exacerbated in the presence of simultaneous neutropenia. Healing ultimately ensues with epithelial proliferation and differentiation and the reestablishment of local oral microorganisms. While the model is presented as a series of linear events, mucositis after chemotherapy develops along a continuum, and during RT all phases occur simultaneously in all tissues due to repeated RT dosing over time.[55]

Risk Factors

Risk factors for the development of mucositis may be categorized as tumor-related, treatment-related, or patient-related factors. In general, tumor-related factors are most prominent in patients with head and neck tumors who require large RT ports and in those with malignancies in which treatment leads to neutropenia. RT-related factors include fraction size, radiated volume-area-diameter, overall treatment time, and cumulative dose.[56] As discussed below, specific chemotherapeutic agents, most notably antimetabolites and alkylating agents, result in a higher incidence and severity of mucositis. Combination chemotherapy and dose-intense and dose-dense regimens are also more likely to induce mucositis. Of note, some of the newer targeted agents such as epidermal growth factor receptor, mammalian target of rapamycin, and tyrosine kinase inhibitors (see below) are also associated with mucosal toxicity.[44,51]

TABLE 4. Phases of Mucositis and Potential for Future Intervention

PHASE	INTERVENTION
Phase 1	Initiation, toxicity, oxidative stress; reactive oxygen species
Phase 2	Upregulation-second messengers: NF-κB
Phase 3	Signaling/amplification: TNF-α, IL-1B, IL-6
Phase 4	Ulceration and inflammation: microbial flora, amplification of proinflammatory cytokines
Phase 5	Healing promotion

NF-κB, nuclear factor-κB; TNF-α, tumor necrosis factor-α; IL, interleukin.

Patient parameters that may influence mucositis incidence and severity include age and gender (primarily dependent upon cancer treatment protocol)[57]; comorbid diseases such as the acquired immunodeficiency syndrome, diabetes, and renal disease; preexisting periodontal disease[58,59]; genetic factors[60]; nutritional status; oral microflora; and use of alcohol and/or tobacco. In addition, the use of dental appliances and failure to floss teeth daily have been shown to result in an earlier (although not statistically significant) onset of mucositis.[58] Patients undergoing either standard-dose or high-dose chemotherapy who are myelosuppressed or immunosuppressed are also at higher risk.

Grading and Measurement

A number of systems have been developed to grade mucosal injury secondary to chemotherapy or RT (Table 5).[61-64] The World Health Organization scale combines mucosal changes, pain, and functionality into a single composite score.[61] The National Cancer Institute Common Terminology Criteria for Adverse Events includes 2 separates criteria: physical examination findings on oral inspection and functionality.[62] Although a 2-part score provides more specific information, reporting and interpreting toxicity data become more complex and challenging. The Radiation Therapy Oncology Group oral mucositis grading system incorporates both an assessment by a medical professional and a functional component graded by the patient.[63] The Oral Mucositis Assessment Scale is a validated scale that provides a semiquantitative scale assessing ulceration and erythema in affected oral sites.[64]

Patient-reported outcomes (PROs) are questionnaires completed by the patient in order to assess symptom burden and functionality without influence, interpretation, or modification by another observer.[65] The Oral Mucositis Weekly Questionnaire (OMWQ)[66] and Patient-Reported Oral Mucositis Symptoms (PROMS)[67] are questionnaires that are solely focused on the assessment of mucositis. The OMWQ demonstrates a high degree of correlation with clinical assessment. Furthermore, studies using the OMWQ during RT have demonstrated the ability to capture a change in symptom burden over short intervals during active treatment. Similarly, the PROMS showed a high internal reliability and correlated well with clinician assessment. The Vanderbilt Head and Neck Symptom Survey (VHNSS)[68] was developed to capture oral function and quality of life in cancer survivors.

Mucositis-related questions are included in most of the general tools that assess head and neck symptom burden including the European Organization for Research and Treatment of Cancer Quality of Life Head and Neck Module (EORTC HN35),[69] the Functional Assessment of Cancer Therapy-Head and Neck subscale (FACT-HN),[70] The University of Texas MD Anderson Cancer Center System Inventory-Head and Neck (MDASI-HN) module,[71] and the VHNSS.[68]

TABLE 5. Methods Available to Assess for Mucosal Injury

WHO[61]	
Grade 0	No signs and symptoms
Grade 1	Painless ulcers, edema, or mild soreness
Grade 2	Pain and ulcers, but can maintain ability to eat
Grade 3	Ulcers, unable to eat due to mucositis
Grade 4	Ulcers, need for parenteral or enteral support
NCI CTCAE[62]	
Clinical examination	
Grade 1	Erythema of the mucosa
Grade 2	Patchy ulcerations or pseudomembranes
Grade 3	Confluent ulcerations or pseudomembranes, bleeding with minor trauma
Grade 4	Tissue necrosis, significant spontaneous bleeding, life-threatening consequences
Grade 5	Death
Functional/symptomatic	
Grade 1	Minimal symptoms, normal diet
Grade 2	Symptomatic but can eat and swallow modified diet
Grade 3	Symptomatic and unable to adequately aliment or hydrate orally
Grade 4	Symptoms associated with life-threatening consequences
Grade 5	Death
RTOG[63]	
Assessment by a medical professional	
Score 1	Erythema
Score 2	Patchy mucositis
Score 3	Greater than one-half of the mucosa affected by a fibrinous mucositis
Score 4	Necrosis and hemorrhage, functional component graded by the patient
OMASS[64]	
Semiquantiative scale	Erythema, ulceration score for each at-risk oral site

WHO indicates World Health Organization; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; RTOG, Radiation Therapy Oncology Group; OMAS, Oral Mucositis Assessment Scale.

Acute Mucositis-Related Effects

Standard-Dose Chemotherapy

Numerous chemotherapy agents have been associated with varying degrees of mucositis when used in standard doses and schedules. Culprit chemotherapeutics include

antimetabolites that affect DNA synthesis, anthracyclines, alkylating agents, other antitumor agents including platinum-based agents, vinca alkaloids, and taxanes.[59] Of note, certain chemotherapeutic drugs such as etoposide and methotrexate are secreted in saliva,[59] which may increase mucosal toxicity.

Standard-dose chemotherapy is associated with an estimated 40% risk of all-grade mucositis. The severity correlates with the number of chemotherapy cycles and the history of mucositis with prior chemotherapy cycles. For some agents, such as fluorouracil, the delivery schedule may alter the incidence and severity of mucositis.[59]

Mucositis secondary to standard-dose chemotherapy usually manifests itself within 7 to 10 days of treatment. Symptoms usually resolve within 1 to 2 weeks, although a more prolonged course of recovery may occur in some patients.[52] In general, symptoms are mild to moderate with grade 3 to 4 toxicities reported in less than 5% of patients. Combined CRT increases the frequency, duration, and severity of mucositis, and in this setting mucositis is often the primary treatment-limiting toxicity.

The management of mucositis begins with supportive measures, which may be considered to be the foundations of care (Table 6). A more detailed review of guidelines for the care of patients with oral mucositis has been published by the Multinational Association of Supportive Care in Cancer (MASCC) and the Cochrane Group.[47,72] Comprehensive dental examinations to identify and remove infections, instituting preventive protocols that include education regarding oral hygiene, and the frequent use of bland oral rinses are considered basic care for oral health maintenance in patients at risk for mucositis. Oral rinses without alcohol, such as baking soda and salt solutions, may improve oral comfort.[73] Patients with severe mucositis require pain management (see below) and intravenous fluids and nutritional support as needed. Hyposalivation may exacerbate mucosal symptoms and therefore hydrating the lips and oral tissue is recommended.[55] Medications that cause or worsen xerostomia should be avoided if possible.[59]

Although numerous preventive therapies for mucositis have been investigated, few studies have provided compelling evidence to support any specific interventions. There are data to indicate that cryotherapy administered during infusion of a cytotoxic agent (ice chips to reduce blood flow to the oral mucosa) can reduce exposure of the mucosa to chemotherapeutic agents and thereby prevent mucositis.[72] The MASCC guidelines recommend 30 minutes of oral cryotherapy to prevent oral mucositis for patients receiving bolus fluorouracil, and suggest cryotherapy prior to treatment with bolus doses of edatrexate.[47] Chlorhexidine has not been shown to prevent oral mucositis and is not recommended by the MASCC[47] or the Cochrane Group.[72] In addition, some of the common commercial forms of chlorhexidine rinses contain alcohol, which is poorly tolerated by patients with mucositis.[47]

TABLE 6. Summary of MASCC Clinical Practice Guidelines for Oral Mucositis

FOUNDATIONS OF CARE
Use a soft toothbrush that is replaced on a regular basis
Use validated tools to regularly assess oral pain and oral cavity health
Dental professionals recommended as part of the health care team throughout treatment and follow-up
Patient-controlled analgesia with morphine for oral mucositis pain in hematopoietic cell transplantation patients
Regular oral pain assessment using validated instruments
RADIATION THERAPY: PREVENTION
Sucralfate not used for prevention
Antimicrobial lozenges not used for prevention
Use midline radiation blocks and 3-dimensional radiation treatment
Use benzydamine in patients with head and neck disease who are receiving moderate-dose radiation therapy
CHEMOTHERAPY: PREVENTION
Use oral cryotherapy for short half-life, bolus chemotherapy (5-FU, edatrexate)
Acyclovir and analogues not used to prevent mucositis (use for prevention of HSV)
STANDARD-DOSE CHEMOTHERAPY: TREATMENT
Chlorhexidine not used to treat established oral mucositis (use for local infection)
HEMATOPOIETIC CELL TRANSPLANTATION: PREVENTION
Pentoxifylline not recommended

MASCC indicates Multinational Association of Supportive Care in Cancer; 5-FU, fluorouracil; HSV, herpes simplex virus.

High-Dose Chemotherapy With HCT

High-dose chemotherapy in patients undergoing HCT is associated with an estimated 70% to 80% incidence of grade 3 to 4 oral mucositis.[59] Mucositis typically peaks 7 to 10 days after HCT and begins to resolve 14 to 18 days after HCT. Temporally, mucosal recovery is related to engraftment.[74] Mucositis is not only frequent, but it is also severe,[73] and this severity is increased in patients treated with TBI.

In the HCT setting, mucositis may involve the entire GI tract. Patients with oral or GI mucositis related to high-dose chemotherapy have more episodes of oral bleeding (gingival and mucosal); higher rates of infection, including gingivitis and candidiasis; and longer hospitalizations per cycle than patients unaffected by mucositis.[55] One study of HCT patients found that 42% rated mucositis as their most significant transplantation-related toxicity.[55]

Severe laryngeal mucositis may cause airway obstruction and necessitate intubation.[74] Risk factors for the development of mucositis in patients undergoing HCT may include the variant methylenetetrahydrofolate reductase (MTHFR) C677T allele, conditioning regimens that include TBI, and a pretransplant body mass index of 25 kg/m^2 or higher.[74]

Oral care and supportive measures are critical for the management of mucositis in patients undergoing HCT. Clinical care guidelines have been developed by the MASCC for all cancer patients with mucositis. These guidelines have been reviewed and endorsed by other groups including the American Society of Clinical Oncology, National Comprehensive Cancer Network, European Society for Medical Oncology, and Oncology Nursing Society, and form the basis for clinical care recommendations (Table 6). Although patients may be inclined to discontinue oral care due to discomfort, discontinuation of brushing results in an increased microbial load and risk of gingival inflammation. In the HCT setting, aqueous chlorhexidine reduces oral infection risk, including gingivitis and candidiasis, and may reduce overall microbial load.[75] Since pain is a predominant aspect of the morbidity of mucositis in patients undergoing HCT, the MASCC continues to recommend patient-controlled analgesia with morphine and topical anesthetic/analgesic agents. Cryotherapy is suggested for the prevention of oral mucositis in patients receiving high-dose melphalan.[47] The use of pentoxifylline, granulocyte–colony-stimulating factor mouthwashes, and acyclovir to prevent mucositis in HCT patients is not recommended (Table 6). Keratinocyte growth factor, which promotes epithelial cell repair through increased cellular proliferation,[55] has been shown to be reduce mucositis and mucositis-associated symptoms in the HCT setting.[72] The MASCC recommends a dose of 60 μg/kg/day for 3 days prior to conditioning treatment and for 3 days posttransplantation to aid in the prevention of oral mucositis.[47] Low-energy laser has been shown to reduce the severity of mucositis with a possible impact on tumor necrosis factor production and is suggested by the MASCC.[47] Weak and unreliable data exist for the use of amifostine, allopurinol, intravenous glutamine, pilocarpine, Traumeel S (Heel, Inc, Albuquerque, NM), chamomile, aloe vera, and honey, and none are suggested in the current guidelines.[59,72]

Radiation Therapy

RT to the head and neck causes mucositis in up to 60% of patients after standard RT and in essentially all patients after hyperfractionation or AF-RT regimens and in combined therapies.[14,56,76] Severe mucositis (grade 3-4) occurs in 34% of patients receiving standard RT and in over 56% of patients receiving AF-RT.[77] Concomitant CRT further increases grade 3 or 4 mucositis; incidence rates range from 50% to 100% depending on the regimen.[59]

RT-induced mucositis usually begins to manifest itself within 2 to 3 weeks of the start of treatment. Initial symptoms are usually mild discomfort and dryness with the development of mucosal erythema. By week 5, frank erythema, ulceration, and pseudomembrane formation are usually present. These are associated with oral pain and odynophagia, resulting in altered oral intake. After the completion of RT, mucosal healing begins and symptoms gradually decrease. For most patients, ulcerations are dramatically improved within 4 to 6 weeks.

Oral pain and odynophagia may limit the intake of nutrients, fluids, and medications, resulting in increased weight loss and the need for feeding tube placement in a high percentage of patients.[77] Severe mucositis also places patients at an increased risk of systemic infections, including streptococcal infections and aspiration pneumonia.[55] These toxicities lead to increased direct and indirect health care costs and decrease quality of life.

In addition to standard supportive care measures, the MASCC recommends the use of 3-dimensional RT and midline radiation blocks to reduce mucosal injury (Table 6).[47,78] The use of IMRT and newer technologies can also reduce mucosal injury through more sophisticated RT planning and delivery. The MASCC also recommends the use of benzydamine for the prevention of RT-induced mucositis in patients receiving moderate-dose RT. Antiinflammatory agents are currently not recommended due to insufficient data. Sucralfate, chlorhexidine, and polymixin/tobramycin/amphotericin (or similar) lozenges/toothpaste are not recommended for the prevention of RT-induced oral mucositis (Table 6).[47,72]

Late Mucositis-Related Effects

Data on the late effects of mucositis are limited.[68] Patients undergoing RT for head and neck cancers may develop mucosal atrophy and telangiectasias, and may experience chronic mucosal pain and sensitivity. Patients will often describe the mucosal pain as a burning or a scalded sensation that may represent neuropathy. Hot and/or spicy and acidic foods and dry air may exacerbate symptoms. Mucosal sensitivity may permanently alter food choices in this population. Management may be improved with attention to the risk factors of hyposalivation, mucosal infection, and the neuropathic components of pain associated with mucositis.

Hyposalivation and Xerostomia

Biology

Saliva serves a number of critical functions in the homeostasis of the oral ecosystem, in the oropharynx and larynx, and in speech and swallowing functions. Saliva reduces the risk of mucosal trauma and promotes healing of damaged mucosa via growth factors. It contains antimicrobial factors that are

active against many bacteria and fungi, and buffers the oral pH via bicarbonate and phosphate.[79,80] One of the most important functions of saliva is to provide the necessary substrates of calcium and phosphate for dental enamel integrity.[81] Saliva provides the first stage of the digestive process and it assists in bolus formation and smooth transport during swallowing. Diminished saliva results in the risk of dental demineralization and caries, and increases the risk of other oral infections such as candidiasis. It can also lead to mucositis, tongue fissures, dysgeusia, difficulty speaking, halitosis, oral soreness and burning, inability to wear dentures, and difficulty chewing and swallowing, culminating in a decreased quality of life.[82,83] Xerostomia is the subjective complaint of dry mouth that usually reflects a decreased presence of saliva.[79]

TABLE 7. Saliva Management

MANAGEMENT
Prevention: cancer treatment planning, amifostine
Sialogogues (with residual function)
Viscous saliva: mucolytic agents
Excess saliva: xerostomic (anticholinergic) medications
Palliation with lack of function: mouth-wetting agent (be aware of the pH of product), presence/absence of fluoride, CaPO4, xylitol
Dental prevention: cariogenic microbial flora (chlorhexidine, xylitol), mineralization (F, CaPO4)
Manage local infection

CaPO4 indicates calcium phosphate; F, fluoride.

Grading and Assessment

Xerostomia may be assessed by PROs such as the Xerostomia Inventory or by practitioner rating systems such as the National Cancer Institute Common Terminology Criteria for Adverse Events. Patient-reported evaluation of xerostomia has been shown to be more reliable than practitioner-assessed scores.[84] Hyposalivation is objectively assessed by measuring stimulated and nonstimulated salivary flow and by individual major gland secretion.[85] Hyposalivation does not always correlate with the perception of dry mouth.[83]

RT-Induced Xerostomia and Hyposalivation

Salivary tissue is sensitive to RT and cumulative doses greater than 30 Gy can cause permanent salivary gland dysfunction.[86] RT causes xerostomia due to indirect damage to epithelial and connective tissue elements of the gland including the blood vessels and nerves, or direct damage to salivary acini and ducts, all of which affect saliva production and secretion.[87,88] Direct tissue damage may be related to p53-related apoptosis due to the development of reactive oxygen species leading to DNA damage and reduced insulin-like growth factor production.[89,90]

RT has a dramatic effect on salivary function when the glands are within the RT field. The serous acini are initially more sensitive to RT. This often results in decreased saliva volume and increased viscosity during RT. However, with continuing RT, mucinous acini may become similarly impaired.[91] The degree of salivary gland destruction is both dose-dependent and contingent on the volume of parotid gland receiving RT. Salivary gland function may begin to recover several months after treatment is completed; however, damage is commonly irreversible and late-effect xerostomia is one of the most common late toxicities noted by patients.[68]

The prevention of damage to the salivary glands is of utmost importance to manage xerostomia (Table 7). Several approaches have been evaluated to minimize salivary gland damage from RT. These include the use of 3-dimensional RT planning or IMRT, pharmacologic agents, and surgical approaches.[92] Three-dimensional RT and IMRT may allow sparing of normal anatomical structures from high-dose RT when possible based on tumor size and location. This approach has the ability to spare salivary tissue and improve long-term xerostomia.[93,94] A number of randomized clinical trials have been conducted comparing salivary outcomes in patients treated with RT versus those treated with RT plus amifostine, an oxygen free radical scavenger.[95] A meta-analysis of these studies concluded that the use of amifostine results in a modest but clinically significant decrease in late xerostomia in patients undergoing RT.[96] Submandibular gland transfer has been performed in an attempt to shield a single submandibular gland from RT by transferring it to the submental space, although this may be less commonly considered due to the use of IMRT.[97,98] Nonviral gene transfer to salivary glands via cationic liposomes has also been explored with the hope of repairing damaged glands to a secretory phenotype and modifying the secretion to include antimicrobial factors or cytokines.[99]

High-Dose Chemotherapy With HCT-Associated Xerostomia and Hyposalivation

Salivary flow rates in patients undergoing high-dose chemotherapy with HCT may be affected acutely by chemotherapy, TBI, and concurrent medications.[100,101] However, the most pressing issue in this population is late-effect xerostomia related to salivary gland involvement by GVHD. Inflammatory infiltration of the salivary glands, as well cytokine release, causes an alteration in the quality of the saliva and reduces salivary quantity under both resting and stimulated conditions.

Chronic GVHD can persist for months to years and occurs in 40% to 70% of surviving patients treated with allogeneic HCT from unrelated matched donors and in 25% to 45% of patients receiving allogeneic HCT from matched siblings. Salivary gland inflammatory infiltration is

more common if patients have oral mucosal GVHD, as well as receive external beam TBI during conditioning.[101] Serum antinuclear antibodies are also associated with GVHD salivary gland disease.[101] A direct correlation has been observed between the degree of GVHD and salivary hypofunction, salivary fluid composition, and histopathological changes of the gland. In patients with GVHD, an overall decrease in saliva secretion is common, but there appear to be higher salivary concentrations of sodium, magnesium, albumin, total protein, immunoglobulin (Ig) G, and epidermal growth factor, perhaps due to increased leakage through injured oral mucosa. There is also a decrease in salivary IgA and inorganic phosphate.[101] Even when these concentrations are increased, the total quantity may be reduced given the decreased salivary volume.[100]

Treatment for GVHD-related xerostomia includes systemic immunosuppressive agents.[100] Primary treatment includes prednisone and cyclosporine, and second-line treatment includes cytokine blocking agents, antimetabolites, cytotoxic antibodies, and new prophylaxis strategies. Immunomodulating modalities, such as extracorporeal photopheresis, during which the patient's mononuclear cells are apheresed and exposed to ultraviolet light prior to reinfusion, are also used.[102] The antimalarial drug hydroxychloroquine and antiinflammatory properties of drugs such as thalidomide and clofazimine are used in GVHD to prevent end-organ injury.[100,101] Blockage of nitric oxide production using oxygen radical scavengers and inhibitors of nitric oxide synthetase may play a future role in GVHD treatment.

Palliation and Supportive Care for Patients With Xerostomia

Palliation of symptoms and a focus on oral health preventive measures are essential and involve several key elements (Table 8). If xerostomia is exacerbated by a medication (most commonly antianxiety medications, antidepressants, antihypertensives, or opioid analgesics), doses should be reduced below the threshold leading to oral dryness or changed (if possible). Dentures should be well-fitting and should not be worn at night to avoid irritation of the mucosa. Intake of water is encouraged to maintain hydration.[83] Tap water is favored over bottled water as bottled water does not always contain fluoride.[85] However, patients should be aware that although a dry mouth is a symptom of systemic dehydration, drinking large volumes of fluid will not overcome xerostomia.[86] Milk may be a useful salivary substitute because it moisturizes, lubricates, and buffers acids and may also contribute to enamel remineralization through its calcium and phosphate content.[86] Patients should consume a low-sucrose diet, and avoid sugar-containing soft drinks and snacks between meals. Patients should also avoid caffeine because it leads to a reduction in saliva production. Patients should avoid citrus and spicy foods.

TABLE 8. Managing Viscous Secretions

MANAGEMENT
Increase serous secretions (sialogogue): pilocarpine, cevimeline, bethanechol
Mucolytics: guaifenesin, n-acetylcysteine
Removal of thick/dry secretions: 1.5% H_2O_2

H_2O_2 indicates hydrogen peroxide.

Tobacco cessation should be strongly encouraged. Snoring and mouth breathing can contribute to xerostomia and therefore managing the conditions that increase mouth breathing (such as nasal congestion) and using a nasal strip can provide some relief.[85] In addition, humidified room air and management of hyposalivation may be beneficial. A physiological means of stimulating the salivary glands through mastication may also help (chewing xylitol gum or sucking sugar-free hard candies).[86]

In patients with residual salivary function, physical stimulation with agents such as sugar-free gum or candies and systemic sialogogues should be considered. In addition to providing oral comfort, stimulation of residual function increases physiologic saliva secretion, which has beneficial effects on oral health and function. Pilocarpine hydrochloride, a nonspecific muscarinic and weak β-adrenergic agonist,[99] was the first drug approved in the United States to be shown to increase salivary flow rates under both resting and stimulated conditions compared with baseline (standard dosing of 5 mg 3 times a day).[103] However, there have been mixed results reported for the administration of pilocarpine during RT as a preventive agent.[79,104,105] Cevimeline is a selective M3 muscarinic receptor acetylcholine analog that when administered orally at a dose of 30 mg given 3 times daily has been shown to increase nonstimulated salivary flow.[106,107] Both pilocarpine and cevimeline are contraindicated in patients with uncontrolled asthma, narrow angle glaucoma, and acute iritis, and caution should be taken in patients with gallbladder disease.[85] Bethanechol (25 mg, given 3 times a day) is a cholinergic stimulant that has been studied for salivary stimulation.[108] It is not contraindicated in patients with reactive airways and those with narrow angle glaucoma, but may increase urinary frequency. Comparative studies of the available sialogogues are limited but suggest that cevimeline and bethanechol may have fewer side effects than pilocarpine.[109,110] Secretory agents have had limited success in patients with advanced salivary dysfunction. Additional therapies include hyperbaric oxygen to improve angiogenesis and fibroplasia in nonhealing tissue, acupuncture, and salivary gland tissue transplantation.

Over-the-counter and prescription salivary substitutes (or mouth-wetting agents) may provide temporary relief of discomfort. Since the duration of relief from these products

is limited, they are most useful when administered prior to bedtime or before speaking. Product selection should be based on personal preference. Products are available as lozenges, rinses, swab sticks, gels, sprays, and denture reservoirs. Saliva substitutes may be based on different components (glycerin and lemon, carboxymethylcellulose, or mucin).[86] The pH of all products used topically should be neutral or alkaline, as acidic products carry an increased risk of dental demineralization and tissue irritation. If glycerin and lemon products are used they should be used with caution in dentate patients because excessive use of lemon salivary substitutes can lead to enamel erosion.[86] The impact of added enzymes to mouth-wetting agents has not been shown to affect health-related outcomes, but comparative studies of preference-of-product show good patient acceptance.[111,112] Patients should be educated to avoid commercial mouth rinses that contain alcohol, which may further irritate and dry out the oral mucosa. Topical anesthetics and analgesics may alleviate pain and antiinflammatory agents may reduce irritation.

Meticulous oral hygiene including brushing (twice a day) and flossing will prevent infection and support dental integrity. For patients at high risk of dental and periodontal disease, the daily administration of fluoride gels through custom-made vinyl trays is recommended to maximize medication delivery.[93,113] If saliva cannot be stimulated, providing dentate patients with a calcium and phosphate source through supplements is required to supply needed building blocks of remineralization. Frequent dental appointments should support a healthy diet, oral hygiene, and early dental interventions when indicated.

Excess Mucous/Secretions

Thick/sticky saliva is a common complaint among patients with head and neck cancer who are undergoing either surgery or RT-based therapy. Surgery may affect saliva function and manipulation by impacting tissue movement and dysphagia due to postsurgical fibrosis that may affect saliva secretion and swallowing. Patients treated with RT often complain of excess "thick secretions" that may be stringy, hard, and difficult to clear. Thick secretions usually develop toward the end of the course of RT and generally last for weeks to months after treatment but may persist long term (6 months).[114] Excessive saliva is most commonly due to due to dysphagia, odynophagia, or tumor and local oral irritation due to inflammation. Altered swallowing function may result in symptoms of excessive secretion due to difficulty or limited swallowing of the saliva. This may result in pooling of secretions, frequent cough, and the increased potential for aspiration. Immediately after tracheostomy, many patients will have excessive secretions; suctioning usually resolves this problem and over time the secretions diminish.

The management of excess or thick secretions varies based on the cause and can be difficult to treat (especially in patients undergoing RT) (Table 8). Patients should be encouraged to maintain adequate hydration to help thin secretions. Humidification with warm air may help to loosen secretions and ease expectoration. Secretions tend to be worse in the morning after they have pooled and thickened in the pharynx overnight. Sleeping with the head of the bed elevated may therefore decrease pharyngeal pooling and aid clearance. A hot steaming shower in the morning may also help to loosen secretions. Carbonated beverages and oral rinsing with bicarbonate solutions may help to break up secretions through effervescent mechanical disruption. Suction may be prescribed but is usually not effective in this group of patients.

Pharmacologic agents may be administered to ease symptoms related to thick secretions; however, some patients do not tolerate the resulting exacerbation of xerostomia. Transdermal scopolamine, hyoscyamine, and atropine have been used with some success. For some patients, stimulation of serous secretions by taste, mechanical stimulation, and sialogogues may help thin secretions. Mucolytic agents such as guaifenesin and n-acetylcysteine may decrease the viscosity of secretions.[115] Finally, patients who develop severe coughing or gagging due to secretions may require a cough suppressant. In some patients with excess thick secretions, medications that cause hyposalivation may improve comfort by decreasing the volume of mucous secretion.

Dental/Periodontal Complications

Dental Demineralization and Dental Caries

The majority of dental complications that occur in cancer patients may be attributable to changes in saliva production and function. As noted above, this is most problematic in patients with head and neck cancer who undergo RT and in allogeneic HCT patients with hyposalivation due to GVHD. Dental demineralization is thought to be mediated through decreased buffering capacity, the decreased availability of enamel substrates (calcium and phosphate), a shift in the oral flora to cariogenic bacteria (*Streptococcus mutans* and *Lactobacillus* species),[116] and dietary changes.[117,118] Demineralization may progress to rampant dental breakdown, advancing periodontal disease (Fig. 2), and osteoradionecrosis (ORN).[119]

Preventive measures are critical to minimize adverse long-term dental outcomes (Table 9). Underlying risk factors for poor dental outcome should be identified and addressed prior to initiating therapy. These include poor prior oral/dental health; diseased teeth, soft tissue, or bone; mineralization status and risk of salivary dysfunction; microbial risk; and dietary risk. Diseased teeth, soft tissue, or bone should be treated prior to initiating cancer therapy.

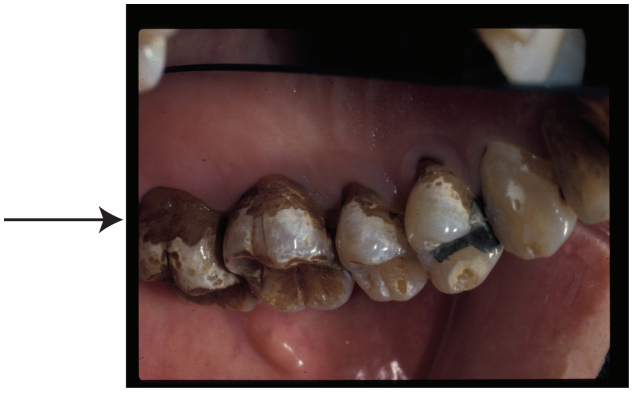

FIGURE 2. Clinical Photograph of the Upper Left Dentition in a Patient One Year After Treatment of Head and Neck Cancer. This photograph shows rampant demineralization of all tooth surfaces and stained tooth structure, with loss of structure (cavitation) noted along the gum margins and cusp tips of teeth.

This is particularly important in patients with head and neck cancer who are undergoing RT. However, dental restoration is difficult and may be ineffective unless the disease process can be controlled.

Calcium, phosphate, and fluoride are necessary for remineralization but if resting saliva is absent or reduced, then it is important to supply these minerals through mouth care products. In high-risk dental patients, ongoing prevention compliance is important through the use of custom fluoride trays (at least 5 days a week, 5-minute applications). In the event of poor compliance, fluoride can be delivered by high-potency brush-on neutral sodium fluoride (1.1%), stannous fluoride, and fluoride varnishes; however, there are no comparative studies of the effectiveness of the various approaches compared with the use of fluoride carriers. Management requires good oral hygiene and the use of agents that decrease cariogenic flora including chlorhexidine, fluoride, and xylitol.[120-122] Many patients often require frequent high-calorie drinks, which increases their caries risk. In these patients, high-calorie liquid supplements are best taken at meals and good oral hygiene is needed to reduce cariogenic bacterial flora and to reduce exposure of the teeth to the sucrose contained in these products. Diet is also an important factor. Milk-based foods should be favored as they decrease the risk of caries, whereas simple sugars, which increase caries risk, should be avoided.

Periodontitis

Chronic periodontitis has been shown to be progressive following RT, with changes in the clinical attachment level observed in 70% of patients.[123-127] Loss of periodontal attachment of the teeth is directly related to the RT field and has been shown to be greater when the jaws are included in the irradiated area.[128] Therefore, periodontal status should be evaluated prior to and after RT to maintain periodontal health in irradiated patients.[125,127,129]

Oral Infections

Oropharyngeal Candidiasis

Oropharyngeal candidiasis is common during cancer care. It is a major cause of morbidity in patients with head and neck cancer and in patients who are myelosuppressed and immunosuppressed. Oropharyngeal candidiasis can result in pain, dysgeusia, anorexia, malnutrition, and esophageal infection leading to dysphagia.[130] Local treatments are recommended as first-line therapy for milder forms of candidiasis. In the setting of local therapy, products that provide prolonged contact time and are not sweetened with sucrose may result in successful prevention and management with a low risk of oral/dental complications.[131]

For myelosuppressed patients, prevention with fluconazole has become standard. The addition of topical antifungals to systemic prophylaxis has been shown to reduce oral colonization, which can lead to a reduced risk of subsequent local and systemic infection (Table 2).[132] Oral candidiasis is most often caused by *Candida albicans*, but increasing cases of *Candida krusei*, *Cronobacter dublinensis*, and other species that may increase resistance to fluconazole have been recognized. These cases may be managed with an increased dose, a change in antifungal treatment, and the addition of topical agents. Amphotericin B and new classes of antifungals including echinocandins may be used in patients with resistant infection. Although other fungal organisms, including *Aspergillus*, *Mucorales*, and *Histoplasma*, may cause head and neck infection, these are uncommon in oral sites. Whenever possible, the management of underlying risk factors such as hyposalivation may facilitate management and reduce the risk of chronic or recurrent infection.

Viral Infections

Herpes viruses have general characteristics in common: primary infection often resulting in latent infection in regional ganglia and in salivary glands with a risk of secondary viral reactivation. Orofacial infection by herpes viruses is common among immunocompromised patients.[133-136] Local/regional infection can lead to systemic infection with encephalitis in patients treated with HCT and/or those who are myelosuppressed.

TABLE 9. Topical Prevention of Dental Demineralization and Caries

PREVENTATIVE AGENTS
Fluoride: 1% to 2% viscous in carriers, 1.1% toothpaste brush-on, 5% varnish, 0.25% to 0.5% rinse
CaPO4: topical brush-on, rinse
Chlorhexidine gluconate rinse 0.12%, gel 0.2% (carriers)
Xylitol rinse, gum, or wafers

CaPO4 indicates calcium phosphate.

Recurrent herpes simplex viruses 1 and 2 have not been shown to reactivate in patients with head and neck cancer after RT,[137] but these viruses are commonly activated after chemotherapy for leukemia and lymphoma and during HCT, leading to the routine use of prophylaxis in seropositive patients. Viral shedding in saliva occurs in the majority of seropositive patients undergoing myelosuppressive chemotherapy. In immunocompromised patients, atypical clinical presentations occur with more extensive or aggressive lesions that may involve keratinized and nonkeratinized sites in the oral cavity.[138] Herpes virus prophylaxis is effective but does not prevent all viral lesions. These may be effectively managed by increasing the dose to therapeutic levels or changing to other antivirals for resistant infection (Table 3).

Herpes zoster commonly affects immunocompromised patients or patients aged older than 50 years. It is characterized by unilateral pain and vesicle formation along nerve distribution, which extends beyond the dermatome in immunosuppressed and myelosuppressed patients. Varicella zoster virus reactivation may precede the diagnosis of underlying cancers such as lymphoma. It may also reactivate following cancer chemotherapy or HCT. Preventive therapy during HCT includes vaccination and antiviral prophylaxis.[139]

Cytomegalovirus, originally isolated in the salivary gland, may cause mononucleosis-like symptoms including pharyngitis, lymphadenopathy, and fever. In myelosuppressed patients, chronic ulceration of the GI tract (including the oral mucosa) can also occur. Cytomegalovirus is latent in the salivary gland.[134]

Human herpesvirus 6 (HHV-6) may cause oral and systemic infection during HCT and has been associated with aphthous-like lesions in a subset of patients. HHV-6 is thought to be transmitted via contaminated saliva and is present in the saliva of a large proportion of the healthy adult population.[140,141] In adults, primary infection with HHV-6 can present as a mononucleosis-like illness. In immunocompromised patients, HHV-6 reactivation can cause serious systemic disease including encephalopathy.[141] Recent, although initial reports, show an association between HHV-6 and squamous cell carcinoma in conjunction with other carcinogens.[142,143] HHV-7 is closely related to HHV-6. It establishes latency in macrophages and T-lymphocytes and reactivates frequently with viral shedding in saliva. The presentation is similar to that of HHV-6.[144,145]

Epstein-Barr virus (EBV) may cause local and systemic infections, and benign and malignant disease in the orofacial region. This includes infectious mononucleosis, oral hairy leukoplakia (OHL), nasopharyngeal carcinoma, B-cell lymphoma, Burkitt lymphoma, and posttransplant lymphoproliferative disorders (PTLD).[146] EBV may cause ulcers, lymphoproliferative syndromes, or OHL in immunosuppressed patients and following HCT.[147] OHL is a benign lesion that is a marker of immunosuppression and has been reported in HCT patients. The lesions present as white, vertical, corrugated patches located primarily on the lateral borders of the tongue.[148] Lymphomas and PTLD may present as a swelling and/or ulcer of the oral cavity and orofacial region. Nasopharyngeal carcinoma may present with orofacial pain, limited jaw movement, cervical lymphadenopathy, and nasal symptoms such as stuffiness and nosebleed.[149]

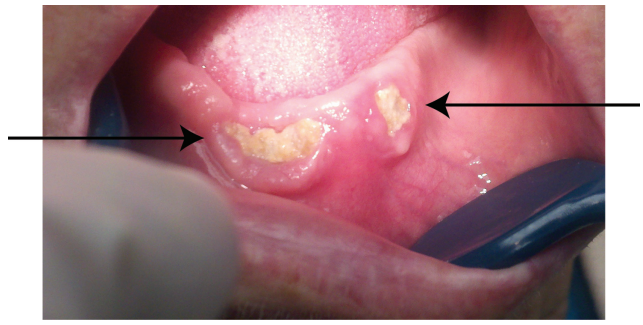

FIGURE 3. Osteoradionecrosis With Exposure of 2 Sites of Bone in the Anterior Aspect of the Mandible. These lesions followed probable denture trauma with resulting necrosis in a patient after radiation therapy for cancer in the floor of the mouth. The chronicity is suggested by the elevated margins of the lesion. There was no significant erythema noted at the margins and no exudate. The lesions were tender to pressure.

The diagnosis of herpetic lesions may be based upon clinical appearance and the location of lesions in seropositive patients, although atypical presentation and cases related to cytomegalovirus, EBV, and HHV-6 may require biopsy followed by immunostaining or polymerase chain reaction.[138] For seropositive HCT patients, prophylaxis consists of oral valacyclovir or acyclovir, and if reactivation is confirmed, therapeutic doses may be provided. Valacyclovir, which has better absorption than acyclovir, may be used for prophylaxis.[136,150] For resistant infection, ganciclovir or foscarnet may be provided. Cytomegalovirus can be managed with valganciclovir, ganciclovir, foscarnet, and cidofovir.[151]

Osteoradionecrosis

ORN of the jaws is a delayed injury caused by the failure of bone healing following RT for head and neck cancer (Fig. 3).[152-154] It may occur in approximately 5% of patients. ORN most commonly affects the mandible and is staged according to the treatment indicated[155] or by lesion size and symptoms (Table 10).[117,156] Lesions surrounded by attached/keratinized tissue appear to have a better prognosis, while those involving cortical bone may progress to pathologic fracture and oral-extraoral/oral-antral fistula. Severe ORN is debilitating and can compromise quality of life and functional prognosis.

Risk factors for ORN include RT, oral surgery, time elapsed between extractions and RT, presence and progression of dental and periodontal disease, association of the tumor with bone, and the high-dose volume of

TABLE 10. Staging Systems for Osteoradionecrosis

AMERICAN ASSOCIATION OF ORAL AND MAXILLOFACIAL SURGEONS	
Stage 0	Nonspecific findings (eg, no exposed bone, radiographic change, pain)
Stage 1	Exposed asymptomatic bone, no evidence of infection
Stage 2	Exposed bone, erythema, symptomatic (eg, pain) evidence of infection
Stage 3	Exposed bone, pain and infection, extending beyond alveolar bone (fistula); pathologic fracture possible
BC CANCER AGENCY STAGING OF OSTEONECROSIS	
Stage 1	Resolved/healed asymptomatic osteonecrosis, mucosa intact, intact mandible
Stage 1a	No pathologic fracture
Stage 1b	Pathologic fracture; reconstructed
Stage 2	Chronic persistent, asymptomatic, nonprogressive osteonecrosis; exposed bone; asymptomatic
Stage 2a	No pathologic fracture
Stage 2b	Pathologic fracture
Stage 3	Active progressive symptomatic osteonecrosis; exposed bone, pain, pathologic fracture/fisular, ostolysis to inferior border of the mandible
Stage 3a	No pathologic fracture
Stage 3b	Pathologic fracture

the horizontal ramus of the irradiated mandible.[157,158] Comorbidities that may increase the risk of ORN include diabetes and collagen vascular disease, tobacco/alcohol abuse, and poor nutrition.

The primary approach to the management of ORN is prevention with comprehensive dental evaluation and treatment prior to RT (Table 11). Managing ORN involves managing the comorbid factors; optimizing oral hygiene; controlling infection with the use of chlorhexidine rinses and systemic antibiotics; nutritional support; devitalized tissue removal (sequestrectomy) and symptom management; and reduction of dental extractions through preventive dental management, endodontics, and crown amputation.[117,156]

Hyperbaric oxygen combined with limited surgery has been shown to offer cure in 18% to 90% of patients, although conflicting support for hyperbaric oxygen is seen in the literature.[118,159-161] Pentoxifylline and vitamin E have also been assessed in phase 2 studies of ORN with good results.[162] A protocol including pentoxifylline, vitamin E, and clodronate has also been suggested to reduce RT-induced fibrosis and bone destruction and to stimulate osteogenesis via the antioxidant pathway.[159] For patients with refractory ORN, microvascular surgical techniques and tissue transfer can be provided if the area of necrosis can be encompassed in a surgical field to which a bone and tissue transfer such as radial bone and vascular tissue transfer can be accommodated. For patients with osteonecrosis caused by bone antiresorptive therapies, bisphosphonates and a new class of osteoclast inhibitor known as denosumab can be used. While denosumab may cause a similar or possibly increased risk of necrosis, the necrosis has a potentially better response to therapy than that seen with bisphosphonates, and it is easy to administer with a low level of severe toxicities.[161]

Management approaches have been based on a modified approach of management for ORN and include reduction in bacterial load using chlorhexidine rinses; antibiotics in the presence of secondary infection; smoothing and nonsurgical removal of sequestrate; and, less commonly, surgical management in the case of progressive disease. Other medical approaches currently under investigation include hyperbaric oxygen therapy, pentoxifylline and vitamin E, platelet-rich plasma, bone morphogenic protein therapy, and osteoblast stimulation.[163,164]

Orofacial Pain

Orofacial pain may be caused by cancers or cancer-related therapy. The incidence of pain varies widely based on the patient population and the type of treatment. For patients with head and neck cancers, 85% report oral pain at the time of diagnosis.[165,166] Pain secondary to oral cancer may be caused by mass effect, pressure, ulceration, inflammation, and invasion.[166,167] Pain that occurs during or after treatment can be due to acute and/or late effects of treatment.[166] Patients with oral cancer rate pain as the worst symptom experienced as a result of cancer therapy, leading to a marked decrease in quality of life.[165,168-170]

It is intuitive that head and neck cancer surgery results in acute postoperative pain requiring the aggressive use of analgesics, including opioids. In addition, it is expected that patients who present with significant tumor-related

TABLE 11. Treatment of Osteoradionecrosis

ACTION	TYPE/USE
Topical antiseptics	Chlorhexidine, povidone iodine
Antibiotics	Penicillin, quinolones, clindaymcin, tetracycline (doxcycycline, minocycline), macrolides, cepahlosporins, metronidazole, and antibiotic rotation (in the presence of signs of infection)
Symptom management	Hyperbaric oxygen, pentoxifylline/vitamin E, clodronate
	Head and neck cancer: sequestrectomy, free vascular flap
Surgery	Sequestrectomy, bone recontouring/smoothing
	Head and neck cancer: free vascular transfer of bone/soft tissue
Other	Ozone therapy, teriparatide, growth factors (eg, bone morphogenic protein)

TABLE 12. Management of Oral Pain

MANAGEMENT
Regular pain assessment and sleep evaluation
Prior to cancer treatment: dental management, oral stabilization of acute/chronic conditions, prevention
Foundations of care: oral hygiene, diet, prevention, bland rinses, frequent oral assessment
Topical treatments: bland rinses, ice, coating agents, local anesthetics/antihistamine, topical analgesics (opioids, tricyclic)
Mixed coating and local anesthetic agents
Level 1: topical and nonopioid analgesics ± adjuvants
Level 2: topical and level 1 and mild opioid analgesics ± adjuvants
Level 3: topical and level 1, powerful opioids and adjuvants; nutritional support
Adjuvants: selective serotonin reuptake inhibitors, antihistamines, benzodiazipines, muscle relaxants, antiseizure medications, physiotherapy, cognitive therapy, acupuncture
Baseline pain control and plan for incident (functional or breakthrough) pain (especially for head and neck cancer and oropharyngeal pain)
Consider avoiding moderate-strength opioids and use the lowest dose and schedule of powerful opioids for cancer pain

pain may find relief after surgical resection. The postoperative pain experience is characterized by nociceptive pain persisting for 1 to 2 months with a gradual improvement over time.[168,171,172] Unfortunately, surgery causes nerve and tissue damage that may result in chronic pain syndromes. Approximately 50% of patients who undergo mandibular bone resection experience regional hyperalgesia or allodynia,[173] with pain persisting in up to 90% of patients.[174] Chronic postoperative musculoskeletal pain, a commonly encountered syndrome, may affect the shoulder (31%-38.5%), neck (4.9%-34.9%), temporomandibular joint (TMJ) (4.9%-20.1%), oral cavity (4.2%-18.7%), and the face and other head regions (4.2%-15.6%).[171,175] Postoperative pain may be exacerbated in those patients treated with adjuvant CRT.[173]

The most common and distressing cause of pain in patients who receive RT for head and neck cancer is mucositis.[176,177] Combined CRT further increases the frequency, severity, and duration of mucositis.[178-181] Mucositis pain usually begins within 3 weeks of the start of RT, peaks at weeks 5 through 7, and persists for several weeks to months following therapy.[182-185] Mucositis pain interferes with daily activities in approximately one-third of patients,[54,77,178,179,186,187] affecting mood in 50% to 60% of these patients.[185]

Opioid analgesics represent the primary medication for the management of pain due to cancer and its treatment. However, opioids do not provide complete relief and many patients experience high levels of pain during cancer therapy, particularly in the oral cavity and oropharynx. Incident and breakthrough pain are also common. As pain persists, it is necessary to increase opioid doses and side effects become an increasing concern (sedation, dysphoria, nausea, constipation). Modification of the World Health Organization analgesic ladder has been recommended in oncology to move from topicals and nonopioids (Step 1) to the lowest effective dose of the strong opioids (Step 3) (Table 12). Topicals and nonopioids should be continued when using opioids as these may promote lower doses or a shorter duration of systemic opioids.

Management should address nociceptive and neuropathic pain to achieve improved pain management,[166] and treatment should be directed toward the pathophysiology of cancer pain; with this approach, it is estimated that patient satisfaction with pain management can be achieved 70% to 97% of the time.[188] Adjuvants are critical in achieving successful pain management and may address the neuropathic components of pain. Individual conditions causing pain should be addressed. For example, if TMJ disorders develop and myalgia/myospasm are present, physical therapy and muscle relaxants may be of value. Dental pain that is coincidental must be diagnosed and the cause addressed. Current recommendations include opioid analgesics to address nociceptive pain. Cannabinoids have also been shown to provide pain management in patients with cancer.[189,190] Neuropathic pain is typically difficult to manage and is approached primarily with the use of centrally acting antidepressants and anticonvulsant medications, along with biopsychosocial treatment and systemic analgesics (Table 13).[166,191-193]

Trismus

Trismus is the inability to normally open the mouth. It can result from high-dose RT exposure to the TMJ region, including the masseter/pterygoid muscles.[194] Trismus also occurs following head and neck surgery in combination with RT or CRT. Early intervention can help to prevent or minimize many of the consequences of RT-induced fibrosis. Active/continuous motion devices have been shown to be effective, and should be provided as preventive protocols because once established, trismus is difficult to manage. The least expensive option is the use of tongue depressors, which have been used for many years to mobilize the jaw, although there is a risk of excessive load application to the teeth and their effectiveness is not documented. Active therapy using devices that apply

TABLE 13. Managing Neuropathy

ACTION	TYPE
Local	Topical when localized
Systemic	Anticonvulsant drugs, tricyclics, serotonin reuptake inhibitors

resistance to the jaw during exercising prevents trismus and may increase the range of motion early in its onset. Active/passive exercise should be initiated as soon as possible following surgical procedures in the head and neck when posttreatment fibrosis may impact the range of jaw movement, and during RT of the head and neck when the pterygoid musculature is included in the RT field. Once restriction has been established, the fibrosis causing the restriction is difficult to mobilize. Pentoxifylline has been considered to prevent trismus and botulinum toxin has been discussed to treat established trismus.

Taste and Smell Disorders

Biology

Taste sensation is based on 5 basic qualities: sweet, bitter, salty, sour, and umami.[195] Umami is associated with a desirable flavor, enjoyment, and pleasure and promotes interest in eating. Taste is mediated by specialized epithelial cells distributed throughout the oral cavity, oropharynx, larynx, and upper one-third of the esophagus. Stimulation occurs when a ligand binds to the extracellular domain of a taste receptor, leading to activation of G proteins, which leads to the generation of second messengers and gating of transient receptor protein ion channels causing nerve depolarization.[196] From the taste buds, sensory fibers conduct afferent signals to the brain via cranial nerves V (trigeminal), VII (facial), IX (glossopharyngeal), and X (vagus), which synapse in the rostral aspects of the solitary tract of the medulla and project via the thalamus to the postcentral gyrus-facial area and olfactory cortex.[197]

Taste Alterations in Cancer

Taste disorders are common in cancer patients. Their frequency and severity are dependent on the cancer and its treatment. Common causes of taste alterations include environmental factors within the oral cavity (oral infection, oral hygiene, recent oral intake), surgical interventions, medications, RT damage to taste buds and salivary glands, and GVHD. Hyposalivation may reduce taste due to limited delivery of tastants to the receptors.[198-201] Oral, dental, and oropharyngeal pathosis and damage to the cranial nerves may affect taste function. Upper aerodigestive tract conditions such as sinus and nasopharyngeal disease may result in taste changes. In addition, changes in touch and temperature sensation mediated by the trigeminal nerve and smell mediated by the olfactory nerve may alter taste perception. Malignant diseases in the head and neck often cause taste changes due to tissue necrosis, oral bleeding, and/or postsurgical wounds.[202] Chemotherapy and targeted therapeutics may affect taste by direct taste receptor stimulation due to secretion in saliva or via gingival crevice fluid (patients frequently describe a metallic or chemical taste when chemotherapy is delivered), and taste change may persist after drug clearance due to damage to the taste buds.[203]

Taste disorders are common in patients with head and neck cancer. They may occur after surgery or dental treatment or from nerve damage that occurs during local anesthesia, surgical manipulation,[204,205] or rigid endoscopy.[206] Postsurgical taste changes are ipsilateral to the procedure and usually resolve without treatment. RT results in taste disorders in 75% to 100% of patients.[201,202,207] The incidence and severity of taste alterations depends on the treatment field.[208] All basic tastes and umami are affected during RT to the oral cavity.[207] Sweet sensation is typically lost first, resulting in increased bitter and salty taste. This is followed by general abnormal taste and a reduction in taste acuity.[199,201,207,209-213] Umami declines during the third week of RT. After RT, taste sensitivity usually recovers within several months after the resolution of mucosal damage.[184,209,211,213-218] However, reduced taste sensitivity may continue indefinitely. Persisting taste loss may be due to damage to taste receptors[214,219] and hyposalivation. Although umami taste may improve by week 8, recovery may be delayed and in some cases may not be restored. Loss of umami taste may be important in diet and oral nutritional intake because it affects interest in eating (enjoyment, pleasure). Loss of umami may therefore have the strongest correlation with decreased quality of life.[212]

Taste changes are common in HCT patients, and GVHD has also been associated with taste reduction and taste change.[202,220] Patient often report persistent salty and sour taste alterations after treatment, which may resolve after 12 months.[202,220-223]

Assessment

Evaluating taste alterations should begin with a history of the complaint, recent use of medication and nutritional supplements, past medical history including tobacco and alcohol use, dental history, and oral intake. A detailed head, neck, and oral examination should be conducted including assessment of salivary gland function and olfactory and taste testing.[207,224-228] The use of PROs including OMWQ,[66] PROMS,[67] and VHNSS,[68] as discussed above, as well as the EORTC Quality of Life (QLQ-C30) questionnaire with an addendum developed to assess oral symptoms and function,[229] can provide rapid evaluation.

Management

Management of taste alterations (Table 14) begins with the identification and treatment of reversible causes. Supportive measures may be applicable to all patients, regardless of the cause. For example, chewing gum or candy may mask unpleasant taste and provide relief in most patients.

TABLE 14. Managing Taste Disorders

MANAGEMENT
Manage xerostomia
Manage oral infection
Maintain oral hygiene
Zinc supplementation
Medication trials clonzepam, gabapentin, dronabinol
Tastants: umami flavors, increased flavor (salt, sweet)

Patients should also be counseled to increase the taste or flavor of food by adding seasoning, rotating their diet, or increasing umami flavoring.[230]

Advances in RT can spare salivary glands and taste receptors in part of the oropharynx from exposure to high doses of radiation. Parotid-sparing IMRT has been associated with a more rapid and more consistent recovery in eating, which may reflect recovery in saliva and taste.[216] Radioprotectors such as amifostine may also contribute to taste maintenance.[231-234]

Zinc supplementation has shown variable outcomes in taste following cancer therapy. A small trial comparing zinc sulfate (45 mg given 3 times a day) with placebo taken during RT reported an improvement in taste in the study group.[235] Another trial comparing zinc sulfate (45 mg/day) with placebo in 169 patients during RT found fewer patients in the zinc group reported taste changes compared with the placebo group (73% vs 84%), but these results were not significant.[213] Zinc supplements may be considered in patients with persistent taste complaints.[209]

Clonazepam may affect taste sensation.[236,237] Topical clonazepam has been used in the management of neuropathic oral conditions and anecdotal data in taste and smell complaints have been published.[238,239] Topical application, while relatively benign, may be a problem for patients with little or no saliva. Using a clonazepam solution may be acceptable but has not been tested. Systemic drug delivery also requires further study in taste management.

Dronabinol (tetrahydrocannabinol) has been examined in a small, double-blind, short-duration trial. Compared with placebo, patients receiving dronabinol reported improved taste (55% vs 10%), increased appreciation of food (73% vs 30%), and a statistically significant increase in appetite.[240]

Recurrent or Second Cancers

The patients at highest risk of oral and other head and neck cancers are those who have had prior head and neck cancer or upper aerodigestive tract cancer, and those who are chronically immunosuppressed following HCT. Patients with human papillomavirus (HPV)-associated oropharyngeal cancer require thorough assessment because it is not known if patients with prior HPV-induced oropharyngeal cancer are at an elevated risk for new or recurrent cancers. Tumors and cancer therapy can suppress the immune response.[241] EBV, HPV, and HHV-8, are associated with PTLD, squamous cell carcinoma, and Kaposi sarcoma, respectively, particularly in immunosuppressed patients. Long-term immune deficiencies are also common following solid organ transplant and HCT.[242-244] Vigilance is therefore required for the early detection of recurrent or new second primary cancers.

Systemic Manifestations of Poor Oral Health

Oral conditions may impact systemic health due to altered or reduced nutrient, caloric, vitamin, and mineral intake and may have systemic effects on energy levels (fatigue), mood (depression), and cardiovascular health. This impact may also affect survival related to the secondary and systemic effects of locoregional head and neck cancer and its treatment, where excess mortality is seen in patients cured of their tumors.[245] Survivorship in patients following chemotherapy and HCT is an active area of research.

Psychosocial Implications of Oral Health Issues

Oral complications of cancer and cancer therapy affect quality of life in the treatment setting and throughout survivorship. Oral disease can cause significant pain, greatly impact oral function and appearance, and cause changes in mood, resulting in anxiety and depression. Those affected can become socially isolated.[114] Oral function has a direct impact on quality of life and an indirect impact through its effects on energy and nutrient intake, which can result in nutritional compromise. Oral health issues are integral to the survivorship of cancer patients. The impact of head and neck cancer and its complications is dramatically illustrated in suicide risk, which is 4 times higher in survivors of this disease than in the general population and approximately double the rate of all cancer patients. Contributing factors include the primary cancer; physical appearance; difficulty with communication, chewing, and swallowing; poor diet/nutrition; lack of taste; difficulty breathing and hearing; pain; and fatigue.[246]

Conclusions

Although some of the acute oral toxicities of cancer therapies may be reduced, they remain essentially unavoidable. The significant impact of long-term complications requires increased awareness and recognition to promote prevention and appropriate intervention. It is therefore important for clinicians involved in cancer treatment and the follow-up of cancer survivors to be aware of these complications so

that appropriate measures can be implemented in a timely manner. Prevention and management is best provided via multidisciplinary health care teams, which must be integrated and communicated effectively in order to provide the best patient care in a coordinated manner at the appropriate time. ■

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