Late Effects of Cancer and Cancer Therapy on Oral Health and Quality of Life

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Abstract

Persisting and chronic oral complications of cancer therapy are common. Oral complications in cancer survivors are underreported but impact oral function and quality of life. Prevention and management of oral complications in cancer survivors requires interdisciplinary care. The purpose of this article is to review the common oral complications in cancer survivors.

Introduction

Oral complications of cancer and cancer therapy, which arise during and continue following therapy, affect oral function and impact general health and, subsequently, survivors' quality of life. Prevention and management of oral complications are required throughout the course of the disease, from diagnosis, through treatment, and following cancer therapy. The impact of acute oral complications in cancer patients is generally recognized; however, the potential negative impact of late oral health problems on symptom burden, oral function, and overall health are underappreciated. As survivorship continues to rise, there is an increased need to determine the impact of late treatment effects and the most effective means of prevention and treatment.

Head-and-neck cancer (HNC) and therapy for the disease cause acute oral complications that impact quality of life. These complications include mucositis and associated pain, hyposalivation, viscous oral secretions, taste change or taste loss, difficulty with mastication and dysphagia, function of oral prostheses, and affected speech. While patients recover from some of the acute effects of therapy, many experience persisting oral complications that impact oral health, general health, and quality of life.

Prior to cancer therapy, the oral and dental status of the patient must be carefully examined, and any medically necessary dental care must be given to prevent or minimize oral and systemic complications during therapy and survivorship. Following cancer therapy, it is critical for the dental team to understand the prior cancer therapy that may limit dental treatment, ongoing medical management, any comorbidities, and prognosis. This is best accomplished with close communication between oncologists and dentists.

Oral Quality of Life and Symptom Burden

Oral complications during and following cancer therapy depend upon the disease under treatment, the stage and location of disease, the medication(s) and dosage, the schedule of therapy, and any patient comorbidities, including individual susceptibility. Radiation and chemotherapy may affect oral tissues, oral mucosa, salivary glands, neurosensory function, dentition, periodontium, and muscular and joint function.

Advances in the chemotherapy management of malignant disease over the past decade include therapy directed at molecular targets expressed by tumor cells and improvements in surgery, radiation, combined therapies, and supportive care. Induction and concurrent chemotherapy is increasingly incorporated in the management of HNC[1] and may lead to more severe and prolonged effects on oral tissues. Posttreatment chemoprevention and maintenance therapy is under investigation for a number of cancers and may become common in cancer control.

Acute complications may lead to persisting mucosal symptoms that result in chronic neurosensory symptoms; salivary gland dysfunction may also become chronic, thereby increasing the risk of late oral and dental complications. Effective prevention and management of oral mucositis during therapy may reduce the severity of chronic symptoms. Chronic sequelae of radiation include mucosal pain, atrophy, infection, fibrosis, salivary gland dysfunction, possible change in taste, and an increased risk of dental and periodontal disease, with risk of mucosal and bone necrosis. The sequelae of chemotherapy include mucosal atrophy/inflammation, neurosensory change (taste and/or pain), salivary gland dysfunction, and impairment of craniofacial and dental growth and development in children.

Quality of life is affected in patients with late effects of cancer therapy. Quality of life in HNC patients more than six months postradiation therapy identified common persisting symptoms, including dry mouth (92 percent), change in taste (75 percent), and difficulty eating (40 percent).[2] The majority of patients experienced pain (58 percent), and 17 percent rated pain as moderate or severe with one-third reporting that the pain interfered with daily activities. Oral health outcomes were reported in 357 HNC patients who were followed for up to five years after cancer therapy and who had reported that dental problems, such as trismus, xerostomia, and thick saliva, increased after one year and continued at their last follow-up.[3] Another study assessed patients up to five years posttreatment, identifying dry mouth, thick saliva, speech changes, dental problems, and sleep disturbance that affected quality of life (all $p<.01$).[4] Similar findings in another study showed a gradual improvement in depression and global quality of life over five years.[5] A prospective study of nasopharyngeal cancer (NPC) patients treated with radiation therapy up to 24 months found poorer global health, fatigue, loss of appetite, and dysphagia (all $p<.01$); xerostomia and thick saliva ($p<.001$); taste change and dental problems ($p<.05$); and pain and emotional function ($p<.005$).[6] These findings were confirmed in another study.[7]

Hyposalivation

Saliva is a complex secretion that provides oral lubrication and wetting, and allows food molecules to reach taste receptors and to develop a bolus for deglutition. Dietary shifts are seen in HNC patients following treatment, with increased consumption of high-carbohydrate foods of moist or pureed consistency. Saliva also possesses antimicrobial and remineralizing effects, as well as growth factors that may be important in tissue repair. Saliva is necessary to maintain dental integrity by providing calcium and phosphate, maintaining pH, and effecting oral flora.

Several approaches have been examined to reduce hyposalivation in cancer patients. Amifostine (WR-2721) is a free radical scavenger approved to prevent hyposalivation in patients undergoing radiation therapy for HNC. A recent meta-analysis demonstrated that amifostine resulted in a decrease in acute and late hyposalivation.[8] Salivary gland transfer out of the radiation field has been discussed; however, the use of advanced radiation technology, such as intensity-modulated radiation therapy (IMRT) to spare salivary tissue, has become standard in HNC radiation therapy, limiting the consideration for this surgical approach. Measurements of salivary flow after IMRT, where the major glands are spared high-dose exposure confirm less severe hyposalivation and improved quality of life.

Sialagogues, such as pilocarpine, cevimeline, and bethanechol, may improve hyposalivation in patients with residual salivary gland function.[9] IMRT with salivary gland sparing may allow stimulation of residual gland function with sialagogues. Products for mouth wetting (salivary substitutes) should be considered for palliation when saliva production cannot be stimulated. Despite these products, patients often rely on carrying water for frequent mouth wetting. There has been no assessment of saliva viscosity and related function, and while mucolytics such as guaifenesin and acetylcysteine can be considered for patients with thickened secretions, their effectiveness is not well documented.

Chemotherapy in breast cancer patients has been shown to cause mucosal lesions, affect salivary function leading to a microbial shift to cariogenic and fungal flora, and cause taste change that may persist for more than six months.[10] Decreased phosphate and secretory IgA also is reported. In stem cell transplantation, hyposalivation persists after six months and at three years.[11] In addition, medications commonly used in supportive care of chemotherapy patients (e.g., antiemetics, analgesics, antianxiety/antidepressants) may cause hyposalivation. Xerostomia and sore mouth are seen in patients who have undergone stem cell transplantation, with more frequent and severe symptoms in myeloablative transplant compared to reduced-intensity conditioning.[12]

Dental Health

Oral hygiene may be compromised following cancer therapy, due to limited intraoral access, increased plaque accumulation, and microbial shifts associated with hyposalivation. Periodontal bone loss is increased in people with hyposalivation and in fields of high-dose radiation therapy. Progressive periodontal disease and periodontal management within the high-dose radiation field represent a risk factor for osteonecrosis.[13] In addition, hyposalivation limiting remineralization and diet change lead to risk of dental demineralization that may progress rapidly, causing rampant tooth destruction. Buffering capacity, mineral exposure, and antimicrobial factors are affected. Fluoride shifts the equilibrium toward deposition of calcium in enamel, and it has antibacterial effects that may be important in protecting against dental damage.

Prevention requires excellent oral hygiene and a noncariogenic diet.[13] The bacterial component can be managed with chlorhexidine rinse. Remineralization of teeth can be favored with the use of fluoride and by providing calcium and phosphate in the oral environment (remineralizing products).

Oral Pain

Oral pain may be due to tumor effects and associated with cancer treatment. Recurrence of pain following treatment can be associated with cancer recurrence. While oral pain severity is expected to decrease following cancer therapy, low-intensity

pain following treatment is reported in the majority of patients at follow-up between six and 12 months and likely continues indefinitely.[14] The persistence of mucosal sensitivity may be due to atrophy of the mucosa, mucosal neuropathy, and hyposalivation. Chemotherapeutic agents may result in peripheral neuropathy, including orofacial neuropathy. Postradiation and postsurgical fibrosis and postsurgical defects in the jaw may lead to change in function and promote temporomandibular disorders (TMDs) that may be compounded by surgical complications and anxiety or depression.

Taste Alterations

Taste is related to sensory mechanisms, including taste, texture, temperature, and smell, that are perceived when placing food or other agents in the mouth. Taste is composed of five basic qualities: sweet, bitter, salty, sour, and umami. Umami is the taste sensation associated with pleasure or desirable flavor, and loss of umami has been suggested to have the strongest correlation with impact on quality of life.[15] Taste is mediated by epithelial receptors, is impacted by hyposalivation, and may be affected by microbial shifts and retention of food in the mouth. Additionally, it is affected by oral hygiene, dental and periodontal disease, mucosal infection, and diet.

Reduced or abnormal taste occurs in up to 100 percent of HNC patients during and following radiation therapy with or without chemotherapy.[13] Recovery of taste is variable, in some studies improving in two to six months following cancer therapy, although taste change may continue indefinitely. The impact of taste change includes reduced interest in food, leading to reduced caloric and nutrient intake. Similar findings are noted in stem cell transplantation, with more severe symptoms in myeloablative transplantation as compared to reduced-intensity conditioning. Temporary change in taste occurs due to solid-tumor chemotherapy, such as that received by breast cancer patients. Chemotherapy may be secreted in saliva, resulting in taste change until the drug is cleared; however, taste change may continue due to direct damage to taste receptors. Tissue necrosis, oral bleeding, and postsurgical wounds may contribute to taste change, halitosis, and altered smell. Taste disorders may also follow oncologic surgery, which may damage the lingual branch of the glossopharyngeal nerve or the chorda tympani.

IMRT may spare salivary glands and thus reduce the impact of radiation therapy on taste. However, low-dose irradiation of wider areas of the oral cavity may impact taste. Radioprotectors, such as amifostine, may have utility in affecting taste by protection of tissue or indirectly by maintenance of saliva.[16] Dietary counseling/modification, addition of seasoning to food, avoidance of unpleasant foods, and food rotation are recommended. Local infection and hyposalivation should be managed if possible. Zinc supplementation may affect taste dysfunction.[17,18]

Postradiation Fibrosis

Radiation therapy and surgery may lead to limited oral opening, limited mobility of the tongue, and trismus that may affect oral function. Trismus may be defined as a maximum jaw opening of <35 mm and severe trismus as a maximum jaw opening of <25 mm; it is reported in up to 45 percent of HNC patients. Radiation fields that include the masseter and pterygoid muscles are associated with trismus.[19] While IMRT has been expected to be associated with reduced trismus, this is not seen in recent studies. Prevention of trismus may be achieved by modifying radiation therapy fields and by introducing active jaw range-of-motion exercises during radiation therapy. Pentoxifylline, which affects fibrogenic cytokine production, has been shown to improve established trismus[19] but has not been studied for prevention. Established trismus may show limited response to jaw exercising. Botulinum toxin has also been assessed for the management of trismus, although its benefits are not clearly documented.

Infection

Local oral infections and increased risk of systemic infection from an oral source may occur in cancer patients. Reactivation of latent organisms and exacerbation of chronic foci of infection, including dental and periodontal infection, may occur. Cancer therapy may lead to shifts in microbial flora that can lead to infection. Chemotherapy can compromise oral mucosal immune defense mechanisms and reduce antimicrobial functions of saliva; myelosuppression and immunosuppression may lead to exacerbation of preexisting sites of chronic infection or predispose the patient to new infection and increase the risk of systemic infection. Latent herpes simplex virus infections exacerbate when host immune defenses are compromised due to malignant disease or the chemotherapeutic regimens. Management may include prophylaxis for seropositive patients who will become myelosuppressed, or early recognition and use of antivirals.

Hemorrhage

Thrombocytopenia may occur in patients on high-dose chemotherapeutic regimens or due to disease involving the bone marrow. Oral hemorrhage can occur when platelet counts are below 25,000/mm,[3] is more likely in patients with gingivitis or periodontal disease, and may occur in ulcerative oral mucositis.

Neurotoxicity

Some chemotherapeutic agents are neurotoxic (e.g., vinca alkaloids, platinum agents, and taxanes) and may lead to orofacial dysesthesia and pain that can be confused with pulpal disease, causing pain. Some patients may develop dental hypersensitivity following cancer therapy that may be due to dental demineralization and possibly neuropathy. Patients may experience symptomatic relief with topical fluorides and/or desensitizing agents, including toothpaste. Pain experience may be impacted by anxiety, depression, and sleep disturbances associated with cancer or cancer therapy.

Temporomandibular Disorders

Orofacial pain in cancer patients may include TMDs. Postsurgical complications, including mandibular discontinuity defects, posttreatment fibrosis, and clenching and bruxism, may be increased, resulting in orofacial pain. These patients may benefit from oral habit appliances, physical therapy—such as massage, physiotherapy, and/or muscle relaxants—and management of mood change and sleep dysfunction.

Compromised Nutrition

Compromised nutrition may occur due to nausea, emesis, and altered oral function. Oral function may be affected by hyposalivation, taste change, oropharyn-

Table 1. Chronic Oral Complications of Cancer Therapy

Oral Complication	Potential Direct Risk Factors	Potential Indirect Risk Factors
Hyposalivation	Radiation, chemotherapy	Dehydration; medications: anticholinergic, antinausea, antidepressant, antianxiety, antihypertensive, and analgesic drugs
Dental demineralization/caries	Hyposalivation, compromised oral hygiene, microbial shifts, diet change	Antibacterials causing microbial shifts; emesis, reflux
Dental sensitivity	Dentinal hypersensitivity, gingival recession, dental demineralization	Neuropathy
Periodontal attachment loss	Radiation, hyposalivation, oral hygiene, microbial shifts	Individual susceptibility
Mucosal sensitivity	Mucosal atrophy, neuropathy, mucositis, hyposalivation, physical/thermal/chemical trauma	Mucosal infections, reactivation of herpes viruses
Taste reduction/taste change/halitosis	Radiation, chemotherapy receptor toxicity, neuropathy, tumor necrosis; oral hygiene, diet, emesis, reflux	Secondary infection (candida, periodontal disease, hyposalivation)
Viral infection	Herpes virus infection (HSV, CMV, VZV, EBV)	Myelosuppression, immunosuppression
Fungal infection	Hyposalivation, tobacco use, prostheses, antibiotics, steroids	Altered local and systemic immunity, myelosuppression, immunosuppression
Bacterial infection	Poor oral hygiene, antimicrobials, hyposalivation Mucosal atrophy Acquired pathogens	Altered local and systemic immunity, myelosuppression, immunosuppression
Hemorrhage	Oral mucositis, ulceration, inflammation, tumor necrosis; gingivitis/periodontitis Physical trauma, infections (e.g., HSV)	Thrombocytopenia, acquired coagulopathy; decreased clotting factors (e.g., DIC, liver pathosis) Genetic susceptibility
Neuropathies	Surgery, radiotherapy, cancer chemotherapy (e.g., vinca alkaloids, platinum agents, taxanes, other specific drug toxicity)	Anxiety, depression, sleep disorder
Trismus, limited movement of oral tissues	Postsurgical/postradiation fibrosis; sclerosis with graft-versus-host disease	Myelosuppression, anemia, nutritional status, diabetes mellitus, tobacco use; immunosuppression
Temporomandibular disorders	Mandibular discontinuity, tissue fibrosis	Anxiety, depression, sleep disorder
Compromised wound healing	Vascular supply, tissue cellularity; radiation therapy, chemotherapy	Salivary hypofunction, secondary infection
Soft-tissue necrosis, osteonecrosis	Radiation therapy, trauma, bisphosphonate drugs, possible antiangiogenic drugs, tobacco use, trauma	Diabetes, tobacco use, nutritional compromise; immunosuppression, mucosal and salivary gland pathosis
Graft-versus-host disease (post-stem cell transplant)	Unrelated donor, mismatch transplant	Prior mucosal conditions
Recurrent, secondary, or other cancers	Radiation therapy, chemotherapy, regional cancerization, tobacco use, alcohol, viral agents (e.g., HPV, EBV)	Immunosuppression
Compromised systemic health and nutritional compromise	Oral function, dysphagia, hyposalivation, taste change, orofacial and mucosal pain, dental status, necrosis	Infection, nutrient/caloric demand, GI dysfunction
Dental and skeletal growth and development (pediatric patients)	Radiation therapy, chemotherapy, direct tissue toxicity	Hormonal effects on growth and development, stage of dental and skeletal maturation at time of therapy

geal mucositis, orofacial movement and pain, and altered or limited mastication and deglutition due to posttreatment fibrosis. The long-term impact of diet shifts on diet quality may result in macro- and micro-nutrient deficiencies. All factors associated with oral function and oral intake should be addressed in management.

Growth and Development in Children

Radiation therapy and high-dose chemotherapy can impact orofacial and dental development in children. Bone growth may be affected in high-dose radiated tissues. Individuals in whom the hypothalamus is affected may have delayed or altered maturation and sexual development. The possible effects on the dentition of cancer therapy include agenesis and alterations in tooth formation and tooth eruption, morphologic changes in enamel, altered crowns of teeth, and shortened and/or conical-shaped roots. Dental malformations may result in reduced occlusal vertical dimension and mobility of teeth with agenesis of roots. These changes may not be clinically apparent, but may be identified on imaging.

Compromised Wound Healing

High-dose chemotherapy, radiation therapy, myelosuppression, and nutritional status may compromise tissue healing due to local and systemic effects that can affect patients who have undergone dental procedures. In addition to cancer therapy, comorbid conditions (e.g., diabetes mellitus, myelosuppression, anemia, tobacco use, and nutritional compromise) may affect wound healing. These factors influence the treatment chosen following cancer therapy.

Guidelines for dental extractions in oncology are primarily based on expert opinion. General recommendations are:

- Expert and minimally traumatic extractions >10 days prior to radiation therapy or anticipated absolute neutrophil count <500/mm^3; antibiotic prophylaxis may be recommended if neutrophil count is <1,000/mm^3
- Minimal tissue trauma and primary closure of surgical site, if possible
- Platelet support if platelet count is <40,000/mm^3

Halitosis

Halitosis in cancer patients can be caused by tissue necrosis, hyposalivation, mouth breathing, poor oral hygiene, altered diet, infection, and oral bleeding. Treatment is directed at diagnosis and treatment of the cause(s) when possible.

Soft Tissue and Osteonecrosis

Risk for osteonecrosis of the jaws is seen in patients following head-and-neck radiation therapy, and in patients provided bisphosphonates for oncologic purposes and possibly antiangiogenic medications. Mucosal necrosis and bone exposure can be asymptomatic or minimally symptomatic and, therefore, not recognized until progressive and symptomatic, resulting in limited recognition and underdiagnosis. Comorbid risk factors include diabetes, immunosuppressive therapy and immunosuppression, local trauma, and tobacco use. Prevention is the primary goal, and pretreatment dental management and preventive dental care to reduce local tissue irritation and dental disease following treatment are critical.

In radiation-associated osteonecrosis, management may include antimicrobials, hyperbaric oxygen, sequestrectomy, and surgery with vascularized free flaps in advanced cases.[20,21] Other adjunctive approaches, including the use of pentoxifylline and vitamin E, are in study. In bisphosphonate-associated osteonecrosis, management includes topical antiseptic rinses, antimicrobials, gentle sequestrectomy, and avoidance of surgery, if possible, with a number of approaches under investigation.

Graft-Versus-Host Disease

Graft-versus-host disease (GVHD) in stem cell transplantation occurs when antigen-mismatched transplants are required. This affects 40 to 70 percent of allogeneic stem cell transplantation patients who may develop oral GVHD, which involves oral mucosa, salivary glands, and taste. Oral manifestations may occur as the primary manifestations or as part of systemic findings. In the oral cavity, this may present as mucosal "autoimmune" disease (lichenoid, lupus-like, or systemic sclerosis, Sjögrens-like), which may be symptomatic. When symptomatic, topical approaches for mucosal changes employing immunosuppressive agents may provide benefit.[22] Due to chronic immunosuppression, viral reactivation may occur early in transplant, most often due to herpes viruses (HSV, CMV, VZV).

Second Cancers

Patients with prior cancers are at increased risk for cancer recurrence and new secondary malignancies. In patients following stem cell transplantation, increased risk of oral cancers is seen five to nine years after treatment; three-quarters of these patients have GVHD before oral malignancy.[23] The majority of oral cancers following stem cell transplantation are squamous cell carcinoma of the tongue, followed by salivary gland malignancies. The increased risk is related to prior exposure to carcinogens (e.g., tobacco and alcohol), viral cofactors, and immunosuppression, and possibly related to prior cancer therapy.

Survivors of transplant may be at risk for recurrence of the primary cancer and to posttransplant lymphoproliferative disorders, which present in the head and neck and in the oral cavity commonly as gingival masses. Increased vigilance during patient evaluation and thorough examination is critical for early detection.

Conclusion

Acute complications are universal in HNC patients and stem cell transplant patients, and more common than in cycled chemotherapy. Chronic complications of reduced saliva volume and increased saliva viscosity impact quality of life and have been shown to be the primary persisting complications of HNC therapy. Increased risk of dental breakdown and periodontal disease may lead to increased risk of osteonecrosis. Neurosensory changes, including taste and mucosal sensitivity, may persist following cancer therapy.

By understanding the acute and late effects of therapy, we may be able to identify interventions that reduce symptom burden and improve functional outcomes and symptom clusters that may be impacted by oral disease. Prevention and management of these complications is best achieved by integrated oral and medical care of survivors of head-and-neck cancer. ■

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