

# Oral health considerations in cancer survivors

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## ABSTRACT

قد ساعد التقدم في علاج السرطان على مدى العقود الماضية في إطالة معدل بقاء المرضى المصابين. وبالرغم من ذلك، فإن المرضى الذين خضعوا لعلاج السرطان، يمكن أن يكونوا عرضة للإصابة بالعديد من المضاعفات التي تصيب الفم، بما في ذلك التهاب الغشاء المخاطي الفموي، والالتهابات المتعددة، نقص اللعاب، تسوس الأسنان، وتنخرفي عظم الفك. أن المرضى الناجين من السرطان يكونوا في خطرمدى الحياة للإصابة في مضاعفات الفم مما يتطلب متابعة جيدة لصحة الفم والأسنان على المدى الطويل بعد الانتهاء من علاج السرطان. ولتخفيف حدة هذه المضاعفات فإنه ينبغي على المرضى المصابين بالسرطان أن يخضعوا لفحص شامل ودقيق لصحة الفم والأسنان قبل الشروع في العلاج وأثناء وبعد العلاج لتحديد أي عدوى نشطة. وبالإضافة إلى ذلك، من أجل الحفاظ على صحة الفم خلال فترات العلاج، ينبغي على المرضى أن يستمروا في المحافظة على نظافة الفم وتنظيف الأسنان بالفرشاة بما في ذلك المناطق المتلاصقة بين الأسنان. أن الهدف من هذا الاستعراض هو مناقشة المضاعفات الفموية المحتملة نتيجة لعلاج السرطان، ومعرفة الاحتياطات الخاصة التي يجب أن نعرفها لعلاج هؤلاء المرضى.

Over the past decade, advances in cancer treatment have helped in prolonging the survival rate for cancer patients. However, the patients who undergo treatment for cancer are potentially at high-risk for developing a number of oral complications, including oral mucositis, infections, hyposalivation, dental caries, and jaw osteonecrosis. Cancer survivors may remain at life-long risk of developing oral complications, and therefore require long-term dental follow-up, well after completion of cancer therapy. Patients should typically undergo thorough oral examination prior to initiation of therapy, during and after therapy to identify any active infection. In addition, and in order to maintain adequate oral health throughout treatment, patients should continue normal oral hygiene with tooth brushing and interproximal cleaning. The aim of this review is to discuss potential oral complications as a result of cancer therapy, and the certain precautions we should be aware of these patients.

*Saudi Med J 2013; Vol. 34 (5): 461-469*

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Patients who undergo treatment for cancer are potentially at risk for developing a number of oral complications, ranging from acute oral complications including oral mucositis and infections, to late complications including hyposalivation, dental caries, and jaw osteonecrosis (Table 1).<sup>1</sup> Cancer survivors, depending on the specific cancer and modalities of therapy, may remain at life-long risk of developing oral complications and therefore require long-term dental follow-up well after completion of cancer therapy. To prevent and/or minimize such complications, appropriate communication between medical and dental treatment providers is critical prior, during and after cancer therapy. Late oral complications in cancer survivors can have tremendous psychological, social, and economic impacts on the patients and those affected by them. Patients that become physically disfigured may become uncomfortable with their appearance and socially withdrawn. Reduced functional ability can have a significant impact on a patient's ability to interact socially. Costs associated with management of symptoms, including prescription and non-prescription medications and devices, can also be considerable.

**Disclosure.** Authors have no conflict of interests, and the work was not supported or funded by any drug company. Dr. Maha A. Al-Mohaya is a member of the Editorial Team, and was therefore excluded from any final editorial decisions regarding this paper.

The aim of this review is to discuss potential oral complications as a result of cancer therapy, and their management, and what are certain precautions we should be aware of, for these patients.

**General considerations prior to beginning cancer therapy.** There is no universal consensus for what is considered “necessary” dental treatment prior to initiation of cancer therapy, with protocols largely based on expert opinion.<sup>2-4</sup> The primary objective of pre-cancer therapy dental screening is to achieve a stable and infection-free oral cavity in order to reduce the risk of developing localized and/or systemic infection during anticipated periods of neutropenia.<sup>5</sup> This becomes essential in the context of myeloablative chemotherapy regimens, such as those used in preparation for hematopoietic cell transplantation (HCT), in particular in patients who may not have received routine dental care prior to their cancer diagnosis. To maintain adequate oral health throughout treatment, patients should continue normal oral hygiene with tooth brushing and interproximal

cleaning, and in patients with a history of gingivitis or periodontal disease, antimicrobial mouthwashes (for example, chlorhexidine) are often prescribed. Patients should undergo thorough oral examination prior to initiation of therapy to identify any actively infected teeth or teeth that have a poor long-term prognosis so that they can be extracted.<sup>6-8</sup>

**Logistics of oral health care management.** Most cancer centers do not have staff dentists or dental facilities; therefore most cancer patients are followed and managed by their local community dentists. It is therefore critical that there is good communication and coordination between the patient, the dentist, and the oncologist. Specialty consultation with an oral medicine specialist or hospital dentist with oncology experience may be ideal, but in many cases such expertise may not be readily available. Good communication and a clear understanding of the patient’s cancer diagnosis and stage, planned therapy, overall prognosis, and potential complications are critical for determining the

**Table 1 -** Acute and late oral complications associated with cancer therapy.

Period	Complication	Patients at risk	Considerations
<i>Acute</i>			
	Oral infection (viral, bacterial and fungal)	<ul style="list-style-type: none"> <li>Intensive high-dose chemotherapy regimens</li> <li>Head and neck radiation</li> </ul>	<ul style="list-style-type: none"> <li>Odontogenic infections may present with pain/fever but without cardinal signs of erythema and purulence</li> <li>Intraoral HSV recrudescence may affect keratinized and non-keratinized mucosal sites</li> </ul>
	Oral mucositis	<ul style="list-style-type: none"> <li>Intensive high-dose chemotherapy regimens</li> <li>Head and neck radiation</li> <li>mTOR inhibitor therapy</li> </ul>	<ul style="list-style-type: none"> <li>Starts 7-10 days after chemotherapy, resolves within 3 weeks</li> <li>Peaks after third week of radiation, resolves weeks after completion of therapy</li> <li>mTOR inhibitor stomatitis appears aphthous-like, develops within first week of therapy</li> </ul>
	Salivary dysfunction	<ul style="list-style-type: none"> <li>Head and neck radiation</li> </ul>	<ul style="list-style-type: none"> <li>Oral burning common</li> <li>Increased risk of candidiasis</li> </ul>
	Oral hemorrhage	<ul style="list-style-type: none"> <li>Thrombocytopenia secondary to chemotherapy</li> </ul>	<ul style="list-style-type: none"> <li>Appears in the oral cavity as areas of active bleeding, petechiae or ecchymosis</li> </ul>
<i>Late</i>			
	Chronic GVHD	<ul style="list-style-type: none"> <li>Patients who received allogeneic hematopoietic cell transplantation</li> </ul>	<ul style="list-style-type: none"> <li>Typically appears after day +100</li> <li>Reticulation, erythema and/or ulcerations, primarily affecting the tongue and buccal mucosa</li> <li>Superficial mucoceles of the palate</li> </ul>
	Jaw osteonecrosis	<ul style="list-style-type: none"> <li>Anti-resorptive therapy</li> <li>Head and neck radiation</li> </ul>	<ul style="list-style-type: none"> <li>Characterized by exposed necrotic bone in the oral cavity</li> <li>Symptoms usually due to secondary soft tissue infection</li> </ul>
	Taste dysfunction	<ul style="list-style-type: none"> <li>Head and neck radiation</li> <li>Chemotherapy</li> <li>Chronic GVHD</li> </ul>	<ul style="list-style-type: none"> <li>Typically recovers after several months</li> </ul>
	Trismus	<ul style="list-style-type: none"> <li>Head and neck surgery</li> <li>Head and neck radiation</li> <li>Chronic GVHD</li> </ul>	<ul style="list-style-type: none"> <li>Develops gradually over time</li> <li>Maintaining oral hygiene and providing dental care can be challenging</li> <li>Requires long-term physical therapy</li> </ul>
	Impairment of craniofacial development in children	<ul style="list-style-type: none"> <li>Chemotherapy or head and neck radiation at a young age</li> </ul>	<ul style="list-style-type: none"> <li>Dental abnormalities include delayed eruption of teeth, microdontia, and tooth agenesis</li> <li>Bone abnormalities include deficient head and neck skeletal growth</li> </ul>
	Salivary dysfunction	<ul style="list-style-type: none"> <li>Head and neck radiation</li> <li>Chronic GVHD</li> </ul>	<ul style="list-style-type: none"> <li>Oral burning common</li> <li>Increased risk of candidiasis and dental caries</li> <li>Prescription and non-prescription management</li> </ul>
	Oral squamous cell carcinoma	<ul style="list-style-type: none"> <li>History of head and neck cancer</li> <li>Recipients of allogeneic hematopoietic cell transplantation</li> </ul>	<ul style="list-style-type: none"> <li>Field cancerization changes increase risk of new primary lesions</li> <li>Well-defined, abnormal mucosal lesions, require biopsy for diagnosis</li> </ul>
mTOR - mammalian target of rapamycin, GVHD - graft-versus-host disease, HSV - herpes simplex virus			

most appropriate dental treatment plan and reducing the risk of developing secondary complications.<sup>9,10</sup> Costs associated with dental treatment must also be considered. Unfortunately, even when considered a medically necessary component of a patient's comprehensive cancer care, medical insurance carriers (at least in the United States) will rarely cover such costs; this is similarly the case with late complications, such as extensive dental caries secondary to severe salivary gland hypofunction.

**Clinical evaluation.** *A) History taking.* Oral evaluation of cancer survivors begins with a comprehensive but focused medical history. This includes information on the type of cancer, date of cancer diagnosis, treatment rendered, and current status. For patients who were treated with HCT, additional features include the date and type (for example; autologous/allogeneic, ablative/non-ablative) of HCT and any relevant graft-versus-host disease (GVHD) history. Any history of complications or serious events during cancer therapy or since completion of therapy should be obtained. A complete list of medications is also essential, and patients with multiple myeloma and solid tumors with bone metastases should be queried specifically about previous and ongoing anti-resorptive therapy.

*B) Clinical examination.* Extraoral examination includes evaluation for any palpable lymph nodes, myofascial tenderness, temporomandibular joint dysfunction, salivary gland tenderness or swelling and perioral lesions. Mouth opening and any associated restrictions and/or deviations should be noted. Intraoral examination includes soft and hard tissue evaluation. Soft tissue examination focuses mainly on identifying any changes suggestive of infection, inflammation, or malignancy. All intraoral mucosal sites should be carefully inspected under a good light source for any abnormalities (for example; erythema, ulceration, swelling, growths); use of gauze and/or a tongue blade may be necessary to adequately evaluate the posterior and lateral aspects of the tongue. Dental examination includes detection of caries, early-decalcified lesions, and faulty restorations. Periodontal examination involves measuring pocket depths and evaluating the teeth for mobility.

*C) Imaging studies.* Intraoral dental radiographs, and in particular bitewing radiographs that best evaluate for the presence of interproximal decay, should be obtained routinely in patients that are at high-risk for developing dental caries (for example; head and neck radiation, and chronic GVHD). Whereas, these are typically obtained

**Table 2** - Prevention of dental caries in high-risk individuals.

Intervention	Rationale	Directions
Oral hygiene and non-cariogenic diet	<ul style="list-style-type: none"> <li>Decreases the substrate available for cariogenic bacteria</li> </ul>	<ul style="list-style-type: none"> <li>Brush teeth at least twice daily using soft-bristled toothbrush</li> <li>Daily use of dental floss</li> <li>Restrict the amount of refined carbohydrates in daily meals</li> <li>Avoid sugary and acidic beverages</li> </ul>
Fluoride products	<ul style="list-style-type: none"> <li>Increases tooth surface resistance to acids and acts as a reservoir for remineralization of early caries</li> </ul>	<ul style="list-style-type: none"> <li>Fluoride toothpaste should be used twice/day</li> <li>Fluoride gel in tray should be applied daily</li> <li>Fluoride varnish can be professionally applied up to 4 times/year</li> </ul>
Calcium-phosphate based remineralizing agents	<ul style="list-style-type: none"> <li>Casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) product provide a source of calcium and phosphate</li> <li>Facilitates remineralization of early carious lesions</li> </ul>	<ul style="list-style-type: none"> <li>Use daily with fluoride</li> </ul>
Xylitol products	<ul style="list-style-type: none"> <li>Unlike sucrose or fructose, xylitol is not utilized by <i>Streptococcus mutans</i> as a source of energy</li> </ul>	<ul style="list-style-type: none"> <li>Use xylitol-containing products (gum, candy) 3-5 times/day</li> <li>Fluoride toothpaste with at least 10% xylitol should be used twice/day</li> </ul>
Routine dental visits	<ul style="list-style-type: none"> <li>Caries screening through clinical examination and bitewing radiographs</li> <li>Restoration of carious lesions</li> <li>Professional dental cleaning</li> <li>Fluoride varnish application</li> </ul>	<ul style="list-style-type: none"> <li>Recall visits every 6 months</li> <li>Bitewings radiographs annually, or more frequent if high caries risk</li> <li>Dental caries should be treated as soon as identified</li> </ul>

every 1-2 years in otherwise healthy patients, they may be needed as frequently as every 4-6 months in patients with a history of significant dental caries developing after completion of cancer therapy.<sup>11-13</sup> Advanced imaging studies, such as computed tomography (CT) and magnetic resonance imaging (MRI), may be indicated to examine suspected lesions in the bone and salivary glands, and to evaluate for the presence of possible metastatic lesions.

**D) Laboratory investigations and diagnostic tests.**

Cancer survivors, even well after completion of primary cancer therapy, may remain at an increased risk for bleeding and infection. Patients with thrombocytopenia require a platelet count to determine bleeding risk prior to undergoing invasive dental procedures such as deep scaling and root planing and extractions.<sup>14</sup> Similarly, patients on anticoagulant therapy may require appropriate testing. Viral culture for herpes simplex virus (HSV) should be obtained from herpetic ulcerative lesions, although empiric therapy should always be initiated based on clinical diagnosis.<sup>15,16</sup> Fungal culture is generally reserved for cases of candidiasis that do not respond to initial empiric topical or systemic therapy.<sup>17</sup> Bacterial culture is of limited utility and generally reserved for cases of persistent purulence despite antimicrobial therapy. Cytology can provide immediate results to confirm or rule out viral or fungal infections. When there are lesions that are suspicious for malignancy, or when the clinical diagnosis is unclear, a tissue biopsy is necessary.

**Overview of acute oral complications associated with cancer therapy.** Acute complications that arise during cancer treatment are largely attributable to anticipated therapy-related side effects, although incidence and severity may vary greatly. Oral mucositis risk is highest in patients receiving high-dose intensive chemotherapy regimens, in particular those used in induction therapy for acute hematologic malignancies and conditioning regimens prior to HCT, as well as patients undergoing radiation therapy to the head and neck region (Figure 1). Mucositis can be associated with significant morbidity and may interfere with delivery of cancer therapy, but once healed is not associated with any long-term complications.<sup>18,19</sup> Management includes localized palliative care with ice chips, coating agents, and topical anesthetics in addition to systemic analgesics and diet modifications, and patients with mucositis may require nutritional support. Preventive measures include removal of sharp tooth edges and replacement of defective dental restorations, and ensuring that removable prostheses are well fitting. Palifermin, a recombinant human keratinocyte growth factor is FDA

approved for preventing the severity and duration of oral mucositis in patients undergoing HCT.<sup>20</sup>

Oral infection is a common complication during cancer therapy due to chemotherapy-induced immune suppression. The risk of infection varies greatly based on the intensity and duration of cancer therapy. Latent odontogenic infections may only become clinically evident and symptomatic in the context of immunosuppression. Teeth with caries extending to the pulp chamber require definitive treatment with either endodontic therapy or extraction, both of which should be completed at least 7-10 days prior to beginning therapy



**Figure 1** - Oral mucositis of the left ventrolateral tongue in a patient undergoing intensive chemotherapy for non-small cell lung cancer.



**Figure 2** - Generalized cervical demineralization (white changes) with early caries formation (cavitated brown areas) in a patient with oral chronic graft-versus-host disease. Equivalent findings can be seen in patients following head and neck radiation.



**Figure 3** - Florid pseudomembranous oral candidiasis in a patient with oral chronic graft-versus-host disease that developed following intensive topical therapy with a high potency corticosteroid oral rinse.



to allow for initial primary healing.<sup>21</sup> Patients with a history of HSV infection (for example; herpes labialis) are at risk for reactivation during immunosuppression and may be prescribed prophylactic antiviral therapy. Oral candidiasis is a frequent complication in cancer patients due to both generalized immunosuppression as well as salivary gland hypofunction. Acute salivary gland hypofunction is nearly universal in patients undergoing head and neck radiation, but may also be reported to varying degrees in patients undergoing intensive chemotherapy regimens.

#### *Late oral complications in cancer survivors.*

**A) Salivary gland hypofunction.** Hyposalivation, a pathologic condition of low saliva secretion, is commonly defined as a resting whole saliva flow rate of  $\leq 0.1$  ml/min and/or a stimulated whole saliva flow rate of  $\leq 0.5$  ml/min; however symptoms of xerostomia may arise due to hyposalivation, and/or due to qualitative changes in saliva composition, without a significant decrease in flow.<sup>22-24</sup>

Salivary gland hypofunction and xerostomia are common in patients treated with radiotherapy for head and neck cancers due to exposure of the major and minor salivary glands.<sup>25-27</sup> It is unclear whether concomitant chemotherapy exerts any further additive effect on salivary gland hypofunction.<sup>28,29</sup> Improved preservation of salivary gland function has been demonstrated with intensity-modulated radiation therapy (IMRT) due to selective reduction of the radiation dose to the salivary glands.<sup>30</sup> With respect to late effects, increased prevalence of xerostomia has been found during and 6 months following adjuvant moderate standard dose chemotherapy regimens.<sup>31,32</sup> Similarly, data on other cancer treatments such as radioactive iodine treatment for thyroid cancer, and total body irradiation prior to HCT, remains sparse.

Several modalities have been investigated in terms of their efficacy in reducing radiation-induced salivary gland injury. The IMRT is recommended as a standard approach in head and neck cancer to limit the radiation dose to critical normal tissues, including the salivary glands, and is associated with lower rates of late xerostomia compared with standard external beam radiation therapy.<sup>33-36</sup> Amifostine is a radioprotective free radical scavenger that is FDA approved to reduce the incidence of moderate to severe xerostomia in patients undergoing postoperative radiation therapy for head and neck cancer, where the radiation field includes a substantial portion of the parotid glands.<sup>37</sup> Amifostine is delivered by infusion or subcutaneously 15-30 minutes before radiation therapy. Symptomatic management of salivary gland hypofunction depends

on frequent water sipping, use of moisturizing and saliva stimulating agents, and sialogogue therapy. Although these treatment approaches provide some relief, results are variable and often insufficient, such that patients may simply rely on frequent water sipping. It is important that patients do not sip drinks containing sugar (for example; soda, juice) as this can increase the risk of dental caries (Figure 2) (Table 2).

**B) Mucosal infections. 1) Oral candidiasis.** *Candida albicans* is a commensal component of the oral microflora in upwards of 70% of healthy individuals. Under normal conditions, these fungal organisms co-exist with the other microorganisms of the oral flora and do not cause disease. However, alterations in the oral environment and/or systemic immunosuppression can result in an overgrowth, leading to clinical oral fungal infection, or candidiasis. The primary risk factors for recurrent candidiasis in cancer survivors are salivary gland hypofunction (see above) and long-term immunosuppression (largely restricted to patients treated with allogeneic HCT with GVHD).<sup>38</sup> Patients with oral chronic GVHD requiring the use of topical corticosteroid therapy (discussed below) are at a significantly increased risk due to intensive localized suppression of mucosal immunity.

The most frequent clinical presentations of oral candidiasis include the pseudomembranous and erythematous forms, with hyperplastic candidiasis only rarely encountered (Figure 3).<sup>39</sup> Oral candidiasis can be asymptomatic or associated with a range of symptoms that include burning, sensitivity, and taste changes. Pseudomembranous candidiasis can be readily diagnosed by visual detection of typical patchy white papules and plaques throughout the oral cavity. The erythematous form, characterized by mucosal erythema only, may be more challenging to diagnose as features may be more subtle. Hyperplastic candidiasis presents as a distinct area of leukoplakia and generally requires biopsy for diagnosis. Fungal culture with susceptibility testing should be reserved for cases that do not respond to initial empiric therapy. Fungal cytology can be useful in non-responsive cases where the diagnosis remains uncertain.

Most cases of oral candidiasis respond readily to topical and/or systemic antifungal therapy. The Infectious Diseases Society of America (IDSA) guidelines recommend the use of clotrimazole troches or nystatin suspension/pastilles as first-line therapy for the management of mild oropharyngeal candidiasis.<sup>40</sup> It should be noted that most formulations of troches/pastilles require saliva to dissolve and contain sugar for flavoring, which is not desirable from a caries

prevention standpoint, especially in patients with hyposalivation. For the management of moderate to severe oropharyngeal candidiasis, the IDSA recommends the use of systemic fluconazole as first-line therapy, and itraconazole or voriconazole, or rarely amphotericin B, reserved for refractory cases.<sup>40</sup> In cases of chronic recurrent infection, long-term prophylaxis (for example; daily topical or weekly systemic antifungal therapy) is a safe and reasonable approach to management.

**2) Recrudescence herpes simplex virus infection.** Cancer survivors who are immunosuppressed (for example; patients with GVHD on long-term immunosuppressive therapy) are at risk for oral reactivation of HSV. Pain and discomfort are common and can lower intake of fluid and nutrients, which in severe cases can lead to dehydration and malnutrition, requiring hospitalization.<sup>41</sup> Importantly, patients that are on prophylactic acyclovir may still develop "breakthrough" infections. At any time, the virus has the potential to reactivate causing recrudescence infection in the form of localized vesicles or ulcers, chiefly on the lip (recurrent herpes labialis) or on the keratinized mucosa of the hard palate, attached gingiva and dorsum of the tongue; less frequently the non-keratinized mucosa may be affected.<sup>42</sup> Lesions generally appear as solitary or crop-like groupings of shallow mucosal ulcerations that are typically highly painful, even when the size is very small; a crusted appearance is generally only encountered when on the lips.<sup>42</sup>

The diagnosis of oral HSV infection can often be made clinically by an experienced clinician based on the history and presenting features. Confirmatory laboratory diagnosis with viral culture can be helpful in cases of breakthrough infection, or when the diagnosis is unclear; if indicated, susceptibility testing can be ordered. Viral cytology can also be useful when a diagnosis requires confirmation; however, it can't be used for virus typing and/or susceptibility testing. Medical management of HSV includes systemic acyclovir and valacyclovir, and in case of acyclovir resistance, intravenous foscarnet is generally effective.

**C) Oral chronic graft-versus-host disease.** Oral features of cGVHD include salivary gland hypofunction and lichenoid mucosal inflammation.<sup>43-45</sup> Mucosal findings include white hyperkeratotic striations, erythema and ulcerations that are most frequently located on the buccal mucosa and tongue. Superficial palatal mucocoeles that develop secondary to inflammation of the minor salivary glands are typically described as an annoyance, and often come and go throughout the day, rarely requiring treatment.<sup>46</sup>



**Figure 4 -** Osteonecrosis of the jaw affecting the right maxilla in a patient with multiple myeloma treated with intravenous zoledronic acid. Note the persistent extraction socket of the canine, and the fact that the surrounding gingiva is healthy appearing other than slight erythema and swelling of the anterior aspect of the lesion.



**Figure 5 -** Limited maximum mouth opening in a patient after radiation treatment for head and neck cancer. Also note the extensive areas of cervical dental decay.

The primary symptom associated with oral mucosal cGVHD is sensitivity, such that eating and drinking foods and drinks that would normally be tolerated becomes painful, potentially affecting nutrition and quality of life. Items that are spicy, acidic, or rough become uncomfortable, and patients need to modify their diets accordingly. In rare cases, long-standing oral cGVHD inflammation can result in band-like fibrosis of the buccal mucosa leading to restricted oral opening and disability.

Management of oral mucosal chronic GVHD is largely driven by symptoms, with the primary goals directed at diminishing pain and sensitivity, maintaining the patient's ability to eat, and increasing the patient's quality of life. Patients may be on systemic immunosuppressive therapy for management of cGVHD but still require aggressive ancillary therapy measures for adequate symptom control. Similarly, patients may be tapered off of immunosuppressive therapy but continue to have symptomatic active oral disease, requiring long-term topical management. In severe cases, even when chronic GVHD is limited to the oral cavity, systemic immunosuppressive therapies may be indicated.<sup>47</sup>

**D) Osteonecrosis of the jaw.** Osteonecrosis of the jaw (ONJ) is defined as exposed necrotic bone in the oral cavity that persists for longer than 8 weeks. It can result from radiotherapy to the head and neck area (osteoradionecrosis [ORN]) and intensive anti-resorptive therapies with intravenous bisphosphonates (bisphosphonate associated osteonecrosis of the jaw [BONJ]) and more recently with denosumab.<sup>48-52</sup> The primary risk factor specific to ORN is the total dose of radiation therapy to the jaws, with the risk being highest during the first 3-24 months following completion of radiotherapy.<sup>48</sup> The primary risk factor for BONJ (and likely also denosumab-associated ONJ) is the total cumulative dose of anti-resorptive therapy. Oral risk factors include surgical trauma (for example; dental extractions), chronic dental infections, and use of removable prostheses; however, approximately 50% of cases develop spontaneously.<sup>53,54</sup>

The diagnosis of ONJ is based primarily upon clinical signs of ulceration of the mucosa (that is, complete loss of overlying mucosa) with exposure of necrotic bone (Figure 4). Secondary infection of the surrounding soft tissue is common, presenting with painful erythema, swelling, and purulence. Some patients with ONJ may also present with complaints of dysesthesia or paresthesia in the affected area as the neurovascular bundle becomes affected by inflammation or infection around the necrotic bone, or due to increased bone deposition and narrowing of the nerve canal, in particular in patients with BONJ. Radiographic features of ONJ include mixed radiopaque/radiolucent lesions, often with a mottled appearance. In some cases the presence of bone sequestra may be noted. All patients should have a comprehensive dental evaluation, and any teeth requiring extraction, or with a poor prognosis, should be extracted prior to beginning therapy. The importance of maintaining good oral health and receiving routine dental care should be emphasized. If post-treatment extractions become necessary, the technique should be as atraumatic as possible, and when feasible, conservative measures should be considered to avoid extraction altogether. Most ONJ symptoms are associated with secondary soft tissue infection; therefore, management includes topical (0.12% chlorhexidine gluconate) and systemic antimicrobial agents. Patients should be instructed to gently brush exposed bone to reduce plaque accumulations. Smoothing and recontouring of the exposed bone, and removal of bone sequestra can help to prevent secondary soft tissue injury, such as tongue ulcerations.<sup>55</sup> Complete healing of ONJ lesions after gentle or spontaneous removal of sequestra may occur, but this is generally not the goal of treatment.

**E) Trismus.** Trismus is defined as maximum interincisal opening <35 mm, and can be assessed using a specialized measuring device.<sup>56</sup> In severe cases, restricted mouth opening can be as little as 5 mm. Patients at risk primarily include those treated for cancers of the head and neck, and to a far lesser extent patients with chronic GVHD, due to mucosal fibrosis as well as sclerodermatous skin changes (Figure 5).

Management of trismus is challenging and requires life-long physical therapy interventions, often with less than optimal results. Physical therapy involves self-directed passive range of motion exercises.<sup>57,58</sup> The most basic approaches involve using 2 hands to stretch the jaw passively (completely relaxed), or stacking tongue depressors, and in some cases these measures may be effective in improving opening and reducing symptoms. Physical therapy devices engineered specifically for the management of trismus are available by prescription, and should be considered in patients with more severe trismus. These include the Therabite Jaw Motion Rehabilitation System (Atos Medical Inc, West Allis, WI) and the Dynasplint® Trismus System (Shulman & Associates Physical Therapy, Towson, Maryland).<sup>59,60</sup> Oral hygiene maintenance is paramount as provision of dental care can be challenging in patients with limited opening.

**F) Malignancy.** Cancer survivors are at an increased risk for malignancy due to their history of cancer, treatment related factors, and individual risks.<sup>61,62</sup> With respect to the head and neck region, and oral cavity specifically, the primary concerns include risk of recurrence of previously treated head and neck cancer, risk of squamous cell carcinoma in patients that have undergone allogeneic HCT, and risk of metastasis to the oral cavity.<sup>63-66</sup>

**Long-term follow-up and oral health maintenance.** All cancer survivors, regardless of their level of risk for developing oral and dental complications, require routine dental care including recall visits and scaling/prophylaxis at least twice a year. In patients at an increased risk for developing complications, routine visits serve to both reduce risk as well as screen. Dentists should play an active role in educating patients as to the possible signs and symptoms of oral complications. Maintaining good gingival health with daily tooth brushing and interproximal cleaning is important to reduce the risk of caries and periodontal disease. Patients at high-risk for developing dental caries require intensive preventive therapy and should be placed on a maintenance program. Patients with a history of gingivitis and periodontitis should be placed on a maintenance program, with reinforced oral hygiene and professional cleaning by a dental hygienist or dentist.



In conclusion, cancer survivors are at risk for developing a wide range of oral complications ranging from rampant dental caries to squamous cell carcinoma. Certain cancers, and cancer therapies, place patients at a much higher likelihood of developing specific oral complications. In some cases complications can be anticipated, and preventive measures can be taken to reduce overall risk. Oral health care specialists can play an important role in preventing, diagnosing, and managing associated oral complications, and should be included as part of every cancer survivor's health care team.

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