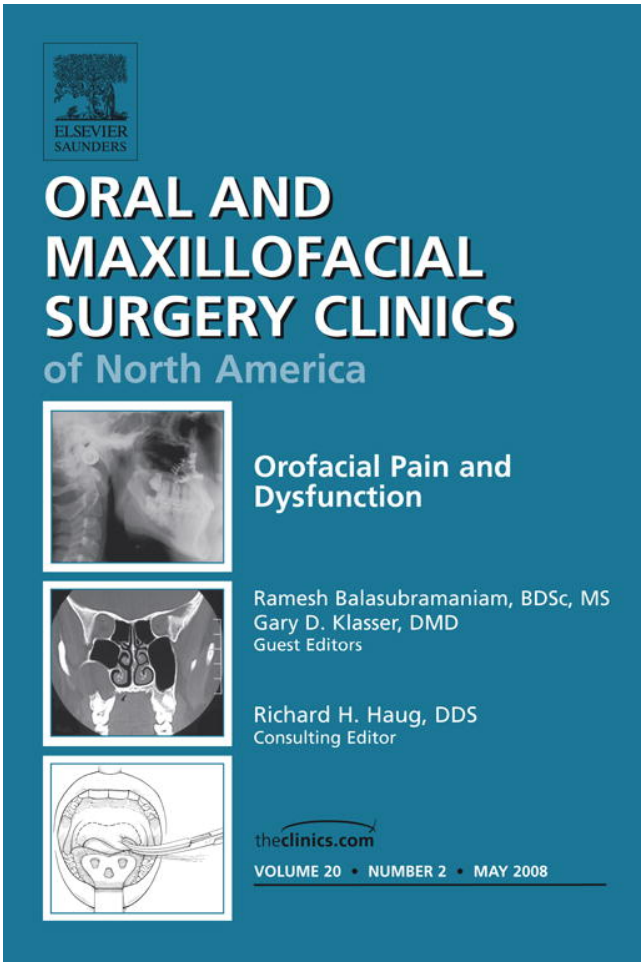

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Cancer and Orofacial Pain

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Pain is commonly associated with cancer, as it is the presenting symptom in 20% to 50% of all cancer patients and is significant in 75% to 90% of patients with advanced or terminal cancer [1]. In head and neck cancer (HNC) patients, pain has been associated with both disease and cancer treatment. Large surveys of HNC patients found that pain was frequently associated with the tumor (87%–92.5%), whereas in 17% to 20.8%, pain was secondary to therapy, and many patients reported pain from both disease and treatment [2,3]. Following treatment of HNC, 78% of patients reported pain in the head, face, or mouth and 54% in the cervical region or shoulder [3]. As many as 70% of patients may suffer pain from more than one site, involving inflammatory or neuropathic pain mechanisms [3].

Cancer pain correlates with increased morbidity, reduced performance status, increased anxiety and depression, and diminished quality of life [2,4]. Orofacial pain management may be particularly challenging as it is often multifactorial, differential diagnosis is complex, and the achievement of pain relief is compounded by cytotoxic treatment protocols. The present article reviews the clinical presentation of cancer-associated orofacial pain at various stages: initial diagnosis, during therapy, and in the posttherapy period.

Pain due to tumor

Pain due to primary head/neck tumor

Orofacial pain may be a presenting symptom of HNC and may motivate patients to seek care from an oral and maxillofacial surgeon. Primary squamous cell carcinomas of the oral mucosa are often associated with pain and other sensory disturbances when at advanced stage of disease, as they may interfere with oral function and induce nerve damage/dysfunction. In a retrospective case series [5], 66.5% of 322 patients with oral cancer reported localized discomfort within 6 months preceding cancer diagnosis. Another retrospective case series found pain to be the chief complaint at the time of oral cancer presentation in 19.2% of cases, with the most common pain complaints being sore throat and pain in the tongue [6]. Furthermore, a large case series of 565 salivary gland cancers found the most predominant complaint to be a lump (95%), with pain reported in 28% of the cases [7]. In rare circumstances, perineural spread of HNC may cause trigeminal neuropathy, paresthesias, and/or headaches [8].

Nasopharyngeal cancers may present with signs and symptoms that have been confused with, and treated as, temporomandibular disorders [9,10], parotid gland lesions [11], and odontogenic infections with trismus [12]. Signs and symptoms of nasopharyngeal carcinomas that mimic temporomandibular disorders include facial pain, limited jaw opening, deviation of the jaw on opening, earache, and headache [9,10,13,14]. In a retrospective case series, 44.2% of 52 patients diagnosed with nasopharyngeal carcinomas presented with orofacial pain described as aching, dull, pressing, or intermittent. Additionally, 13.5% of these patients complained of joint clicking, pain during chewing, and limited opening [9].

Osteosarcomas of the jaws are uncommon, representing 5% to 13% of all osteosarcomas

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[15–17]. For primary jaw tumors, the most common presenting feature is painless extraoral or intraoral swelling [16]. However, pain may develop in as many as 50% of the cases, and neurosensory disturbances of the trigeminal nerve have been reported in 21.2% of cases [17].

Intracranial malignancies may give rise to orofacial pain and/or headache, with the most common presentation being similar to that of classic trigeminal neuralgia (TN) [18]. The oral and maxillofacial surgeon must be cautious in the presence of these symptoms so as to not misdiagnose and mismanage these patients for TN when a central lesion is present. In a large series of patients presenting to neurology clinics with facial pain, the incidence of intracranial tumors has been found to be 0.8% to 5.9% [18,19]. Further evaluation of presenting symptoms associated with intracranial tumors has revealed that peripherally located tumors tend to cause an unusual facial pain presentation associated with sensory loss [19]. Middle fossa tumors may present as TN, but usually cause severe pain of an atypical nature and are associated with progressive neurologic deficits [19]. Posterior fossa tumors are most likely to cause TN-like symptoms, often accompanied by subtle neurologic deficits [19]. Furthermore, in a prospective study of cancer patients, new or changed headache was the presenting symptom for 32.4% of 68 cancer patients with intracranial metastases. Factors such as non–tension-type headache pain or new or changed headache [20] with duration of less than 10 weeks and vomiting were individually predictive of intracranial metastatic disease, although no information from the neurologic examination significantly contributed to diagnosis [21]. The clinical presentation is therefore often misleading and neurologic assessment may be of limited value. Ultimately, neuroimaging is required for diagnosis of intracranial tumors and should be considered for all patients presenting with symptoms of trigeminal neuralgia, neurologic deficits, and new or changed headaches [21].

Orofacial pain associated with metastatic malignancy

Metastatic orofacial tumors are rare, though they affect jaw bones more often than the oral soft tissues [22]. The breast is the most common primary source for tumors metastasizing to the jaw bones, followed by lung and prostate, and metastatic lesions most commonly occur in the posterior mandible, angle of the jaw, and ramus [22,23]. In the oral soft tissues, the lung in males and breast in females are the most common primary sources for metastases, and the attached gingiva is the most common affected site followed by the tongue [22,24]. Pain is a rare complaint in soft-tissue metastases [24], whereas in metastatic disease of the jaw bones, pain has been reported in 39% and paresthesias in 23% of patients [25]. In a retrospective case series of metastatic disease in the jaws, 60% of 114 cases reported the metastatic lesion in the oral region to be the first indication of an undiscovered primary malignancy at a distant site [23].

Orofacial pain in systemic cancer

Manifestations of systemic cancers may affect the head and neck structures, causing pain and loss of function. Lymphoma is the second most common neoplasm occurring in the oral region [26] and accounts for less than 5% of all head and neck malignancies [27]. Over 71,000 new cases of lymphoma, 44,000 new cases of leukemia, and 19,000 new cases of multiple myeloma are expected in 2007 [28]. Extranodal lymphoma may present as a local mass, with most common sites being the tonsil and sinuses, which may or may not be ulcerated, and is associated with discomfort in approximately one half of patients [29]. Lymphomas and leukemias may also induce pain by infiltration of pain-sensitive structures such as periosteum and gingiva [30]. Multiple myeloma may present with osteolytic lesions of the skull and/or jaw and is typically unaccompanied by oral symptoms [31]. However, when such lesions are adjacent to teeth, odontogenic pain is common and presents a radiologic diagnostic challenge as the osteolytic lesions appear to be associated with teeth but are actually related to systemic disease [32]. Consequently, histologic analysis of osteolytic lesions is recommended to obtain an accurate diagnosis [31].

Orofacial pain secondary to non-metastatic malignancy at a distant site (referred pain)

Rarely, orofacial pain has also been reported in patients suffering from a distant non-metastasized cancer, most commonly from the lungs [33–37]. In such circumstances, the facial pain is almost always unilateral, frequently described as severe and aching, and usually is continuous and progressive. Reviews of the literature have revealed that the pain is most commonly localized

to the ipsilateral ear (84%–91%), the jaws (48%), and the temporal region (38%). An elevated erythrocyte sedimentation rate has also been reported [33,36]. The mechanism by which a mass in the lung can refer pain to the face presumably involves either direct tumor invasion or compression of the vagus nerve by malignant lymph nodes [34,35]. Additionally, orofacial pain may be caused by activation of nociceptive pathways in mediastinal or head and neck structures [37].

Acute pain during cancer therapy

Surgical procedures

Acute pain is common secondary to surgical procedures for head and neck cancer. Surgery-related pain usually involves acute inflammatory responses related to the extent of the surgery and may be associated with a variable degree of concomitant nerve injury.

Acute pain secondary to chemotherapy/radiation therapy (mucositis)

Oral mucositis is a common acute complication of chemotherapy (CT) and/or radiation therapy (RT) and typically manifests as erythema and/or ulceration of the oral mucosa (Figs. 1 and 2). Chemotherapy-induced mucositis affects the labial and buccal mucosa, tongue, floor of mouth, and soft palate, all of which are more severely affected than attached, heavily keratinized tissues such as hard palate and gingiva. Unlike CT damage, radiation damage is anatomically site-specific, and toxicity is localized to irradiated tissue.

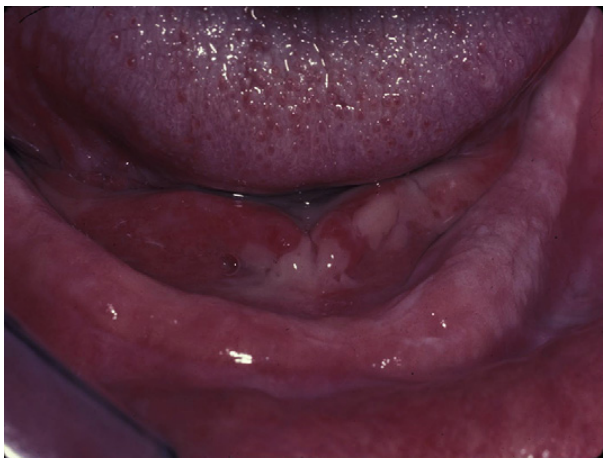

Fig. 1. Oral mucositis on the floor of mouth secondary to cancer chemotherapy.

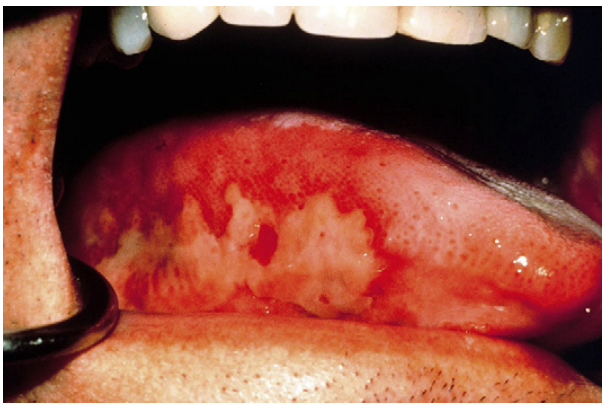

Fig. 2. Ulcerative and erythematous mucositis on the right lateral tongue secondary to radiation and chemotherapy for a right-sided base of tongue squamous cell carcinoma.

In chemotherapy-induced mucositis, erythematous mucositis typically appears 5 to 14 days after initiation of treatment, and ulcerative mucositis initially emerges approximately 2 weeks after initiation of treatment [38,39]. However, the biologic tissue changes begin immediately, as cytotoxic cancer therapy causes direct injury to replicating basal epithelial cells and disturbances in mucosal immunity [39,40]. Ulcerative mucositis occurs in approximately 40% of patients receiving standard CT and about 75% of patients who undergo hematopoietic stem cell transplants receiving high-dose CT. In about half of the patients with ulcerative mucositis, the lesions are severe and painful [40,41] and the breakdown of the epithelial barrier is a potential portal for systemic infection [39,42]. Medical intervention is often required with severe ulcerative mucositis and may lead to a modification or interruption of cytotoxic therapy, which may negatively affect treatment outcome and increase morbidity and mortality [41,43]. Mucositis is self-limiting when uncomplicated by infection and typically heals within 2 to 4 weeks after cessation of cytotoxic CT.

In RT, oral mucositis is the result of cumulative tissue dose and is almost universal in patients undergoing treatment involving the oropharynx. The degree of damage is dependent on treatment regimen-related factors, including type of radiation used, total dose administered, field site, and field size/fractionation. Mucositis pain is common (58%–75%) and may be severe, interfering with daily activities and oral function that affect the patient's quality of life [44–46]. Pain often escalates at week 3, peaking at week 5, and persisting

for weeks with gradual remission of signs and symptoms [45]. Duration of radiation-induced oral mucositis typically extends for 6 to 8 weeks [38,45]. Radiation-induced damage also differs from CT-induced changes in that irradiated tissue tends to manifest permanent damage that places the patient at continual risk for oral sequelae. The oral tissues are thus more easily damaged by subsequent toxic drug or radiation exposure, and normal physiologic repair mechanisms are compromised as a result of permanent cellular damage [42]. A retrospective cohort study of 204 patients who underwent RT found that oral mucositis was associated with increased weight loss and an incremental increase in treatment costs, depending on the severity of mucositis [47]. Combined CT and RT has been documented to result in increased frequency, severity, and duration of mucositis [47–49].

Treatment for oral mucositis involves meticulous oral hygiene and symptomatic management in a stepped approach beginning with bland rinses such as 0.9% saline and/or sodium bicarbonate solutions, followed by topical anesthetics, mucosal coating agents (eg, milk of magnesia, liquid Amphogel, Kaopectate, Gelclair), and then systemic analgesics [42,50–53]. However, these management approaches have not been subjected to controlled clinical trials. Oral care protocols generally include atraumatic cleansing of the oral mucosa, maintaining lubrication of the lips and oral tissues, and relieving pain and inflammation. As has been evaluated in Cochrane database systematic reviews [54,55], many agents and protocols have been promoted for prevention of mucositis or palliation of symptoms and have been found to provide some benefit at preventing or reducing the severity of mucositis associated with cancer treatment.

Oral infection

Acute oral infections of the mucosa (eg, bacterial, viral, and fungal), dentition/periapices, and periodontium may occur due to exacerbation of latent or prior chronic infection, changes in flora that occur secondary to cancer treatment, or indirect damage to oral structures and tissues, all of which may contribute to oral pain [56–59].

Bacterial

Both indigenous oral flora and hospital-acquired pathogens have been associated with bacteremias and systemic infection during myelosuppression secondary to high-dose CT [60]. Other oral sites, including the dentition, periapices, and periodontium, can also become acutely infected. Cancer patients undergoing high-dose CT who have chronic periodontal or pulpal/periapical disease may develop acute infections with associated systemic sequelae, and inflammatory signs may be masked due to the underlying myelosuppression [56,57,61]. Frequency and severity of bacterial infections typically begin to decrease approximately 3 to 4 weeks after cessation of CT and generally coincide with immune reconstitution [59]. Dental management of potential odontogenic and periodontal infection before initiation of CT can substantially reduce the risk of acute infectious flares [58,62,63], and mouth-care protocols that reduce microbial colonization of the dentition and periodontium are important during myelosuppression [62,63]. Bacterial infections may occur throughout the course of head and neck radiation and should be treated as soon as possible to reduce pain and the spread of infection.

Fungal

Candidiasis is a common clinical infection of the oropharynx in patients during and following CT and/or RT (Fig. 3). A number of variables contribute to its clinical expression, including immunocompromised status, mucosal injury, and xerostomia [64]. In addition, antibiotics used during prolonged neutropenia and/or concurrent steroid therapy typically alter oral flora, thereby creating a favorable environment for fungal overgrowth [65]. In irradiated patients, candidiasis develops secondary to the hyposalivation caused by

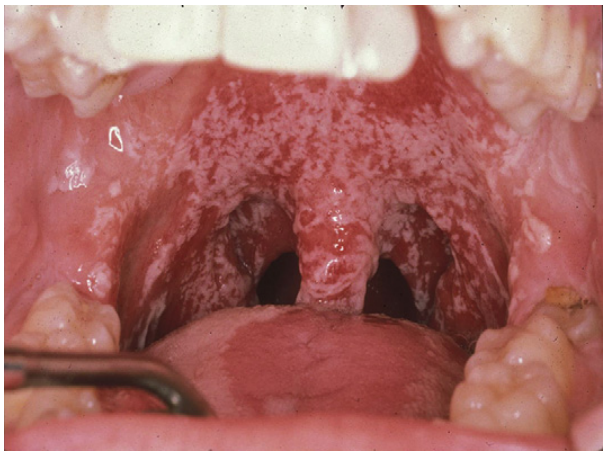

Fig. 3. Oropharyngeal pseudomembraneous candidiasis secondary to cancer therapy.

RT. Although superficial fungal infections may be treated with topical antifungal agents, systemic medications are often indicated for treating fungal infections in the oral cavity. Deep fungal infections may develop in immunocompromised cancer patients, including infection by aspergillosis, histoplasmosis, and mucormycosis [66]. The clinical presentation is not pathognomonic; lesions may appear similar to other oral toxicities and are painful. Microbiologic documentation is essential, and systemic therapy must be instituted promptly owing to high risk for morbidity and mortality.

Viral

Viral infections can cause a variety of diseases that range from mild to serious conditions in patients receiving cancer therapy. The severity and impact of these lesions, including risk for systemic dissemination, dramatically increases with worsening immunosuppression [67]. The ulcerations caused by viral infections can be painful and persistent. In most instances, herpes simplex virus (HSV), varicella zoster virus (VZV), and Epstein-Barr virus (EBV) infections result from reactivation of latent virus, whereas cytomegalovirus (CMV) infections can result from either reactivation of a latent virus, or via a newly acquired virus [68]. Prophylaxis with antiviral medications (eg, acyclovir, valacyclovir, gancyclovir, famciclovir, foscarnet) for patients receiving high-dose CT and undergoing hematopoietic stem cell transplantation has considerably reduced the incidence of these diseases. In high-dose CT and hematopoietic stem cell transplantation patients not receiving antiviral prophylaxis, HSV lesions typically emerge during the period of most significant immunosuppression, from a few days before transplant through day 35 posttransplant [67]. Orofacial VZV lesions are typically observed from approximately 3 to 12 months posttransplant, with allogeneic transplant recipients being at highest risk [69]. Oral lesions associated with CMV have been documented in patients who have undergone marrow transplantation [70,71]. EBV does not appear to be clinically significant in CT recipients, although hairy leukoplakia has been reported in stem cell transplant patients. However, hematopoietic stem cell transplant patients who are immunocompromised for a prolonged period may be at risk for development of EBV-related lymphomas (posttranplant lymphoproliferative disorders) of the head and neck region, especially when T-cell–depleted grafts are used for allogeneic transplant [72]. Current studies indicate that patients receiving head and neck RT are not at increased risk of viral reactivation specifically related to therapy, although occasional instances of simultaneous oral HSV lesions occurring during therapy have been reported [69,73].

Acute graft-versus-host disease

Patients who have received allogeneic or matched unrelated hematopoietic stem cell transplants are at risk for graft-versus-host disease (GVHD), which is the result of donor cells that react with and destroy recipient tissue. Acute GVHD can occur at the time of white cell recovery, as early as 5 days posttransplant, ranging from 5 to 47 days [74], and most commonly presents as a pruritic rash on the skin, followed by involvement of the liver and gut. Oral mucosal lesions occur in only about one third of acute GVHD cases and constitute a minor component of this problem [75,76]. Acute oral GVHD has been described as erythematous, desquamative and ulcerative lesions and/or lichenoid lesions that may be symptomatic and can involve multiple areas of the oral cavity [76].

Chronic pain secondary to cancer treatment

Chronic mucosal changes

Chronic changes involving oral mucosa are the result of hypovascular, hypocellular, and hypoxic changes that occur during cancer treatment, most commonly RT [40,77]. Types and severity of these changes are directly related to radiation dosimetry, including total dose, fraction size, and field size.

Chronic mucosal sensitivity

Chronic mucosal sensitivity may persist long after oral tissues heal following cancer treatment. In a survey of patients who have undergone RT, results indicated that 43% of 65 respondents reported at least mild sensitivity 1 year following treatment [48]. This chronic pain may result from permanent damage to oral tissues, including epithelial atrophy, submucosal fibrosis, neurologic sensitization, and/or neuropathy.

Slow-healing mucosa

The chronic mucosal changes may lead to an atrophic, friable mucosal barrier [40,77], which may predispose oral tissues to ulceration following trauma or injury. Soft-tissue necrosis may

then ensue due to reduced vascularization of the tissue and poor wound healing. Pain will generally become more prominent as soft-tissue necrosis progresses. Infection secondary to tissue injury increases the risk. Soft-tissue necrosis can involve any mucosal surface in the mouth, though nonkeratinized surfaces appear to be at moderately higher risk.

Chronic graft-versus-host disease

Chronic GVHD usually arises as an extension of acute GVHD in which the disease evolves directly from acute GVHD (progressive) or following a period of recovery from acute GVHD (quiescent). However, chronic GVHD may also develop in patients with no history of acute GVHD (de novo) or as an abrupt onset of multisystem involvement and manifestations of both acute and chronic GVHD (explosive) [20,74]. Chronic GVHD changes can be recognized as early as day 70 posttransplant [75,76], with recognition earlier in patients receiving nonidentical related or unrelated donor transplants [74]. Chronic GVHD can affect oral tissues and often mimic autoimmune conditions [75–78]. Common oral findings include atrophy, erythema, and lichenoid lesions, possibly with an erosive component and fibrosis consistent with progressive systemic sclerosis, as well as persistent reduction in salivary function (Fig. 4). Oral GVHD has also been linked with oral precancerous and malignant lesions [79]. Oral symptoms of GVHD include xerostomia and increased pain and sensitivity to acidic or spicy foods, alcohols, and flavoring agents, especially mint flavors in toothpaste and oral care products. Management of chronic GVHD may include topical or systemic steroids and/or immunosuppressants as well as management of hyposalivation, increased caries risk, and infection associated with hyposalivation.

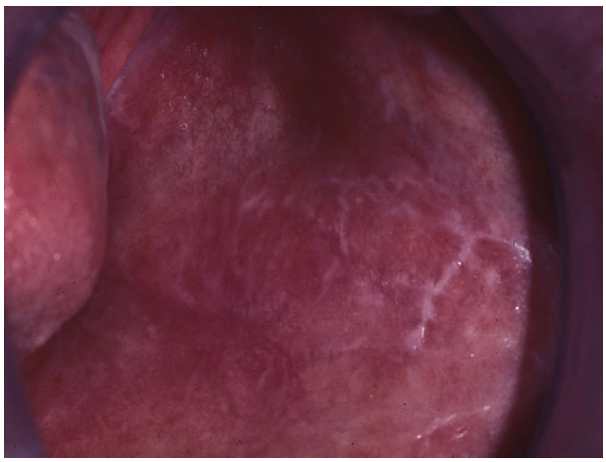

Fig. 4. Lichenoid changes to the buccal mucosa in a patient with chronic graft-versus-host disease.

Neuropathic pain

Neuropathic pain is defined by the International Association for the Study of Pain as pain initiated or caused by a primary lesion or dysfunction in the nervous system [80]. This dysfunction in the nervous system may be exacerbated by persistent, unrelieved nociceptive (inflammatory) pain associated with the tumor or cancer treatments, such as surgical procedures and neurotoxicities due to CT and RT or combinations of these treatments. Neuropathic pain is an extremely debilitating form of pain that occurs when peripheral, autonomic, and/or central nerves are affected. Additionally, changes occur in the immune system that modifies the normal function of nociceptors. These alterations in pain processing at the peripheral and central levels produce characteristic symptoms such as hyperalgesia, allodynia, and paresthesia [81]. The International Association for the Study of Pain [80] defines hyperalgesia as an increased response to a stimulus, which is normally painful; allodynia as pain due to a stimulus, which does not normally provoke pain; and paresthesia as an abnormal sensation, whether spontaneous or evoked.

Grond and colleagues [3] in a study involving 377 patients diagnosed with HNC found that 11% of the patients had neuropathic pain related to treatment. Unfortunately, in HNC patients, neuropathic pain has not been well characterized in terms of sensory report (location, intensity, quality, and pattern) or sensory quantification (allodynia and hyperalgesia).

Neuropathic pain secondary to surgical procedures

Surgical procedures used in the treatment for HNC commonly result in acute orofacial pain and may lead to painful posttraumatic neuropathy. Resection of the mandible for tumor excision will inevitably lead to sensory impairment [82], with 50% experiencing regional hyperalgesia or allodynia. At 2 to 5 years postmaxillectomy, approximately 90% of patients reported persistent pain [83]. The severity of the neuropathic pain may be increased following RT. In addition to tissue injury at tumor resection, morbidity has been found to be increased by neck dissection [84]. Sist and colleagues [85] evaluated 25 patients

with persistent pain for at least 1 month following neck dissection. The sample consisted of patients with moderate to severe pain ranging from 1 month to 27 years in duration. They found that all patients had at least one type of neuropathic pain: spontaneous, continuous burning pain (81%), shooting pain (69%), and/or allodynia (88%). A study by van Wilgen and colleagues [86] found that neck pain was present in 33% of their sample of which 96% reported some form of neuropathic pain. Contrary to these studies, Talmi and colleagues [87] described three groups of patients after neck dissection procedures and found neck pain to be an uncommon finding and the most frequently affected cranial nerve is the trigeminal nerve—in particular, the sensory component. This most often results in reduced or altered sensations in a dermatomal distribution with the presence of allodynia and hyperalgesia [88].

Treatment-related toxicity (chemotherapy, radiotherapy)

Chemotherapeutic agents used in the treatment of HNC often initiate painful peripheral neuropathies that often affect the orofacial region. This debilitating adverse effect may result in the inability to provide the patient with the full chemotherapeutic regimen and limit ideal dosing, thereby greatly affecting survival rate. This side effect known as chemotherapy-induced peripheral neuropathy (CIPN) is commonly seen during CT cycles [89]. Typically, the neuropathic pain resolves with or without symptomatic treatment. However, in some patients, this resolution does not occur and may evolve into a chronically painful condition. In these patients, the symptoms cause a notable decrease in functional capacity and overall quality of life [90]. Prevalence during treatment is variable among agents, the intensity of treatment (dose intensity and cumulative dose), other ongoing therapies (such as surgery and RT), age of the patient, and the use of combinations of CT agents [91]. Estimates of prevalence range from 4% to 76% during CT [92,93]. Preexisting nerve damage such as that caused by diabetes, alcoholism, inherited neuropathy, or paraneoplastic syndrome may increase the incidence and severity of CIPN [94]. Commonly used neurotoxic agents such as the taxanes (paclitaxel, docetaxel), vinca alkaloids (vincristine, vinblastine), platinum-based compounds (cisplatin, oxaliplatin), thalidomide, and bortuzamib appear to be the most responsible for precipitating CIPN. The majority of the CIPN demonstrate a mixed sensory (positive and negative symptoms) and motor (muscle weakness and atrophy) signs [95]; however, autonomic dysfunction (hypotension, cardiac conduction irregularities, impotence, and bowel and bladder involvement) may also be present. Interestingly, both small-diameter sensory fibers—unmyelinated C fibers and thinly myelinated A-delta fibers—and large myelinated A-beta fibers are affected by chemotherapeutic agents, with the large fibers being preferentially injured by CT agents such as vinca alkaloids, taxanes, and platinum-based compounds [89,96,97]. Unfortunately, at present, little is known about the cellular and molecular mechanisms responsible for CIPN and prevention is not available.

Radiation therapy plays an important role in the management of HNC. Most patients treated with a curative intent currently receive a dose between 50 and 70 Gy (Gray unit—absorbed dose of radiation) given over a 5- to 7-week period, once a day, 5 days a week, with 1.8–2.2 Gy per fraction. This regimen is not without toxicity [98]. The early or acute effects depend on the radiated fields and include skin/mucosal reactions, nausea, diarrhea, and neutropenia and are usually self-limiting. Late effects, including connective tissue fibrosis, neural damage resulting in neuropathic pain, and secondary malignancies, can occur long after completion of RT [99]. The radiation tolerance of normal tissues depends on total dose, dose per fraction, total time of exposure, volume, radiation quality, and adjunctive therapies [100]. Acute toxicities are more prevalent with higher doses per fraction, altered fractionation (hyperfractionation), concomitant boost, higher total dose, and when combined with chemotherapy [101]. The frequency and size of each treatment (fractionation) have been shown not to affect the occurrence in a brachial plexopathy model; however, it has been shown that there is an elevated morbidity to neural tissues with high-dose regimens [94,102].

Taste is altered as an early response to RT and may present as a reduction in taste sensitivity (hypogeusia), an absence of taste sensation (ageusia), or a distortion of normal taste (dysgeusia) [103]. Taste impairment greatly impacts the quality of life of the patient and, coupled with other RT-related comorbidities such as mucositis, hyposalivation, dysphagia, and reduced food enjoyment, RT may affect the nutritional status and overall health of the patient [98,104–106]. During a curative dose of RT, taste function becomes

impaired during the first week for bitter flavor and gradually worsens. Taste loss may begin with radiation doses of 20 Gy and decreases with cumulative doses; with 30 Gy all taste qualities are affected. Ninety percent of all patients experience a loss of taste when the cumulative dose has reached 60 Gy [107–109]. Direct radiation damage to the taste buds or innervating fibers is the proposed caused of taste loss [107,109]. Histologically, taste buds show signs of degeneration and atrophy at 10 Gy (2 Gy/day), whereas at therapeutic levels the architecture of the taste buds is almost completely destroyed [107]. It has been found that taste loss is usually transient, gradually returning to normal or near normal levels within 1 year following RT; however, it can take as long as 5 years [110]. The loss of taste is a result of the damage to the neural component of taste and is related to the reduction in salivary flow rate.

Musculoskeletal pain

Postradiation osteonecrosis

Postradiation osteonecrosis (PRON) is another well-recognized complication of head and neck RT that may be associated with pain. Loss of bone vitality occurs secondary to injury to osteocytes, osteoblasts, and osteoclasts as well as relative hypoxia owing to reduction in vascular supply [77,111]. These changes can lead to a reduced capacity of soft tissue and bone to recover from injury, predisposing to soft-tissue necrosis and osteonecrosis [111,112].

The risk for PRON is directly related to radiation technique, dose, and volume of tissue irradiated. Patients who have received high-dose radiation (>60 Gy) to the head and neck are at risk for PRON for life, with an overall risk of approximately 4% to 15% after standard fractionation [111–113]; the risk increases more significantly after 66 Gy [114]. PRON more frequently involves the mandible versus the maxilla, likely owing to greater bone density and unilateral vascular supply to each half of the mandible [111,112]. Presenting clinical features include symptomatic or asymptomatic exposure of necrotic bone or bone sequestrae, diminished or complete loss of sensation, fistula, and infection (Figs. 5 and 6) [111,115,116]. Pathologic fracture can occur as the compromised bone is unable to appropriately undergo repair at the involved sites.

Prevention of PRON begins with comprehensive oral care and assessment before head and neck RT. Dentition that exhibits poor prognosis and is within high-dose fields should be extracted before radiation therapy, and patients should be educated regarding excellent compliance with oral care. Patients who develop PRON should be comprehensively managed to include removal of bony sequestrae and topical antibiotics (ie, tetracycline) or antiseptics (ie, chlorhexidine) that may contribute to wound resolution [111,112]. Analgesics for pain control are often effective. In cases associated with pain and progression, hyperbaric oxygen therapy is recommended for management of PRON [112]. Hyperbaric oxygen therapy increases oxygenation of irradiated tissue, promoting angiogenesis and enhancing osteoblast repopulation and fibroblast function. Hyperbaric oxygen therapy is usually prescribed as 20 to 30 dives at 100% oxygen and 2 to 2.5 atmospheres of pressure. If surgery is needed, 10 dives of postsurgical hyperbaric oxygen therapy are recommended [112].

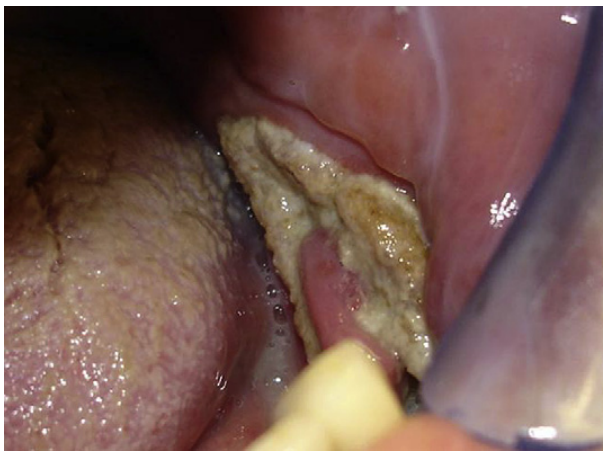

Fig. 5. Postradiation osteonecrosis of left mandible following standard fractionation radiation treatment.

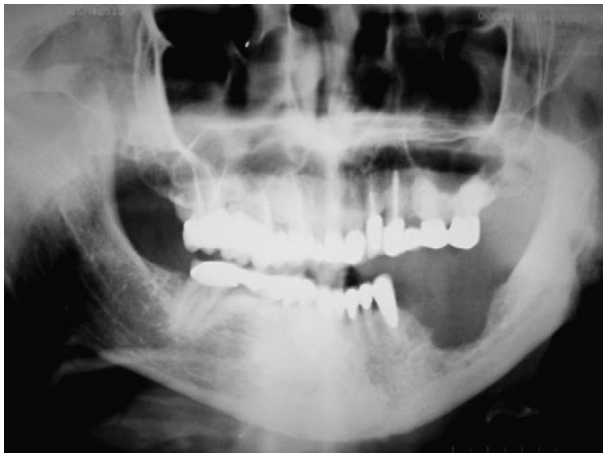

Fig. 6. Postradiation osteonecrosis of left mandible following standard fractionation radiation treatment.

Bisphosphonate-associated osteonecrosis

Oral bisphosphonates are commonly used in the management of osteoporosis, and high potency, intravenous bisphosphonates are important agents in cancer treatment, including malignancies, metastatic disease of bone, and hypercalcemia of cancer. Bisphosphonates are synthetic analogs of inorganic pyrophosphate that have a high affinity for calcium and are generally divided into two main classes based on the presence or absence of a nitrogen side chain. Those that contain nitrogen are the most potent, as the nitrogen side chain prevents these drugs from being metabolized, allowing them to accumulate with ongoing effects. The main pharmacologic effect of bisphosphonates is the inhibition of bone resorption, mediated by a decreased function of osteoclasts [117–119]. They inhibit both osteoclastic activity and osteoclast recruitment and diminish the lifespan of these cells [120], thereby causing an increase in bone deposition and mineralization [121,122]. Bisphosphonates also have antiangiogenic effects, further contributing to a decrease in bone remodeling [123,124]. Recently, osteonecrosis and osteomyelitis of the jaws have been recognized in patients treated with bisphosphonate medications (Fig. 7). Bisphosphonate-associated osteonecrosis (BON) appears to occur only in the oral and maxillofacial region and not elsewhere in the body skeleton. This may be due to the jaws having a greater blood supply than other bones and a more rapid bone turnover rate related both to their daily activity and the presence of teeth, consequently causing bisphosphonates to be highly concentrated in the jaws [125,126].

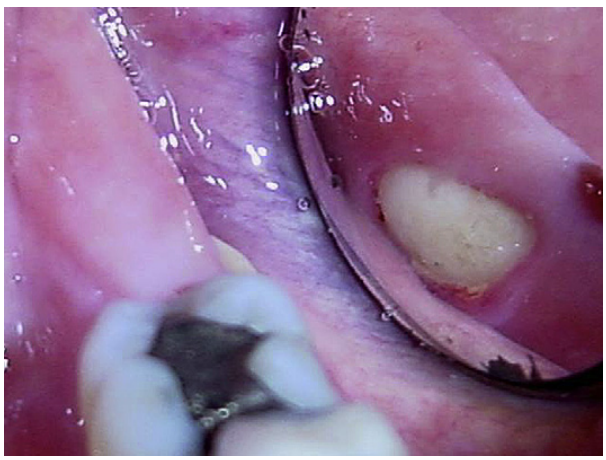

Fig. 7. Bisphosphonate-associated osteonecrosis involving the mylohyoid area (mirror image).

On the basis of retrospective surveys of patients treated with intravenous bisphosphonates, the prevalence of BON ranges from 7% to 10% for patients with multiple myeloma and 3% to 4% for those with breast cancer [127,128], whereas the prevalence of BON in patients taking oral bisphosphonate medications is much lower [129]. The risk of BON appears to be related to duration of therapy and type of bisphosphonate medication. The cumulative hazard of developing BON increased from 1% after 12 months of intravenous bisphosphonate infusion treatments up to 11% to 13% at 4 years [127,128]. Furthermore, the cumulative hazard of developing BON was significantly higher in those who received zoledronic acid alone (1% at 12 months, 15%–21% at 48 months) compared with the group with pamidronate alone or with subsequent zoledronic acid (0% at 12 months, 5%–7% at 48 months) [127,128]. A possible explanation for the difference in these findings is the more potent inhibitory effect of zoledronic acid on bone turnover and a stronger antiresorptive activity compared with pamidronate [127,128].

Prior to initiation of bisphosphonate therapy, patients should have a dental examination, and therapy should not be initiated until all dental treatment is completed [125,126,130]. Dental treatment is aimed at eliminating infections and preventing the need for invasive dental procedures in the near and intermediate future. For patients receiving bisphosphonate therapy, management should include avoidance of surgical procedures, including tooth removal, if at all possible. If patients develop BON, current guidelines do not recommend surgery beyond superficial debridement, such as rounding-off sharp bony projections that produce soft-tissue inflammation and pain [125,129,131]. However, recent literature has reported successful surgical intervention in cases of BON that are refractory to conservative management [132]. Long-term antibiotics, if indicated, and 0.12% chlorhexidine are recommended [125,126,130]. Treatment should be directed at eliminating or controlling pain and preventing progression of the exposed bone. There is no scientific evidence to support discontinuation of bisphosphonate therapy to promote healing of necrotic osseous tissues in the oral cavity, owing to the extensive half life and effect in bone [130,133]. Hyperbaric oxygen therapy may be beneficial in patients with bisphosphonate-induced exposed bone, though cessation of bisphosphonate medication is necessary to achieve remission.

A randomized controlled trial to evaluate the efficacy of hyperbaric oxygen therapy in treating BON is currently in progress [134].

Trismus and other musculoskeletal presentations

In HNC, trismus may develop due to tumor invasion, surgical treatment, and/or RT, if the masticatory muscles and/or the temporomandibular joint (TMJ) is involved, or a combination of these factors [135–137]. The prevalence of trismus after HNC treatments ranges from 5% to 38% [138,139]. Surgical treatment may induce scar tissue, which reduces mouth opening due to scar contraction and fibrosis of the masticatory muscles. Additionally, RT may induce fibrosis and atrophy in the masticatory muscles and/or TMJ as a late radiation effect [135,136,140,141]. This muscle fibrosis, on the basis of animal studies, evolves over several years and is most likely the result of increased cytokine production, proliferation of fibroblasts, synthesis of matrix proteins, and loss of vascular supply due to RT [142–144]. Dijkstra and colleagues [145], in a cross-sectional study, determined that 35 mm or less was the appropriate criterion for trismus, on the basis of the extent of the restrictions perceived in mouth opening and mandibular function by HNC patients. Trismus may increase morbidity because the limitation in opening interferes with oral hygiene, speech, nutritional intake, examination of the oropharynx, and dental treatment.

Trismus occurs with unpredictable frequency and severity. Generally, it is a late-treatment effect that develops 3 to 6 months after RT, often becoming a lifelong problem [136,146]. It has been suggested that the severity of the trismus is dependent on the configuration of the radiation field (unilateral or bilateral), the radiation source, and the radiation dose [135]. Contrarily, Steelman and Sokol [137] reported no correlation between reduced interincisal distance and total radiation dosage to the TMJ region. Nguyen and colleagues [147] also did not find a relationship between dosage and postradiotherapy complications, including trismus. However, other authors reported that trismus as a result of alterations to the TMJ develops only after high radiation doses [136], whereas others support the finding that trismus involving the masticatory muscles may develop after fairly low doses and worsens with increasing doses [135,141]. Goldstein and colleagues [135] suggested that the most critical factor in the development of postradiation trismus is probably due to the inclusion of the pterygoid muscles in the treatment field. This may explain the differences observed among the various studies reported in the literature.

Masticatory and/or cervical muscle pain may be found in HNC patients owing to tumor invasion and/or cancer therapy. Morbidity of these structures is not very well described in the literature. Shah and colleagues [148], in a retrospective study of 51 patients having different types of neck dissection, found that neck tightness was reported in 71% of the cases together with shoulder discomfort reported in 53% of the cases. They concluded the reported muscle pain had a substantial negative effect on quality of life. In an assessment of quality of life study following surgical management, it was found that neck and shoulder symptoms commonly followed neck dissection and decreased pain was seen in selective neck versus modified radical neck dissection [149]. In another study, of 25 patients with persistent neck pain after neck dissection, it was found that 72% of the patients reported cervical muscle pain [85]. In a study assessing patients who underwent neck dissection, with and without RT at least 1 year before the study, it was found that cervical muscle pain was present in up to 46% of the patients and was associated with a significant reduction in range of motion [86]. It is possible that the mechanisms responsible for trismus may also be responsible for the muscle pain.

It is important for the oral and maxillofacial surgeon to be aware of these conditions as he or she may be involved in the treatment of these adverse effects. In patients who present with trismus and/or muscle pain, the goal would be to restore lost interincisal opening and to alleviate pain and dysfunction. Exercises to increase mouth opening and improve mandibular mobility, including the use of prosthetic appliances (dynamic bite openers), rubber plugs, and tongue blades, may be used to treat trismus; however, once established, limited increase in range of movement can only be achieved. Involvement of orofacial pain practitioners and physical therapist to establish muscle pain control and restore function may be warranted. Regardless of the approach, patient compliance and perseverance are essential for success because dramatic results are not achieved immediately [98].

Summary with an emphasis/impact on oral and maxillofacial surgeons

Cancers involving the head and neck may originate in the oral cavity, salivary glands,

paranasal sinuses, nasal cavity, nasopharynx, pharynx, larynx, and/or lymph nodes in the upper neck. The close proximity and dense arrangement of blood vessels, nerves, and the central nervous system make these head and neck structures susceptible to nerve damage and pain. Classification of orofacial pain in cancer patients is complex and may be based on numerous pain mechanisms (eg, nociceptive/inflammatory, neuropathic), the location and extent of tumor, and the stage of treatment. Since orofacial pain is a well-recognized symptom associated with systemic and distant cancer and its treatment, it is imperative that the oral and maxillofacial surgeon has an understanding of various pain presentations. Successful pain management requires knowledge of, and attention to, multiple pain mechanisms that may contribute to the patient's pain presentation.

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