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Oral Complications of Head and Neck Cancer Therapy

Review Article

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Abstract: Current therapies for Head and Neck cancer treatment are extremely advanced. Though, they cause oral complications which have deleterious effects on basic life functions, affect oral and overall health, may lead to significant morbidity and treatment discontinuation and have an impact on survivorship and quality of life. As new therapies are introduced, a new spectrum of oral complications is rising, compromising the mucosal integrity and the salivary function, that may not be recognized, reported and treated properly. Oral complications, often permanent and extremely painful, may include mucositis, xerostomia, dysgeusia, infections, trismus and fibrosis, risk of dental disease and necrosis of the jaw, neurosensory disorders and when targeted therapies and immunotherapy are involved, aphthoid and lichenoid lesions can also be reported. Increased awareness is required for the prevention and management of these complications, which can be best provided by a multidisciplinary team.

Keywords: *Oral complications • head and neck cancer • radiotherapy • chemoradiotherapy • targeted therapy • immunotherapy*

1. Introduction

Head and neck cancer (HNC) is among the 10 most common cancers worldwide. Oral and pharyngeal cancer is the 6th most common cancer worldwide and the 7th most common in Europe with estimated incidence and mortality rates of 3.1% and 2.8%, respectively, in Europe in 2018[1,2,3].

A multifaceted approach is needed to treat HNC including surgery, radiotherapy (RT), chemotherapy (CT), targeted therapy (TT), immunotherapy (IT), or a combination of these treatments accordingly to the location, type, stage and former cancer treatments.

Even though current treatments are extremely advanced, there are still acute (developing during therapy) and chronic (developing months to years after therapy) HNC therapy complications (Table 1), which have a major impact on survivorship and quality of life (QoL)[4], as well as economic consequences when managing oral complications[5].

– Oral complications due to RT are site specific, localized to the irradiated tissues, which tend to

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become permanent, therefore the patient is in a lifetime risk. Oral complications may include mucositis, pain, xerostomia, dysgeusia, infections, osteoradionecrosis, trismus and dental caries.[6]

- Oral complications due to CT are in general of shorter duration than RT's. Oral mucositis, pain, xerostomia, dysgeusia, infections and medication related osteonecrosis of the jaw may be reported[6].
- Oral complications due to TT (Cetuximab) and IT (Nivolumab, Pembrolizumab) have a more favorable complications profile with lower incidence and severity[7,8]. Cetuximab is a monoclonal antibody targeting the epidermal growth factor receptor (EGFR). There have been reported aphthoid lesions in non-keratinized mucosa, mucositis, xerostomia and dysphagia[7,8,9,10] related to Cetuximab administration. Nivolumab and Pembrolizumab are immune checkpoint inhibitors. They are monoclonal antibodies targeting programmed cell death-1 (PD-1). Their complications are related to the activation of the immune system[11]. Xerostomia, dysgeusia, lichenoid reactions, mucositis and medication related osteonecrosis of the jaw have been reported in patients receiving Nivolumab or Pembrolizumab[7,12,13].

Several complications might be mild with few symptoms, so the occurrence may be underestimated, as the oral cavity and oral symptoms may not be evaluated in the medical setting.

Severe oral complications can compromise cancer therapy. Treatment schedule modifications, dose reduction or discontinuation may be needed for the resolution of oral lesions, affecting patient's survival. Oral health care is mandatory before, during and after a cancer treatment[14].

The impact of these complications is obvious in the 4 times higher suicide risk, in HNC survivors than in the general population and the approximately double rate of all cancer patients[15].

This is a brief review of the oral complications due to the HNC therapy and their clinical implications.

2. Oral mucositis

Oral mucositis (OM) is an acute complication that affects the patients receiving RT (up to 80%), CT (up to 40%) [16], TT (about 7%)[17], IT (about 2%)[10] or a combination of them (up to 100%)[7,18,19] (Table 2).

There is a distinction between "oral mucositis" (describes the inflammation of oral mucosa resulting from chemotherapeutic agents or ionizing radiation) and "stomatitis" (refers to any inflammatory condition of oral tissue including oral mucositis)[20,21] (Table 3).

Table 1: HNC therapy complications. HNC: Head and Neck Cancer.

Complications	
Acute	**Chronic**
Oral Mucositis	Xerostomia
Pain	Pain
Xerostomia	Trismus
Dysgeusia	Dysgeusia
Infections	Infections
Lichenoid reactions	Dental caries
Aphthous lesions	Osteoradionecrosis of the jaw
	Medication related necrosis of the jaw

Oral mucositis initially presents as erythema that progresses to painful mucosal ulcerations covered by pseudomembranes. It affects the nonkeratinized oral tissues, such as the buccal and labial mucosa, the lateral tongue, the soft palate and the floor of the mouth[22,23] (Table 4). Ulcerations are associated with oral pain and odynophagia, which limit oral intake[24]. Severe mucositis may also increase the possibility of systemic infections and aspiration pneumonia[16].

Risk factors for the development of mucositis may be patient, treatment, or tumor related. Age, gender, comorbidities, genetic factors, use of tobacco and alcohol, preexisting periodontal diseases and oral microflora are patient related risk factors. Cumulative radiation dose, fraction size, radiated area size and overall treatment time are risk factors related to RT. Concurrent chemotherapy results in a higher incidence and severity of OM[16]. Hyposalivation may exacerbate mucosal symptoms[24].

Radiation induced OM is a locoregional complication, however, it can have systemic impact due to cytokine release. Oral mucositis begins at cumulative doses of around 15 Gy, presents as erythema of the oral mucosa after approximately 20 Gy and progresses to ulceration covered by pseudomembranes after approximately 30 Gy[25]. OM can peak near the end of RT and usually resolves after 2–6 weeks of the completion of therapy, thought it may persist for 5–24 months[26,27].

OM induced by CT develops within 1 week of drug administration and peaks within 2 weeks. When it is uncomplicated by infections, it usually heals within 2–4 weeks after the cessation of CT. Severity depends on the chemotherapeutic agent, the number of chemotherapy cycles and the patient's age and oral health. Oral mucositis may be induced by chemotherapeutics like anthracyclines, alkylating agents, platinum-based agents, vinca alkaloids and taxanes. Moreover, some chemotherapeutics like Methotrexate and Etoposide are secreted in saliva, which may increase mucosal toxicity[16].

Table 2: Oral complications induced by Head and Neck Cancer therapies.

RT	CT	TT	IT
Mucositis	Mucositis	Mucositis	Mucositis
Dysgeusia	Dysgeusia		Dysgeusia
Xerostomia	Xerostomia	Xerostomia	Xerostomia
Infections	Infections		
Dyspagia	Dyspagia	Dyspagia	
		Aphthoid lesions	
			Lichenoid reactions
Pain	Pain	Pain	Pain
Neuropathy	Neuropathy		
Trismus, fibrosis			
Dental, periodontal complications	Dental, Periodontal complications		
Osteoradionecrosis	Osteonecrosis related to medication		Osteonecrosis related to medication

RT: Radiotherapy, CT: Chemotherapy, TT: Targeted therapy, IT: Immunotherapy

Table 3: Definition of terms used for conditions occurring during Head and Neck Cancer therapy.

Term	Definition
Oral Mucositis	Inflammation of oral mucosa resulting from chemotherapeutic agents or ionizing radiation, typically manifesting as erythema or ulcerations
Stomatitis	Refers to any inflammatory condition of oral tissue, including mucosa, periapices, and periodontium and includes infections of oral tissues as well as oral mucositis
Nociceptive Pain	Arises from damage to non-neural tissues due to the activation of nociceptors
Neuropathic Pain	Is caused by damage of the somatosensory nervous system
Xerostomia	Subjective feeling of oral dryness
Salivary gland dysfunction	Changes in quantity and/or quality of saliva
Salivary gland hypofunction	Decreased salivary output.
Hyposalivation	Decreased salivary output, due to salivary gland hypofunction. Whole saliva flow rate: unstimulated saliva ≤0.1 ml/min; stimulated saliva <0.7 ml/min
Dry mouth	Term used to indicate either xerostomia or salivary gland hypofunction or both
Dysgeusia	Taste alteration
Ageusia	Loss of taste
Hypergeusia	Heightened taste sensitivity
Hypogeusia	Reduced taste sensitivity

In HNC patients receiving chemoradiotherapy (CRT), OM may appear earlier in the treatment course, last longer, be more severe and extend beyond the RT fields[23].

Targeted therapies like agents targeting the EGFR inhibitors amplify OM[28]. Cetuximab as monotherapy has been found to induce OM in 7% of the patients[7,17,29], while a higher incidence of severe mucositis is observed when combined with RT[30] or CRT[28,31], resulting in extension to sites beyond the sites that receive high-dose of RT with broad involvement of the oral mucosa including the labial mucosa[8,32,33].

Administration of PD-1 inhibitors can sporadically induce nonspecific oral mucosal inflammation. OM is reported in patients receiving Nivolumab[34,35] or Pembrolizumab[36].

There is a profound clinical impact of OM; OM is associated with increased oral pain, dietary modifications, feeding tube placement, gastrostomy, dehydration, weight loss[24], fatigue, anorexia, and reduced performance status, frequent hospitalization and breaks in treatment. Ulcerations may persist for several months beyond expected healing, causing prolonged symptomatology[27]. Furthermore, OM is

Table 4: Diagnosis of oral mucosa's complications.

Diagnosis	Clinical manifestation	Symptoms	Site
Mucositis	Painful ulcerations covered by removable pseudomembranes	Pain	nonkeratinized mucosa; buccal mucosa, lateral tongue, soft palate, floor of mouth
Candidiasis	Removable white pseudomembranes	Burning sensation, mucosal soreness, taste alterations	Dorsal side of the tongue, soft and hard palate, labial commissure
Herpes	Small vesicles that eventually rupture to become shallow painful ulcerations	Pain	Keratinized oral tissues, lips
Bacterial infections	Necrotising ulcerative gingivitis, periodontitis	Pain, bleeding	Gingiva
Aphthous like (aphthoid) lesions	Single or multiple, painful, well-circumscribed, round/ovoid superficial ulcers, with a gray central area, surrounded by an erythematous halo	Pain	Nonkeratinized oral tissues; buccal mucosa, soft palate, ventral and lateral side of the tongue, floor of the mouth
Lichenoid reactions	Whitish papules, reticular or linear, confluent in places, sometimes with erythema	Pain, soreness, or asymptomatic	Dorsal and lateral side of the tongue, lips, gingiva, hard palate, buccal mucosa

associated with diminished QoL and significant health and economic outcomes with increased resource requirements and healthcare costs[5,37].

2.1. Management

Management of OM is an unmet need, since it is symptomatic, trying to relieve the pain and maintain the normal function of oral cavity. Many centers use a locally compounded mouth rinse containing lidocaine. Other ingredients are often combined, like antifungal, antibiotic or steroid drugs. However, its efficacy is limited in clinical evidences[16].

According to MASCC guidelines[14] there are recommendations in favor of benzydamine mouthwash to be used to prevent oral mucositis in patients with HNC receiving moderate RT dose (up to 50 Gy), without concomitant CT; and of 30 min of oral cryotherapy to be used to prevent oral mucositis in patients receiving bolus 5-fluorouracil (5FU) chemotherapy. There are also suggestions in favor of oral care protocols to be used to prevent oral mucositis in all age groups and across all cancer treatment modalities. Low-level laser therapy (wavelength around 632.8 nm) could be used to prevent oral mucositis in patients undergoing RT, without concomitant CT; and systemic zinc supplements administered orally may be of benefit to prevent oral mucositis in oral cancer patients receiving RT or CRT.

Furthermore, there are recommendations against the use of PTA (polymyxin, tobramycin, amphotericin B) and BCoG (bacitracin, clotrimazole, gentamicin) antimicrobial lozenges and PTA paste to prevent oral mucositis in patients receiving RT for HNC; the use of iseganan antimicrobial mouthwash to prevent oral mucositis in patients receiving RT or CRT for HNC; the use of sucralfate mouthwash to prevent oral mucositis in patients receiving RT or concomitant CT for HNC and the use of sucralfate mouthwash to treat oral mucositis in patients on RT for HNC. Additionally, there are suggestions against the use of chlorhexidine mouthwash, misoprostol mouthwash and systemic pilocarpine, administered orally, to prevent oral mucositis in patients receiving RT for HNC.

3. Pain

Oral pain is one of the most prevalent, debilitating and feared consequence. Pain results to increased use of feeding tubes and opioid medication, increased cases of hospitalization and treatment breaks, even increases medical costs[1,2,37]. Chewing, swallowing, speaking, and other oral functions trigger pain constantly. During RT for HNC, OM induced pain generally starts at cumulative doses of around 30 Gy, peaks at about 50 Gy and persists for 2–4 weeks since the completion of RT[1,3]. Cramet et al.[38] studied HNC survivors at 1 to 20 years after diagnosis. Among survivors, 45.1% reported pain and 11.5% reported severe pain. Mucositis pain interferes with daily activities in approximately one-third of patients, affecting mood in half of them[16].

Pain may also develop from treatment induced polyneuropathy[10] following CT, hormonal therapy, TT, IT and RT[7,8] Platinum agents, Fluorouracil (5FU) and Taxanes are chemotherapeutic agents that could produce pain. Targeted therapy may cause neurotoxicity and mucosal (aphthous like) ulcerations resulting pain, while immunotherapy could result in pain by stimulating immune-inflammatory processes[7,10,23,39]. Patients receiving RT for HNC may develop mucosal atrophy and telangiectasias and may experience chronic

mucosal pain and sensitivity; it sometimes is described as a burning or a scalded sensation that may represent neuropathy[16,40]. HNC therapy-induced pain can be nociceptive and/or neuropathic (Table 3). Nociceptive pain is commonly induced by the damaged tissues in the oral cavity. Persistent unrelieved nociceptive pain induced by OM ulcers as well as the actual therapy-related neuron damage can exacerbate the dysfunction in the nervous system, producing neuropathic pain (NP)[40].

Osteoradionecrosis and medication related osteonecrosis of the jaw may also cause pain; pain and swelling are included in the clinical presentation[6].

Moreover, OM in HNC patients treated with RT/CRT is often complicated by candidiasis and herpetic infection, thus altering pain characteristics; candidiasis is often associated with a burning sensation of the mouth[41], while herpetic infection was observed to aggravate radiation-induced ulcerative OM and exacerbate pain, as it is associated with painful ulcerations in the oral cavity[42].

Xerostomia and the consequent lack of lubrication of the oral mucosa increase the mucosal friction during oral functions, making it vulnerable to greater trauma and pain[43].

3.1. Management

There is a lack of progress in the treatment of oral mucositis pain.[44] Treatment aims to reduce the patients' symptoms; the drugs and interventions used for the management of OM have various effects on the induced oral pain[45]. Management should address both nociceptive and neuropathic pain[40]. Systemic analgesic pain medication (paracetamol or NSAIDs), as per WHO pain management ladder, modified by Vadalouca et al.[46] may be provided to treat oral pain. Opioids remain the first-line treatment for pain associated with peripheral neuropathy. Adjuvants such as anticonvulsants[46] are critical in achieving successful pain management and may address the neuropathic components of pain[16,40,46,47]; agents like antidepressants, local anesthetics, and corticosteroids as well as Vitamin E, alpha-lipoic acid, acetyl-L-carnitine, and erythropoietin have been also used to treat neurotoxicity[48]. Management may be improved by taking care of hyposalivation and mucosal infection[16].

According to MASCC guidelines[14], there are suggestions in favor of the use of 2% morphine mouthwash to treat pain due to OM in patients receiving CRT for HNC and the use of 0.5% doxepin mouthwash to treat pain due to OM.

4. Xerostomia

Xerostomia is defined as the subjective sensation of oral dryness; it may be secondary to salivary gland disfunction or hypofunction with changes in quantity and/or quality of saliva[16,49]. The term "dry mouth" is also used to indicate either xerostomia or hyposalivation or both (Table 3). Xerostomia is a frequent and debilitating acute complication, which in many cases develops into a chronic condition. Xerostomia may increase the risk of secondary oral infection (e.g., candidiasis), pain, dental and periodontal disease, mucosal trauma, taste disfunction, dysphagia and speech difficulty[16,24,50].

Salivary glands are sensitive to RT. Doses greater than 30 Gy can cause permanent damage and xerostomia[16,50] RT causes xerostomia due to direct damage to salivary acini and ducts and indirect damage to epithelial and connective tissue elements of the gland like blood vessels and nerves. The serous acini are initially more sensitive to RT. This often results in decreased saliva volume and increased viscosity. However, during RT, mucinous acini may become similarly impaired[16,19,51].

Moderate xerostomia is reported in less than 7.5% of patients receiving PD1 inhibitors[10]; 6%–6.5% of patients treated with Nivolumab and 4%–7.2% of patients treated with Pembrolizumab[7].

Antiemetics administered for the management of nausea and vomiting due to CT may also cause xerostomia[52]. The antiemetics reported to cause xerostomia are 5-HT3 receptor antagonists[53], dopamine antagonists[54], cannabinoids[55], benzodiazepines[56], NK1 receptor antagonists[57] and the atypical antipsychotic Olanzapine[58]. Olanzapine is reported to induce mostly xerostomia; however, one animal study reported dual secretory effects: xerostomia and sialorrhea[58].

Xerostomia is reported as a lifelong morbidity having important effects on oral health and QoL; it resolves completely in only 20%–30% of patients, 1 year after the completion of RT[48].

4.1. Management

Salivary substitutes (or mouth-wetting agents) and the frequent use of bland oral rinses (like warm chamomile) may provide temporary relief of discomfort. The pH should be neutral or alkaline, as there is a risk of dental demineralization and tissue irritation when acidic products are used. Milk may be a useful salivary substitute because it moisturizes, lubricates, and buffers acids and may also contribute to enamel remineralization through its calcium and phosphate content[16].

If residual saliva gland function is present, oral comfort could be provided by physical stimulation with sugar-free gum or candies and systemic sialagogues. Pilocarpine hydrochloride, Cevimeline, and Bethanechol have been used to increase salivary flow with mixed results[50]. Both Pilocarpine and Cevimeline are contraindicated in patients with uncontrolled asthma, narrow angle glaucoma, and acute iritis and caution should be taken in patients with gallbladder disease. Bethanechol is not contraindicated in patients with asthma and narrow angle glaucoma but may increase urinary frequency. In MASCC guidelines[14], there is a suggestion against the orally systemic administration of Pilocarpine, in patients receiving radiation therapy for head and neck cancer.

Additional therapies include hyperbaric oxygen to improve angiogenesis and fibroplasia in nonhealing tissue, acupuncture, and salivary gland tissue transplantation[16]. Hypnosis has also shown effectiveness in improving salivation and decreasing xerostomia[59].

Patients should also lubricate the lips with lip balm or lip cream in order to avoid lip dryness. Products based on petrolatum jelly should not be used on the lips; they promote mucosal cell dehydration and may lead to potential risk of secondary mucosal infection[47].

5. Dysgeusia

Dysgeusia is frequently underreported and overlooked and is impacting patients' QoL as it can lead to malnutrition and weight loss[23,48]. In HNC patients under treatment, there are several taste function changes including taste alteration, loss of taste, hypersensitivity, or hyposensitivity[48]; they usually are all reported under the term dysgeusia (Table 3).

In patients receiving RT alone, the incidence of dysgeusia is 16–100%, depending on the study. Radiotherapy has a direct cytotoxic and antiproliferative effect on the epithelium of the tongue and on the gustatory nerves[48]. Taste impairs during the first week of treatment, becomes worse during the second week, reaching the greatest impairment during the third or fourth week of treatment. Improvement can be found between the end of the 1st and the 2nd month post RT and normal or near-normal levels of taste can be observed within 1 year after RT; however, changes may persist up to 7 years post RT or even indefinitely[16,23].

Chemotherapy and targeted therapeutic agents may affect taste by direct taste receptor stimulation due to secretion in saliva or via gingival crevice fluid (patients frequently describe a metallic or chemical taste when chemotherapy is delivered), and taste change may persist after drug clearance due to damage to the taste buds[16,48]. Patients treated with 5-FU, Taxanes, Cyclophosphamide, Doxorubicin and Cisplatin may develop taste changes, including ageusia or hypogeusia[60].

Moderate dysgeusia has been noted in less than 4% of PD1 inhibitors treated patients[7].

Hyposalivation may reduce taste due to limited delivery of tastants to the receptors.

Damage to the cranial nerves and oral, dental, and oropharyngeal pathology may affect taste function changes, mediated by the trigeminal nerve, correlated with touch and temperature sensation. Moreover, smell mediated by the olfactory nerve may alter taste perception[16,48].

Dysgeusia is highly reported among patients with reduced dietary intake and weight loss and when associated with oral mucositis and xerostomia, affected patients' appetite[24].

5.1. Management

Management includes dietary changes in food choices, seasoning (spices, flavoring) and avoiding unpleasant foods. Amifostine may reduce the severity (not the incidence) of dysgeusia. Zinc sulfate supplementation has inconsistent outcomes in clinical studies[48]. Centrally acting medications like Clonazepam, Pregabalin, Gabapentin, Cannabinoids and Megestrol have been used considering that changes and damage in mucosal C-fiber and Aδ- fiber may impact taste[16,23].

6. Infections

During ulcerative OM, patients are more prone to infections because the oral microbial flora is altered and the oral cleansing property of saliva is diminished by reduced salivary flow; odontogenic, periodontal and dormant viral infections usually become reactivated. Ulcers can be colonized by Candida species, Herpes virus, and bacteria. Differential diagnosis of OM, candidiasis and herpetic infection is important, as candidiasis and herpetic infection superimposed on mucositis can aggravate the mucosal condition and exacerbate pain, consequently causing—in clinical practice—a reduction of the patient compliance to the therapy. The differentiation of candidal pseudomembranes and the herpetic ulcers covered by the fibrinous exudate from the pseudomembranes and the ulcers of the ulcerative phase of mucositis, in

case of concurrent development, is at times difficult yet mandatory (Table 4).

6.1. Candidiasis

Oral candidiasis is the most common infection in HNC patients treated with RT/CRT. The prevalence of candidiasis during RT is about 38%[41,61].

Candidiasis is often associated with a burning sensation of the mouth or accompanied by burning pain,[41] mucosal soreness and taste alterations. It can result in dysphagia affecting oral intake, nutritional status and oral medications' administration[23].

It presents like erythematous and pseudomembranous candidiasis, and angular cheilitis[23] and may affect the dorsal side of the tongue, the soft and hard palate, and the labial commissure[61]. Diagnosis can be challenging as candidiasis' symptoms may overlap OM's. The symptomatology may variate from no symptoms, to pain, burning sensation, odynophagia, dysgeusia, sensation of coating in the mouth and yeast smell.

Olanzapine (an atypical antipsychotic) administered for the management of nausea and vomiting due to CT has been also associated with oral candidiasis[62].

6.1.1. Management

The use of systemic Fluconazole is recommended as a first-line therapy for the management of moderate–severe oropharyngeal candidiasis[41]. Nicolatou-Galitis et al.[61] reported significant reduction in candida carriage and elimination of oral candidiasis together with significant reduction in severe mucositis at the end of RT and significant reduction of treatment interruptions in patients receiving a daily dose of 100 mg Fluconazole when compared to controls. For Fluconazole-refractory fungal disease, Itraconazole or Posaconazole are recommended. Amphotericin B and Itraconazole have been used for oropharyngeal candidiasis in oncology patients, with good efficacy[41]. These agents are best for short use; prophylactic use in certain oncology settings (HNC patients receiving RT over 6–7 weeks) can be problematic. The emergence of resistant species is one important concern with such prophylactic use. Additionally, systemic use of agents may be limited by their side effects, especially for Amphotericin B.[41]

The addition of topical antifungals, like Miconazole oral gel to systemic prophylaxis has been shown to reduce oral colonization, which can lead to a reduced risk of subsequent local and systemic infection[47].

Whenever possible, the management of underlying risk factors, such as hyposalivation, may facilitate management and reduce the risk of chronic or recurrent infection.

6.2. Herpetic infection

Reactivation of latent herpes simplex virus type-1 (HSV) is one of the most common causes of viral infection in HNC patients receiving RT/CRT[42]; herpes virus primary infection often results in latent infection in the trigeminal ganglion and in salivary glands. Small vesicles appear extra-orally and intra-orally along the affected branch of the trigeminal nerve. These eventually rupture to become shallow, painful ulcerations covered by a fibrinous exudate, disseminating throughout the oral cavity[42,63] (Table 4). Differential diagnosis between herpetic ulcers and OM's ulcers must be under consideration. Diagnostic criteria include abrupt appearance of severe, extensive ulcers and/or early initiation of ulceration, within the first 2 weeks of RT. Trigger factors for HSV reactivation may be the radiation-induced epithelial damage and the psychosomatic stress of the patient[42].

The prevalence of herpetic infection among patients receiving CRT is 29–43% depending on the study[42,64].

Herpetic infection was observed to aggravate radiation induced oral ulcerative mucositis and exacerbate pain as it is presented with painful ulcerations in the oral cavity[42].

6.2.1. Management

Management considerations include topical and systemic antiviral medication, and palliative therapy such as analgesia and maintenance of fluids and electrolytes. Acyclovir and Valacyclovir are the most used drugs[42,65]. Pain can be controlled with topical anesthetic agents or nonsteroidal anti-inflammatory and adjuvant drug therapy drugs.

6.3. Bacterial infections

Oral mucositis can also be complicated by bacterial infections in the immunocompromised patient; oral microorganisms can be systemically spread in neutropenic patients. Poor oral hygiene and hyposalivation increase the oral microbial load and alter the oral flora[6,63]. The bacterial infections usually extend the mucosal damage by direct stimulation of infiltrating

macrophages, which release additional proinflammatory cytokines[48].

Panghal et al.[66] reported a predominance of Gram+ bacteria (Staphylococcus aureus and Staphylococcus epidermidis) in the oral cavity of patients receiving RT or CRT and a predominance of Gram– bacteria (Klebsiella pneumonia) in patients receiving CT. The predominance of Gram+ bacteria as infectious pathogen in patients receiving RT or CRT may be because RT leads to damage of the mucosal barriers and increases the risk of infection with Gram+ oral (and GI) flora[66].

6.3.1. Management

It is important to eliminate potential sources of oral infection as conventional signs and symptoms of infections like swelling may be absent due to immune suppression[63].

Oral care protocols that reduce microbial load such as oral mouthwashes of 0.12% chlorhexidine digluconate or of 0.8% hydrogen peroxide are important. In cases of bacterial infections, the use of topical or systemic antibiotics including both anti-Gram+ and anti-Gram– antibiotics is recommended[6].

7. Dental complications

Patients with HNC under RT are at high risk of developing rampant decays, the "Radiation caries", due to direct enamel and dentin modifications and indirect effect of xerostomia, with accelerated decalcification of mineralized tissues[48]. When the teeth are in the irradiation field, irradiation causes decreased circulation through pulp, secondary fibrosis, and degeneration of the odontoblast processes. The effect of irradiation on tooth structure is dose dependent. Doses under 30 Gy cause minimal damage, doses 30–60 Gy increase the risk of tooth damage two to three times, while in doses over 60 Gy, there is a tenfold increase of tooth deterioration possibility[19]. Dental demineralization is thought to be mediated through the decreased buffering capacity of the saliva, the shift to cariogenic bacteria of the oral flora (Streptococcus mutans and Lactobacillus species), and the dietary changes[16]. After RT, salivary viscosity is increased and salivary pH becomes cariogenic, decreasing from 7.0 to 5.0, making minerals of enamel and dentin dissolve easily[19]. A correlation between CT-induced vomiting and dental erosion has been also reported[67]. Demineralization may progress to teeth fractures and consequent extractions and osteoradionecrosis of the jaw (ORN)[16].

Radiation caries has a quick progress, affect the cervical margins and the smooth tooth surfaces where caries is unusual in nonradiated patients; the affected teeth become discolored and demineralized, with erosions in the cervical region, which makes them fracture easily. The lesions are painless and may develop within 3 months of the completion of radiotherapy[19,48].

The prevalence in patients receiving chemoradiation ranges from 14%–21%[48].

7.1. Management

As saliva is absent or reduced, fluoride that is necessary for remineralization must be supplied through mouth care products; patients should use a strength fluoride tooth paste or gel to enhance enamel remineralization. The risk of occurrence of radiation caries is lifelong, so patients should be instructed to maintain adequate oral hygiene and to attend regular posttreatment dental checkups[16,19,48].

8. Fibrosis and Trismus

Fibrosis is a late effect from HNC RT. Trismus is a result of high-dose RT exposure to the temporomandibular joint (TMJ) region and of masticatory muscles' fibrosis with a tendency to be a persistent and chronic condition[16,48]. Trismus also occurs following head and neck surgery in combination with RT or CRT[68]. Radiotherapy is a repetitive injury, where widespread fibrosis is observed due to excess production of fibroblasts and extracellular matrix[48], and therefore, it can affect tongue function and swallowing, depending on the affected muscles, lingual or pharyngeal constructive muscles. There is a cut of a maximum mouth opening below 35 mm, where trismus is defined.[69] At this point, functional abnormalities of the maxillofacial structures are present. The incidence of trismus in HNC patients varies between 5% and 45% depending on the study[23,68]. Galitis et al.[68] reported a 37.5% of patients with trismus at the end of radiotherapy, while the reduction of mouth opening was seen in all the patients and the mean mouth opening reached the levels of trismus. Oral mucositis, with its subepithelial changes, may facilitate the development of fibrosis, with a subsequent limited mouth opening. Fibrosis may also affect the salivary glands by substitution of the gland parenchyma with fibrous tissue[48].

8.1. Management

Fibrosis and subsequent trismus, once established, are difficult to manage. In case of TMJ and masticatory muscles are included in the RT field, patient should preventively exercise by active, passive and supportive stretching of the muscles of mastication during RT. Active motion devises have been developed and tongue depressors have been used for jaw mobilization. Pentoxifylline and vitamin E as well as Low Level Light Therapy (LLLT) and botulinum toxin have potential application for prevention and/or treatment of fibrosis and trismus[16,23].

9. Osteoradionecrosis of the jaw

Osteoradionecrosis (ORN) of the jaw is an RT-induced complication, which causes significant morbidity to the patients. Definition includes irradiated bone, which becomes devitalized and exposed in the oral cavity, persisting without healing for 3 months and without tumor recurrence[48,70]. It may occur in approximately 5% of patients receiving a total radiation dose of 50 Gy or more, most commonly in the mandible[16]. Diabetes, collagen and vascular disease, tobacco and/or alcohol abuse and poor nutrition may increase the risk of ORN[70]. It is not yet clear whether radiation schedules by 3-dimensional conformal radiotherapy (3D-CRT) and intensity modified radiotherapy (IMRT) affect the risk of developing ORN; the main risk factor is the total radiation dose delivered[71]. Bone radiation (50 Gy or more) may lead to hypovascularity and osteocytes apoptosis, which causes infection, poor wound healing and bone necrosis. Most of the ORN cases occur after local trauma or dental extraction. Up to 50% of cases follow dental extractions. Spontaneous ORN is reported in almost 35% of all cases[71]. Thus, pre-radiation oral evaluation and dental management is crucial. Patient may complain of oral pain and swelling. Clinically, ORN may present with tooth mobility, exposed necrotic bone, fistula formation, or pathologic fracture or with a combination of these. Radiographically, ORN presents as poorly defined radiolucencies with areas of radiopacity[16].

9.1. Management

The aim in the treatment of ORN is the elimination of the necrotic bone and the improvement in the vascularity of the remaining radiation-damaged tissues[70]. Treatment includes control of infections with the use of chlorhexidine rinses and systemic antibiotics, surgical debridement and local sequestrectomy and, less commonly, surgical management in the case of progressive disease[71]. The use of hyperbaric oxygen remains controversial although it may be used to improve wound healing[16,70,71]. Pentoxifylline and vitamin E with or without Clodronate, in order to reduce RT-induced fibrosis and bone destruction and to stimulate osteogenesis via the antioxidant pathway, have also been assessed in the treatment of chronic progressive ORN with good results[16,71]. Other medical approaches include platelet-rich plasma, bone morphogenic protein therapy, and osteoblast stimulation[16]. Preventative strategies include a comprehensive dental evaluation before radiotherapy with elimination of infectious foci and extraction of any non-restorable tooth 3–4 weeks before radiation treatment. The cure rate of limited ORN by conservative therapy is approximately 50%, and the cure rate of surgical approaches when conservative therapy has failed is approximately 40%[71].

10. Medication related osteonecrosis of the jaw

Medication related osteonecrosis of the jaw (MRONJ) is a complication related mainly with the exposure to drugs with antiresorptive effects for osseous metastases or myeloma. However, there are reported cases associating MRONJ with agents that have no antiresorptive properties, such as TT, IT (Nivolumab) and administration of cytotoxic CT (concomitant administration of Gemcitabine, Vinorelbine and Doxorubicin)[12,34]. MRONJ is an underdiagnosed complication, with nonspecific symptoms in early stages. In most cases, a diagnosis of MRONJ requires exposed bone, or bone that can be probed through a fistula (intraoral or extraoral), persisted for more than 8 weeks, without history of radiation therapy to the jaw or obvious metastatic disease[72]. The 8-week period may be appropriate in cases of post-extraction sockets, but this observation time may not be needed when there is a clear diagnosis. In addition, there are reports of nonexposed forms of MRONJ, which should also be included in the differential diagnosis[73]. Local dental and/or periodontal infections are reported preceding to the appearance of necrotic bone in patients receiving antiresorptive therapies[74]. The radiographic findings of sclerosis or absence of the lamina dura of the involved teeth as well as periapical radiolucency and periodontal ligament widening may be indicative of early MRONJ presence[6,75]. MRONJ related to non-antiresorptive drugs has an earlier onset time and may have better prognosis since there is greater likelihood of healing and

shorter healing time compared to bone targeting agents related osteonecrosis of the jaw[12].

10.1. Management

Topical antibacterial mouth rinses and systemic antibiotic therapy, surgical debridement and local sequestrectomy along with maintaining optimal oral hygiene and eliminating active dental and periodontal diseases may be considered for conservative management in cases with no obvious disease progression or uncontrolled pain, or discontinuation of cancer therapy as a result of MRONJ. Surgery is indicated in patients with MRONJ who do not respond to conservative approaches. Several adjuvant treatments under investigation include low-level laser therapy, ozone oil, platelet-rich plasma / platelet-derived growth factor[73] and Pentoxifylline with vitamin E[76].

11. Lichenoid reactions

Immune checkpoint inhibitors are monoclonal antibodies that modulate the effects of immune checkpoints; Programmed Cell Death protein 1 (PD-1) is a co-inhibitory signal responsible for immune suppression. Anti-PD1 inhibitors due to their mechanisms of action, are associated with autoimmune-like/inflammatory side effects, with collateral damage to normal organ systems and tissues, including the skin, gastrointestinal, hepatic, pulmonary, mucocutaneous, and endocrine system[11,77]. The most common cutaneous adverse events include lichenoid reactions, eczema, vitiligo, and pruritus. Cases of lichenoid oral mucosal lesions and oral lichen planus are observed in patients treated with Nivolumab or Pembrolizumab[7,78,79]. Lesions can be spotted to the dorsal and lateral side of the tongue, lips, hard palate, the buccal mucosa or gingivae or on all of these, as whitish papules, reticular or linear, confluent in places, sometimes with erythema[7,80] (Table 4). These toxicities require prompt recognition and intervention.

In patients receiving anti-PD1 therapy, with preexisting autoimmune disease, there has been reported a flare of their underlying autoimmune condition[81] suggesting a potentially higher risk of side effects[13].

11.1. Management

According to the ESMO guidelines[83], topical emollients, oral antihistamines and/or topical or systematic steroid administration may be considered such as Betamethasone cream[78], Clobetasol ointment[47] or Prednisone 0.5–1 mg/kg with tapering over at least 4 weeks[82,83].

12. Aphthoid lesions

Agents targeting the EGFR, like the monoclonal antibody Cetuximab, also represent an important strategy in cancer management. Cetuximab, is used for HNC treatment in combination with RT or CRT. The therapeutic inhibition of EGFR is associated with cutaneous or mucosal toxicities in most of the patients; EGFR has a key role in homeostasis of the epidermal and epithelial cells. Saraswat et al.[17] reported aphthous-like lesions observed in about 7.8% of the patients treated with Cetuximab[17].

They are painful, single or multiple, well circumscribed round or ovoid superficial lesions, having a gray central area surrounded by erythematous halo, involving the non-keratinized oral mucosa (Table 4). They appear shortly after starting treatment with rapid onset and gradual disappearance[7,9,84].

12.1. Management

According to the ESMO guidelines,[83] topical or systematic administration of steroids are considered as the first line of therapy. Topical steroids like dexamethasone mouth rinse (0.1 mg/ml) and clobetasol ointment (0.05%) may be useful in the management of isolated ulcerations[16,83]. Systemic administration of 1 mg/kg oral prednisone/prednisolone for 1 week followed by dose tapering over the second week[83] is suggested for highly symptomatic ulcers, while Wang et al.[82] suggests prednisone 0.5–1 mg/kg with tapering over at least 4 weeks.

13. Oral Management at Cancer Therapy

Systematic examination of oral cavity is recommended as part of patients' monitoring.

Clinicians should be alert to the potential for increased toxicity with escalating dose or treatment duration when therapy demonstrates gastrointestinal mucosal toxicity. Systematic assessment of the oral cavity following treatment permits early identification of lesions[85]. Oral hygiene and other supportive and palliative care measures are important to minimize the severity of the lesions[86].

After cancer therapy, routine systematic oral hygiene is also important for reducing incidence and severity of oral sequelae, for restoring functional and esthetic impairments and for removing the remaining foci of infection[87]. Patients should be followed up every month for the first 3 months, every 3 months for the first year and every 6 months from there on[88].

14. Conclusion

Treatment-related oral complications require increased awareness and recognition to promote prevention and appropriate intervention in order to limit dose modifications and preserve patients' QoL. It is noteworthy that treatment-related oral changes can be underreported when relying upon patient's report who may be hesitant to report them, as patients are afraid of a therapy adjustment. Treatment-related toxicities are also associated with high costs; patients often visit the emergency departments, are hospitalized, and are in need of supportive agents for pain management and palliation. It is important to be aware of these complications so that appropriate measures can be properly implemented; multidisciplinary health care teams must be integrated and effectively communicating in order to provide the best patient care. Experienced oral health care professionals should be included. Further research into the epidemiology, pathobiology, and analysis of HNC-related toxicities would help in minimizing acute and late effects of therapy.

Author Contributions

All authors have critically revised the paper and have approved the version to be published. Furthermore, authors MK, ONG, AV, and VK have contributed to the conception and design of the work and the acquisition, analysis, and interpretation of data for the work; authors EP, EV, and AP have contributed to the analysis and interpretation of data for the work; authors EK, MT, AZ, ZL, and EG have contributed to the acquisition and interpretation of data for the work.

Disclosure

The authors have no conflicts of interest to declare.

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