

Review Article

Dental Management of Head and Neck Cancer Patients Treated with Radiotherapy and Chemotherapy

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Abstract

Radiotherapy (RT) induced oral complications are complex, dynamic pathobiological processes that predispose patients to serious clinical disorders. The head and neck region is composed of numerous structures, each with an inherent response to radiation that is largely governed by the presence or absence of mucosa, salivary glands, or specialized organs within that site. Irradiated mucocutaneous tissues demonstrate increased vascular permeability that leads to fibrin deposition, subsequent collagen formation, and eventual fibrosis. Irradiated salivary tissue degenerates after relatively small doses, leading to markedly diminished salivary output. Radiotherapy-induced damage in the oral cavity is due to harmful effects of radiation on oral mucosa, dentition, salivary glands, masticatory musculature and bone. Thus, timely treatment planning and prevention is important and needs to be done before radiotherapy to avoid complications such as osteoradionecrosis (ORN). Chemotherapy may be administered as an adjunct to RT. Patients undergoing concurrent chemotherapy and RT are at greater risk for oral mucositis and secondary oral infections such as candidiasis.

Keywords: Oral cancer; Radiotherapy; Oral complications

Abbreviations

HNC: Head and Neck Cancer; RT: Radiotherapy; ORN: Osteoradionecrosis; IMRT: Intensity Modulated Radiation Therapy; DEJ: Dentinoenamel Junction; TMJ: Temporomandibular Joint

Introduction

Cancer has become a big threat to human beings globally. According to Indian population census data, the rate of mortality due to cancer in India was about 806000 existing cases by the end of the last century. Cancer is the second most common disease in India responsible for maximum mortality with about 0.3 million deaths per year [1].

Head and neck cancers (HNC), which are often treated with radiation therapy (RT) utilizes ionizing radiation and produces therapeutic effect by semi-selectively damaging the genetic material of vulnerable malignant cells directly or through the production of free radicals that result in cell death [2].

Complications of radiotherapy arise by the same process that damages normal cells, especially those that are rapidly dividing or less capable of repairing radiation induced damage [3]. In the oral cavity these can be cells of the mucous membrane, underlying soft tissue, tooth, periosteum, bone, glands and vasculature resulting in specific radiation syndromes. Such syndromes include xerostomia and dysgeusia from salivary gland damage, mucositis from epithelial damage, pathological alterations in the normal flora alterations, radiation caries, reduced mouth opening from changes in collagen structure and osteoradionecrosis of the jaw (ORN) from reduced bone healing capacity [4-8].

A lack of tooth sensitivity was noted during the placement

of restorations without anesthesia in patients who had received radiation therapy. Clinical data suggests normal blood flow and sensitivity of dental pulp are impaired in such patients. Radiotherapy may potentially lead to decreased vascularization within the dental pulp with the possibility of subsequent fibrosis and atrophy. The determination of pulp status is the key procedure to evaluate health or pathology of the pulp and is an important factor for decision making regarding whether endodontic intervention such as pulpotomy or pulpectomy are necessary [9].

Management of oral health is especially important for the HNC patient as oral complications are common both during and after radiation. While the majority of oral complications are unavoidable consequences of ionizing radiation (deterministic), some are preventable [10]. The incidence of some complications is associated with treatment factors, such as in the case of osteoradionecrosis and dental extractions [11]. As oral complications are common, potentially preventable and have iatrogenic factors, it is essential that those working with HNC patients be aware of the prevention and management of radiotherapy-related oral complications.

In this article we aim to highlight the current management strategies of dental complications during and after radiotherapy and chemotherapy.

Oral complications of head and neck RT

Xerostomia and salivary gland hypo function: Xerostomia is the most common oral complication of head and neck RT. On an average, 64% of patients treated with conventional head and neck RT still experience moderate to severe permanent xerostomia after 22 years of radiation therapy [12].

Salivary glands are very sensitive to radiation. There is a sharp

decrease in the salivary flow rate during the first week of RT with conventional fractionation (2 Gy/day). The decrease in flow rate continues throughout the treatment period, especially when both parotids are irradiated [13]. This correlates to the dose and duration of RT. There is immediate serous cell death accompanied by inflammatory cell infiltration, and then continuous reduction of salivary flow rates. Patients often complain of thick, ropy saliva and a sensation that there is too much saliva because it is difficult to swallow.

With conventional RT, xerostomia is permanent. Salivary gland-sparing intensity modulated radiation therapy (IMRT) is associated with gradual recovery of salivary flow over time, and improved quality of life as compared to conventional RT [14,15]. Residual salivary flow can be stimulated by sialogogues such as pilocarpine or cevimeline and/or use of sugarless gum.

Radiation mucositis: Mucositis is a common acute short-term complication of head and neck RT. It is characterized by ulceration in the oro-esophageal and gastrointestinal mucosa, resulting in significant pain and dysphagia [16].

Mucositis initially presents clinically as erythema after 4-5 days of therapy, corresponding to cumulative doses of 10 Gy to the head and neck. The patient often complains of oral burning or intolerance to spicy food. As the mucositis progresses after cumulative radiation doses of 30 Gy (approximately two weeks), ulcers develop. Radiation-induced mucositis can involve any radiation-exposed area, including the hard palate. It may be worse in tissue in direct contact with metallic restorations. Radiation-induced mucositis peaks at two weeks post RT of 60-70 Gy. This ulcerative phase may last for up to 5-7 weeks following RT, with gradual healing. Chronic mucositis is a rare occurrence following RT [17].

Mucositis has a significant health and economic impact on cancer patients. It is one of the most common reasons for a break in the administration of RT [17]. Measures specifically designed to prevent and treat oral mucositis can be provided by the patient's oncology team. The dentist can assist by providing basic oral care consisting of patient education, disease control, and oral hygiene instruction. These measures can decrease the microbial load in the oral cavity and prevent other complications associated with therapy. In addition, patients who have heavily restored teeth may benefit from the use of silicone mucosal guards worn during RT to reduce the severity of mucositis associated with scatter of radiation off metal restorations [18,19].

Oropharyngeal candidiasis (OPC): This is a very frequent complication of cancer therapy; up to 27 percent of patients undergoing RT present with evidence of OPC [20]. It may present as a pseudo membranous candidiasis (thrush), with thick white plaques that wipe off, or as generalized erythema and burning discomfort. Clotrimazole has been shown to be effective for treatment of OPC; Clotrimazole 10 mg troches administered five times per day are effective in treating mild to moderate OPC [21]. Although initially encountered during RT, it also can present a long-term problem in patients with xerostomia. Antifungal prophylaxis may be beneficial in high-risk patients.

Dental caries: After standard RT there is a profound shift in the

oral micro flora to a predominance of acidogenic microbes, primarily *Streptococcus mutans* and *Lactobacilli*, coincident with a decrease in salivary flow, and an increase in caries risk [22]. Dental caries in irradiated patients may develop rapidly, as early as three months after RT. Lesions typically involve the cervical portions of the teeth; however, caries may affect any tooth surface, including those typically resistant to dental caries such as the incisal edges of the mandibular incisors [23].

RT also affects the dental hard tissues increasing their susceptibility to demineralization [24]. Springer et al. concluded in a study that irradiation is thought to have a direct destructive effect on dental hard tissue, especially at the dentinoenamel junction (DEJ) [25]. Besides destruction at the DEJ, significant micro-morphometric differences in the demineralized nature of irradiated enamel occur, suggesting that enamel is less resistant to acid attack after irradiation [25]. It was observed that minimal tooth damage occurs below 30 Gy; there was a 2-3 times increased risk of tooth breakdown between 30 and 60 Gy likely related to salivary gland impact; and a 10 times increased risk of tooth damage when the tooth-level dose is above 60 Gy indicating radiation-induced damage to the tooth in addition to salivary gland damage. These findings suggest a direct effect of radiation on tooth structure with increasing radiation dose to the tooth [26].

Cisplatin is a potent cytostatic agent frequently used in the treatment for malignant tumors. Seifrtova et al. [27] in their study stated that when dental pulp stem cells were exposed to 5, 10, 20, or 40 mmol/L cisplatin they had a greater genotoxic stress response compared with normal human dermal fibroblasts. Cisplatin is high concentrations activates mitogen-activated protein kinases and apoptosis in dental pulp stem cells and not human dermal fibroblasts. Gene p53, being tumor suppressor protein, is an essential regulator of the cell cycle and apoptosis and plays an important role in Cisplatin activity. There is evidence in the literature that the use of chemotherapeutic agents such as cisplatin can lead to an increased inflammatory response in the arterial vessel wall [9].

Dental caries can progress and involve the pulp due to lack of tooth sensitivity in patients who had received radiation therapy to head and neck. The risk of rampant tooth decay with its sudden onset and osteoradionecrosis is a lifelong threat. Thus, the diagnosis of pulp vitality is highly important in patients with malignant oral and oro pharyngeal tumors undergoing radiotherapy because changes can involve periradicular tissues and predispose patients to developing osteoradionecrosis [9].

Periodontal disease: RT effects on periodontal health include direct and indirect changes in the oral micro flora caused by radiation-induced xerostomia. Accelerated periodontal attachment loss and increased risk for osteoradionecrosis (ORN) associated with periodontal disease are the main problems associated with RT. RT causes changes in both bone and soft tissue that can produce hypovascular, hypocellular and hypoxic bone [28,29]. The affected bone fails to remodel leading to increased risk of infection, which can lead to osteoradionecrosis.

Ebstein et al. in a study showed increased tooth loss and greater periodontal attachment loss in teeth that were within high-dose irradiated sites [30]. Because attachment loss in teeth was greater in the irradiated fields, the dentists must consider the impact of

increased attachment loss on remaining teeth, when planning dental treatment before RT.

Osteoradionecrosis (ORN): ORN is caused by the hypoxic, hypocellular, hypovascular deterioration of bone that has been irradiated. Marx [28] has proposed that this results from the radiation-induced deficient cellular turnover and collagen synthesis in a hypoxic, hypovascular and hypocellular environment in which tissue breakdown exceeds the repair capabilities of the wounded tissue. Clinically, ORN may initially present as bone lysis under intact gingiva and mucosa. This process is self-limiting because the damaged bone sequesters, then is shed with subsequent healing. If the soft tissue breaks down, the bone becomes exposed to saliva and secondary contamination occurs. Sepsis may also be a complication by dental extraction or surgery, producing a more aggressive form. This progressive form may produce severe pain or fracture, and require extensive resection.

A retrospective study showed reduced incidence of ORN following IMRT for head and neck cancer. This reduced incidence was attributed to parotid sparing and better dental treatment, which reduced the number of dental extractions and surgical procedures required post-radiotherapy [10].

Trismus: Trismus can be a significant side effect of RT, especially if the lateral pterygoid muscles are in the field. In a study, patients in whom the pterygoid muscles were irradiated and not the temporomandibular joint (TMJ), 31 percent experienced trismus. In addition, radiation to the TMJ also was associated with a decrease in maximum vertical opening [31,32]. Limited mouth opening can interfere with proper oral hygiene and dental treatment. Therefore, before RT starts, patients who are at risk for developing trismus should receive instruction in jaw exercises that will help them maintain maximum mouth opening and jaw mobility. Tongue blades can be used to gradually increase the mandibular opening. Dynamic bite opening appliances have also been used [33].

The dentist should measure the patient's maximum mouth opening and lateral movements before RT, and reevaluate mandibular opening and function at follow-up dental visits. For patients who experience reduced mouth opening, the intensity and frequency of the exercises should increase, and a physical therapy regimen prescribed.

Management

Frequent follow-up should be done for patients after completion of radiotherapy. Scaling and root planning should be done under proper antibiotic coverage if proper oral hygiene is not maintained by the patient. Carious lesions should be restored immediately. Dental extractions after irradiation should be avoided and postponed if possible. Consequently, endodontic therapy should be the treatment of choice in many cases. Endodontic therapy has been shown to be a viable alternative to exodontia, since traumatic injury will be kept to a minimum thus reducing the risk of osteoradionecrosis [34,35].

Goals of dental management

1. Goals during cancer therapy
 - a. provide supportive care
 - b. provide treatment

2. Long-term, post-treatment goals
 - a. manage xerostomia;
 - b. prevent and minimize trismus;
 - c. prevent and treat dental caries;
 - d. prevent post radiation osteoradionecrosis (ORN)

Management of mucositis

Methods used to prevent and treat mucositis include good dental hygiene such as frequent brushing with a soft, regularly replaced toothbrush, regular flossing, four-hourly non-medicated oral rinses, adequate hydration and avoidance of oral irritants such as alcohol and tobacco, use of mucosal-coating drugs and pain management therapy [36].

Patients with Oropharyngeal pain require oral care along with systemic analgesics which include opioid analgesics. Mucositis should be treated conservatively to prevent further tissue irritation and damaging of the remaining regenerative epithelial cells [37]. Locally applied drugs used to prevent or treat mucositis include vitamin E, anti-inflammatory substances, cytokines and multidrug topical mouth rinses [38,39]. The Multinational Association of Supportive Care in Cancer (MASCC) and the International Society of Oral Oncology (ISOO) updated guidelines recommend that sucralfate, chlorhexidine and antimicrobial lozenges not be used for the prevention of radiotherapy induced oral mucositis [40]. Other agents that have been found useful include aloe vera gels and honey products [41,42].

In patients with metal fillings, mucosal guards made of putty silicone impression material are used to cover the teeth to prevent radiation backscatter, thus reducing incidence of local mucositis [43]. Patients should receive appropriate analgesia for their pain.

Management of oral candidiasis

Topical treatments (topical polyenes, azoles, chlorhexidine) are recommended as first-line therapy for milder forms of candidiasis. Drugs that provide prolonged contact time and are not sweetened with sucrose may help more in successful prevention and management with a low risk of oral/dental complications [44,45].

For myelosuppressed patients, prevention with fluconazole should be started. Topical antifungals along with systemic prophylaxis (azoles, caspofungin (micafungin), amphotericin B) has been shown to reduce oral colonization, which can lead to a reduced risk of subsequent local and systemic infection [45]. Increased resistance to fluconazole has been seen in oral candidiasis causing organism *Candida albicans* and other species like *Candida krusei*, *Cronobacter dublinensis*. Such cases can be managed with an increased dose, a change in antifungal treatment and the addition of topical agents. Amphotericin B and some new classes of antifungals like echinocandins can be used in patients with resistant infection. Management of underlying risk factors like hyposalivation may facilitate management and reduce the risk of chronic or recurrent infection.

Management of trismus

High-energy radiography beams and sophisticated multiple-field techniques can be used to reduce the dose of radiotherapy to

the temporomandibular joint and to the mastication muscles. Early signs of trismus must be identified. A simple test to identify trismus is done, called the three finger test, in which the patient is asked to insert three fingers into the mouth. Passive and active physiotherapy devices are used in management of trismus. These instruments include aggregated tongue blades or forced opening with finger pressure several times per day [39].

Management of osteoradionecrosis

Local debridement, antibiotic treatment and ultrasonography can be performed and is found to be successful if diagnosed early [46]. In patients with advanced disease, the use of hyperbaric oxygen coupled with resection of necrotic bone is indicated [47].

Management of xerostomia

Doses of medications causing xerostomia (antianxiety medications, antidepressants, antihypertensives or opioid analgesics) can be decreased to reduce oral dryness. Intake of water is encouraged to maintain hydration. Caffeine should be avoided as it leads to decreased saliva production. Tobacco cessation should be encouraged.

Salivary substitutes to relieve symptoms and sialogogic agents to stimulate saliva can be used [48].

Sialogogues like Pilocarpine hydrochloride, a nonspecific muscarinic β -adrenergic agonist [49], was the first drug approved that showed increased salivary flow rates under both resting and stimulated conditions compared with baseline (standard dosing of 5 mg 3 times a day). A study indicated that the efficacy of oral Pilocarpine was dependent on the dose distributed to the gland [50]. A newer muscarinic agonist, Cevimeline, selective M3 muscarinic receptor, can be administered 30–45 mg three times daily for 52 weeks-very few adverse effects, increased unstimulated but not stimulated saliva [51]. Contraindications to both the drugs include asthma, iritis, and glaucoma. Lemon candy can be sucked to increase the amount of whole saliva secretion and hence improve oral dryness. Sugar-free gums containing xylitol may stimulate salivary flow, buffering, sugar clearance and can prevent dental decay [52].

Oral mucosal lubricants/saliva substitutes are the treatment of choice for patients who do not respond to pharmacological gustatory or masticatory stimulation. Saliva substitutes are based on different substances, including animal mucin, carboxymethyl-cellulose, xanthan gum and aloe vera. All may relieve xerostomia, but a common major disadvantage is the generally short duration of relief they provide. Topical anesthetics and analgesics may alleviate pain and anti-inflammatory agents may reduce irritation.

Manual acupuncture using auricular points supplemented with electro-stimulation is a well-described method for providing relief from xerostomia. It is administered twice weekly for 6 weeks, xerostomia problems significantly improved and un-stimulated whole saliva flow rates increased [53].

Stem cell replacement therapy may be a good option to treat radiotherapy-induced hyposalivation but a better understanding of the mechanism is still needed [54].

Management of radiation-induced caries

The restoration of radiation induced dental caries can be extremely challenging due to difficult access to cervical lesions which

leads to incomplete excavation of caries. The cavity preparation can be difficult to define and provide little mechanical retention [55]. Also, selection of an appropriate restorative material is difficult due to the challenging oral environment found in irradiated patients. The chosen material should have appropriate adhesion, prevent secondary caries and resist dehydration and acid erosion. McComb et al. [56] proved the effectiveness of fluoride-releasing materials in the prevention of recurrent caries in irradiated patients.

Radiation induced changes in enamel and dentine may compromise bonding of adhesive materials [55]. Free radicals are released in dentin due to hydrolysis of water molecules leading to denaturation of collagen and reduction in its mechanical properties [56]. These free radicals interfere with the polymerization of resins [57]. Thus, composite restorations are not a good restorative option in these patients as there are chances of loss of retention and recurrent caries [58]. However, glass ionomer cements seem to be an effective alternative restorative material [59]. Hu et al. [59] proved in a study that glass ionomers can prevent development of secondary caries, even after loss of restorations. Glass ionomers showed good handling, adhesion and physical properties. However, lack of salivary buffering in xerostomic patients can lead to a reduction of normal plaque pH and in turn lead to the formation of hydrofluoric acid and erosion of the glass ionomer [60].

Mouth rinse solutions and remineralizing toothpastes containing casein derivatives coupled with calcium phosphate (CD-CP) were found effective in preventing caries in irradiated patients [61].

Extensive caries increases the risk of involvement of pulp. Radiation therapy may alter pulp vascularity and can affect its repair capacity [62]. When caries involves the pulp in the radiation field, endodontic treatment is preferred to extraction to minimize the risk of ORN.

Patients should be made aware of the importance of maintaining good oral hygiene. They should be instructed about the benefits of using custom carrier trays for application of fluoride or chlorhexidine gels throughout life. It is imperative to keep patient under supervision to reduce the incidence of radiation caries.

Conclusion

All the members of the treatment team must be informed of the oncologic treatment plan. Oral care should be initiated at the onset of treatment, with the goal of reducing morbidity and improving compliance.

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