Review Article

Effects of Head and Neck Radiotherapy on the Oral Cavity and Direct Restorative Materials

Apinya Limvisitsakul[1], Anussara Prayongrat[2], Pisol Senawongse[1]

[1]Department of Operative Dentistry and Endodontics, Faculty of Dentistry, Mahidol University, Bangkok, Thailand

[2]King Chulalongkorn Memorial Hospital, Department of Radiation Oncology, Bangkok, Thailand

Abstract

Many intraoral complications that result from high-energy electromagnetic waves of radiation can occur in patients undergoing head and neck cancer therapy. Information about the impact of radiation therapy on the oral cavity and restorative materials is important and enables patient assessments, evaluations, and management as well as treatment planning. Therefore, this article aims to highlight the current understanding and management of dental needs in patients after radiation therapy. This report discusses radiation-induced mucositis, salivary gland hypofunction, alveolar bone changes, trismus, dentition breakdown, and radiation caries. Moreover, the impact of radiotherapy on the properties and clinical efficacy of restorative materials are included in this report.

Keywords : Head and neck cancer, Management, Radiotherapy, Restoration

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Correspondence to :
Pisol Senawongse, Department of Operative Dentistry and Endodontics Faculty of Dentistry, Mahidol University 6 Yothi Street, Rajthevi Bangkok 10400, Thailand Email: pisol.sen@mahidol.ac.th

Introduction

Head and neck cancer is one of the most common cancers in Thailand. According to a report of the National Cancer Registry and findings from local and international publications, head and neck cancer is among the top ten leading types of cancers in the Thai population. The risk factors associated with head and neck cancer include tobacco use, alcohol consumption, human papillomavirus (HPV) infection and Epstein-Barr virus (EBV) infection.[1] Surgical resection, chemotherapy, radiation therapy, and immunotherapy, either as a single modality or combination, are used for head and neck cancer treatment.[2]

Radiation treatment (radiotherapy or irradiation) uses high-energy particles (e.g., electrons and protons) or electromagnetic waves (photon beams such as X-rays or gamma rays) to destroy cancer cells. Dividing cancer cells are more sensitive to radiation than normal tissue such as the salivary gland, or the spinal cord.[3,4] The radiobiological effect of radiation is mainly related to DNA damage and occurs by two mechanisms. First, ionizing radiation directly interacts with nuclear DNA, causing damage to the nucleotide bases, single-strand breaks (SSBs), and double-strand breaks (DSBs); these are known as direct effects. Moreover,

radiation induces the ionization of water (75 % of cell components and other molecules), leading to an increased production of free radicals within the cells, which further damages the DNA; this is known as an indirect effect, as shown in Figure 1.

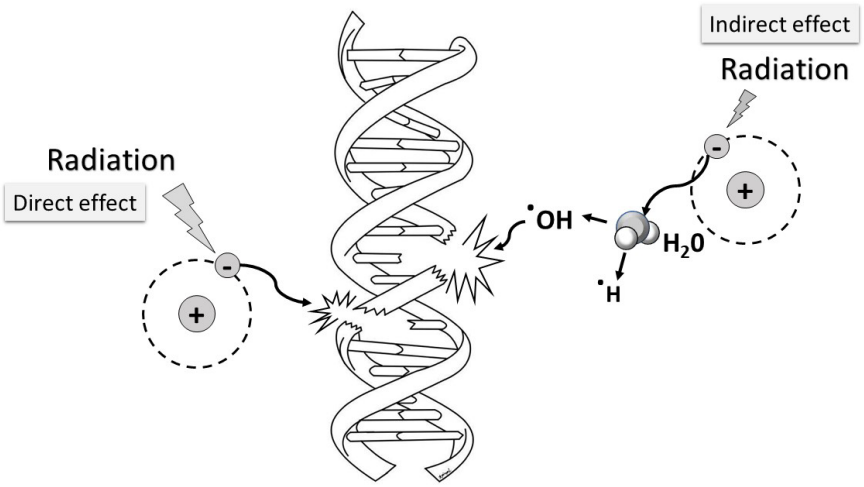

Figure 1 *The direct and indirect effects of radiotherapy (modified from Ito A et al., 2006)*[5]

The destruction of DNA interferes with the cellular ability to pass on genetic information, replicate and repair, resulting in cell death.[2,6]

Radiotherapy can be categorized by the type of delivery as external radiation (teletherapy), internal radiation (brachytherapy), and systemic radiation. Teletherapy refers to radiation treatment given by an external radiation source at a distance from the body. Teletherapy is the most common type of radiotherapy used in cancer treatment, especially for head and neck cancers. Brachytherapy is a cancer treatment that places radioactive material directly inside or close to the tumor. This approach is suitable for treating a smaller area with a higher dose and requires a shorter treatment time than teletherapy. Systemic radiation refers to the use of radiation in a liquid form, which is injected into a vein or swallowed by the patient into the body to target the tumor.[7]

There are many oral adverse effects of head and neck radiotherapy, such as sore mouth (oral mucositis), ulceration, intraoral infection, dry mouth (xerostomia), taste change (dysgeusia), radiation caries, stiff jaw (trismus), progressive periodontal attachment loss, and osteoradionecrosis (ORN). These conditions affect the quality of life of a patient. The degree and progression of the complications are related to the irradiated dose, volume of normal tissues and maturity of affected cells. This review summarizes the radiation-induced effects on oral structures.

In total, 65 reports were included in this study. There were seven reports about radiation therapy and 32 reports about oral adverse effects such as trismus, alveolar bone changing, salivary hypofunction, dentition breakdown. There were 16 reports used in discussion about the effect of radiation on restorative material and bonding performance. In addition, there were ten reports used in discussion about oral management.

A selection of 65 electronic searches were conducted for scientific reports that discussed the effect of head and neck radiation therapy on oral tissue structures and restoration materials based on *in vivo* and *in vitro* studies without any restrictions on publication year. Medline, PubMed, and Google Scholar were screened. The following keywords were used: head and neck cancer, radiation, radiotherapy, oral effect and complication. The search process was repeated in each database.

Radiation-induced mucositis

Mucositis is an acute side effect of head and neck radiotherapy and usually occurs approximately three weeks after the start of treatment.[8] Common symptoms reported

by patients include pain, burning sensations and swallowing discomfort. The mucous membrane or mucosa consists of an epithelial cell layer overlying the connective tissue, which is more susceptible to radiotherapy because of its rapid cellular division. Therefore, epithelial cell loss and reduced cell renewal induced by radiotherapy cause mucosal atrophy, ulceration and mucositis.[9]

Radiation-induced xerostomia/dry mouth/salivary gland hypofunction

Saliva is an exocrine solution consisting of 99 % water and 1 % of a variety of electrolytes and proteins. Ninety percent of saliva is secreted from three pairs of major salivary glands: parotid, submandibular, and sublingual glands. The average total flow of saliva ranges from 1-1.5 L per day. In unstimulated situations, the percentage contributions to salivary flow are as follows: 20 % from the parotid glands, 65 % from the submandibular glands, 7-8 % from the sublingual glands, and less than 10 % from the minor salivary glands. In simulated situations, the parotid gland is responsible for more than 50 % of the secretions.[10] Saliva plays a role in maintaining oral health and is involved in protection, digestion, lubrication, facilitating oral processing, maintaining a neutral pH, and preventing tooth demineralization.[11] Radiation causes damage to salivary gland cells, resulting in salivary fibrosis, a reduced salivary flow rate, altered salivary composition, and xerostomia. There are two mechanisms of radiotherapy-induced salivary gland hypofunction. The first mechanism is the direct effect on the DNA of acinar cells of the salivary gland, leading to cell death. The second mechanism is the radiation-induced changes in microvascular endothelial cells within the salivary gland. Ionizing radiation increases the permeability of endothelial cells, leading to interstitial edema. High pressure in the interstitial area causes compression of the gland's channels and progressive ductal obstruction. Because radiation induces hypocellularity, hypovascularity, and hypoxia, the salivary glands become atrophied and fibrotic.[12,13] As a result, oral dryness (xerostomia) occurs as an early symptom of radiation therapy and lasts for several months. The severity of radiation-induced salivary hypofunction depends on the irradiated dose and volume of salivary gland tissues.[11]

In an attempt to increase tumor control and decrease toxicity from cancer therapy, advanced radiotherapy technology, such as intensity-modulated radiotherapy (IMRT), has been developed. IMRT is a treatment planning algorithm that maximizes dose conformity to tumors and minimizes unnecessary dose to surrounding normal tissues. In head and neck irradiation, IMRT allows for a decreased dose to the parotid gland compared to conventional techniques, as shown in Figure 2.

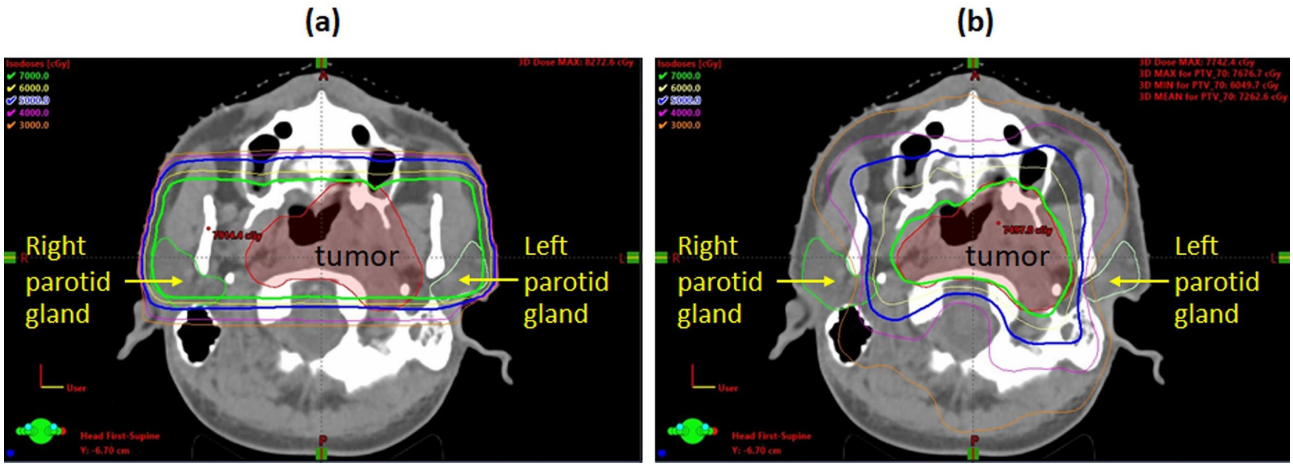

Figure 2 *Radiation dose distribution with the conventional radiation technique (a) and intensity-modulated radiotherapy (IMRT) technique (b). Radiation doses of 50 Gy (green line) and 70 Gy (blue line) to the microscopic (subclinical) and gross tumor volumes, respectively. The recommended median dose to the parotid glands is <30 Gy (orange line), and these glands are better spared by the use of the IMRT technique*

Clinical studies involving nasopharyngeal carcinoma patients reported that the xerostomia rate was significantly reduced with IMRT treatment compared to with conventional techniques (39 % versus 82 %), leading to an improved xerostomia rate and better quality of life for patients.[14-16] Currently, IMRT is considered a standard radiotherapy technique for nasopharyngeal carcinoma and is widely accepted in other types of head and neck cancers.[17]

Radiation-induced alveolar bone changes and osteoradionecrosis

Radiation treatment has detrimental effects on osteocytes and the microvascular system. The severity of the bone response depends on the maturity status of the bone and radiation dose. If the bone is affected in the early dividing stage, growth retardation occurs.[18,19] Three common terms of radiation-induced changes in the irradiated bone are bone loss (atrophy), radiation osteitis, and ORN.[20] Radiation-induced microvascular impairment contributes to the hypocellular, hypovascular, and hypoxic conditions of bone tissues. Alterations in the remodeling cycle also lead to bone loss and loss of healing potential. However, the effects of radiation on the remodeling process are still controversial. Some studies have reported that radiation directly disturbs proliferation and damages osteoblast cells, which are responsible for the bone forming process.[19,21] In contrast, some reported that osteoclasts were more sensitive to radiation than osteoblasts.[22] Wright *et al.* demonstrated that irradiated bone had increased osteoclast cell volume but there was no difference in osteoblast volume compared to non irradiated control bone at one-week post radiotherapy. The radiation-induced proliferation of osteoclasts is responsible for the bone matrix resorbing process, leading to bone atrophy.[23]

ORN is a term describing the death of exposed bone that results from radiation-induced failure of the healing process, as shown in Figure 3.

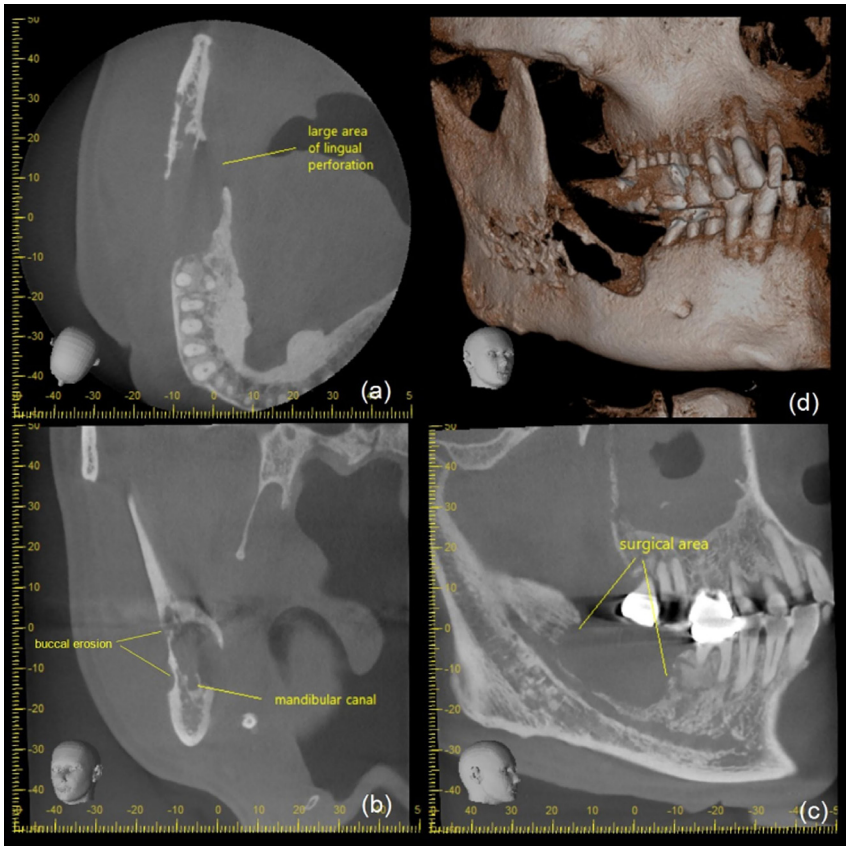

Figure 3 *Shows the Cone beam computed tomography (CBCT) images of ill-defined bone destruction. The patient had a history of radiation therapy for nasopharyngeal cancer and sequestrectomy of osteoradionecrosis at the right posterior region of the mandible: axial view (a), coronal view (b), sagittal view (c), and 3D volume rendering view (d)*

This complication occurs more commonly in the mandible than in the maxilla due to the poorer blood supply and higher bone density of the mandibular bone.[24] ORN can occur with or without infection or injury.[25] Orofacial fistulas, pain, ulceration and necrotic bone exposure for longer than three months are clinical symptoms of ORN. There are many risk factors associated with ORN progression. Local risk factors include the tumor site, tumor stage, radiation field, radiation dose, poor oral hygiene, and trauma (such as dental extraction, implant placement, biopsy, and periodontal surgery before or after radiotherapy). Systemic factors associated with the development of ORN are advanced age, smoking, alcohol consumption, immunodeficiency, and the underlying medical conditions of the patient.[20,24,26]

The alteration of alveolar bone after radiotherapy depends on the severity of bone destruction. Radiograph images can show a widening periodontal ligament followed by bone sclerosis, periodontal disease-like bone loss, and bone resorption.[18] The widening of the periodontal ligament (PDL) space is commonly observed within three years after radiation, especially in patients who receive radiation doses greater than 45 Gy. The difference between radiation-induced widening of the PDL with resorption and periodontal disease or periapical infection is the epicenter position, as shown in Figure 4.

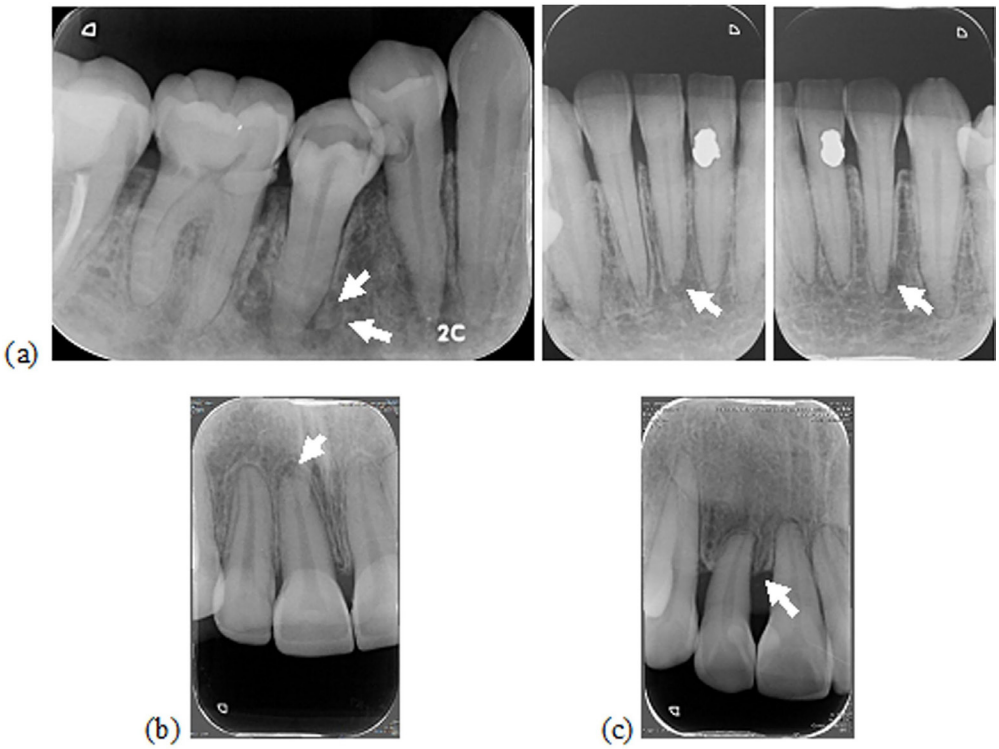

Figure 4 *Periapical radiograph of the combination of bone sclerosis and bone destruction around the teeth and alveolar crest and the widening of the PDL space in patients who had a history of radiation therapy for cancer in the base of the tongue (a). The periapical film of patients with periapical disease in the anterior maxillary teeth due to accidental trauma showing a radiolucent and widening PDL at the apex of the root (b). In another case, the periapical film of a patient with periodontal disease in the right lateral maxillary teeth due to traumatic occlusion showed horizontal bone loss of the alveolar crest (c)*

Periodontal disease causes alveolar crest bone resorption, whereas periapical disease shows lesions at the apex of the root. When there are radiation effects, radiographs show no definite initiating point with no clinical manifestation of periodontal or periapical disease.[20]

Radiation-induced trismus

Trismus refers to restricted mouth opening due to a tonic contraction of the mastication muscle.[27] Trismus is a complication of head and neck radiation therapy. The prevalence of trismus after radiotherapy is dependent

on the radiation dose and treatment technique.[28] A study by Bensadoun reported that the prevalence of trismus in the conventional radiotherapy group was 25.2 %, while it was 5 % in the IMRT group. In a study of patients who received both radiotherapy and chemotherapy, it was found that the trismus prevalence was 30.7 %. Greater radiation doses, especially those exceeding 60 Gy, may be related to the higher severity and prevalence of trismus.[29,30] Radiotherapy may have detrimental effects on the masticatory muscle which can lead to the abnormal proliferation of fibroblasts, which causes fibrosis of the skin and muscle. Impaired mandibular motion significantly affects quality of life. Limited mouth opening results in difficulties with eating and speaking, and compromises oral hygiene. There are various methods for treating and managing trismus, such as drugs, devices, exercise and physiotherapy.[30]

Moreover, radiotherapy of the head and neck muscle affects not only the masticatory muscle but also the neck muscle. High-dose radiation induces neck muscle spasms with or without pain. The motions associated with head turning, lifting and yawning may be affected.[31] Therefore, the tightness of the neck muscles may disturb the motions needed for teeth brushing, which affects the oral hygiene of the patient.

Radiation-induced dentition breakdown and radiation caries

Radiotherapy increases the likelihood of dentition breakdown, especially in the cervical area, cuspal region, incisal edge, and loading area. Tooth destruction originates from an enamel microcrack and then progresses to localized enamel delamination, generalized delamination and dentin exposure, as shown in Figure 5.

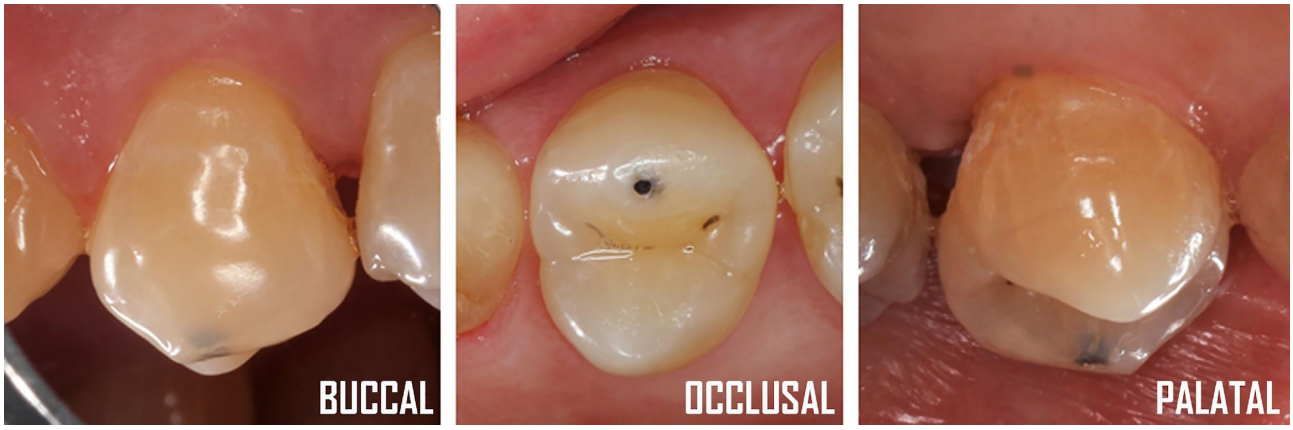

Figure 5 *Tooth destruction in the cuspal region in patients who had undergone head and neck radiation therapy*

The severity of dentition breakdown depends on the radiation dose.[32] Radiation-induced alterations to the microstructures of enamel and dentin were demonstrated by a reduction in microhardness and elastic modulus.[33,34] In contrast to a previous study, Brauer *et al.* did not find a significant dose-response relationship between radiation dose and elastic modulus and hardness.[35] In an *in vivo* study, there were significant differences in optical retardation values of birefringence at the cervical region of enamel between teeth extracted from irradiated head and neck cancer patients versus those extracted from the control group. Irradiated teeth presented slight morphologic alterations in enamel with evident interprismatic space, cracks in the dentinal structure, dentinal tubule obstructions, and increased destruction of the collagen network with fragmented fibers on scanning microscope images.[36,37] Furthermore, several studies reported the effects of radiation on the organic matrix of tooth structure. Reed *et al.* reported that radiation decreased the protein/mineral ratio of dentin and increased the stiffness of the tooth structure.[33] In contrast, Springer *et al.* found no direct effects of radiation on the collagen and extracellular matrix of dental tissue.[38] Collagen and protein-based organic matrix is a major component of the dentin-enamel junction (DEJ), which is

referred to as a boundary structure between enamel and dentin. An *in vivo* study revealed that radiation induced activation of the MMP collagenase enzyme, leading to collagen destruction in the DEJ.[39,40] Both DEJ destruction and increased stiffness of the tooth structure cause enamel delamination and dentin exposure.

After radiation treatment, dental caries rapidly occur and progress. This is a multifactorial condition that is related to radiation effects and includes hyposalivation, postradiation microbial changes, dentition impairment, and oral pain. As previously mentioned, saliva is a necessary substance that has buffering, cleansing and protective abilities and can reduce the progression of caries and maintain oral health.[41] Hyposalivation due to radiation therapy plays a major role in caries development. The critical pH of dentin is higher than that of enamel (approximately 6.7 and 5.5, respectively). Therefore, the effects of radiation-induced alterations to tooth microstructures, enamel delamination, and dentin exposure promote more susceptibility to dental caries in irradiated patients.

Radiation effects on direct restorative dental materials

Restorative dental materials are substances that are used to reconstruct or enhance the patient's teeth. The direct restorative materials include amalgam, glass ionomer cement and resin composite.

Amalgam is a material that has a strong buffering capacity and antibacterial effect.[42] It requires cavity preparation for mechanical retention. There are no reports about the adverse effects of radiation on the properties of amalgam. However, artifacts from amalgam restoration adversely affect the image quality of computed tomography scans (CT scans), leading to little information for the radiation treatment planning process. Moreover, amalgam results in an inaccurate dose calculation to the tumor and nearby normal tissues. Therefore, it has been suggested that resin composite should be used before radiation treatment instead of amalgam filling.[43]

Glass ionomer cement is a fluoride-releasing material that has a buffering capacity and antibacterial effect. This material marginally inhibited caries in the clinic in a two-year observation of xerostomic irradiated head and neck cancer patients.[44-46] Glass ionomer cement easily loses anatomical form and marginal adaptation.[44] Although glass ionomer cement has a chemical bond to the tooth structure, material dislodgement has been reported.[46] There was no clarification on how irradiation can effect the retention loss of glass ionomer cement. Yesilyurt C *et al.* examined the FTIR spectroscopy on irradiated and non-irradiated set glass ionomer cement specimens and reported that the irradiation did not have any effect on material structure.[47] However, Reed *et al.* explained that the irradiation altered the dentin microstructure.[33] So, it might be assumed that the altered substrate is the reason for the retention loss of glass ionomer cements.

Resin composite is the material of choice for a minimal intervention concept that does not require extra tooth preparation during the restoration procedure. Radiation can cause minimal chemical changes to resin composites.[48,49] However, there are many reports showing that radiotherapy does not have a significantly negative effect on the mechanical properties of resin composites.[49-52] With no buffering capacity or antimicrobial effect, resin composites led to a higher susceptibility to marginal caries than glass ionomer cement during a two-year observation.[44,45] The effects of radiation on the bond strength properties of resin composites are controversial. Several *in vitro* studies showed a lower bond strength in irradiated teeth, especially with the etch-and-rinse adhesive system.[53-57] In contrast, Da cunha *et al.* reported no significant radiation effect on the bond strength in irradiated teeth.[58] Moreover, an *in vivo* irradiation study by Galetti *et al.* showed no significant difference in bond strength between the irradiated and control groups.[59] Radiotherapy showed no negative effects when restoration was performed prior to the radiation procedure.[53-55]

Intraoral management in radiotherapy patients

The adverse effects of radiotherapy result in diminished long-term quality of life for patients. Oral mucositis and hyposalivation can impair the ability of patients to swallow, speak, and sleep. Oral biological changes and infection are often experienced by irradiated head and

neck cancer patients. Moreover, radiation effects on tooth microstructure induce dentition breakdown. Therefore, dental caries commonly occur in xerostomic patients and rapidly progresses. Post radiotherapy patients are classified in the high or extremely high-risk group for caries.[60,61] Comprehensive care with an emphasis on preventive treatment is essential for these patients. Routine monitoring every three months, neutral fluoride, and chlorhexidine solution are recommended to prevent and reduce caries risk in irradiated patients.[44,45,62] Xerostomia is a long-term late effect because radiotherapy causes irreversible damage to the salivary glands. Pharmacologic treatment with sialagogues shows no significant improvement in the saliva flow rate, but sialagogues lead to subjective quality of life improvements.[63] Palliative treatment with saliva substitutes such as gels, sprays, oils, and mucin substances can reduce the symptoms of dry mouth.[64] Because of the critical pH of dentin, the use of oral moisturizers with a pH of 6.7 or higher is helpful in preventing dentin demineralization.[65] The reduction in alveolar bone healing ability due to radiation effects leads to a higher incidence of ORN; therefore, patients should pay attention to potential oral infections and avoid any procedures that cause injury to irradiated bone. Additionally, radiation-induced alveolar bone alterations can be seen on radiographs and lead to misdiagnosis and inappropriate treatment. In this regard, information about the radiation treatment field and dose is helpful for an accurate inter pretation of the imaging results and proper management. Oral and dental management for post radiotherapy patients requires a multidisciplinary approach to improve long-term quality of life.

Conclusions

Patients undergoing radiation therapy for head and neck malignancies are prone to a variety of intraoral complications, including mucositis, xerostomia, dry mouth, salivary gland hypofunction, alveolar bone changes, osteoradionecrosis, dentition breakdown, radiation caries and effects on restorative materials. Strategies for preventing and treating these complications may be required.

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Conflicts of interests - The authors of this report have no conflicts of interests to declare.

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