

## Review Article

# RADIOTHERAPY IN ORAL CAVITY: CONSEQUENCES AND CURRENT MANAGEMENT REGIMES

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### Abstract:

Inclusion of the oral cavity, salivary glands, and jaws in the radiation treatment portals for patients who have head and neck cancer is governed by the location of the primary tumor and lymph node metastases. Acute changes produced by radiotherapy are observed in the oral mucosa (erythema, pseudomembrane-covered ulcerations), salivary glands (hyposalivation, changed salivary composition), taste buds (decreased acuity), and skin (erythema, desquamation). Late changes can occur in all tissues. The resulting oral sequelae may cause substantial problems during and after radiation therapy and are major risk factors in determining patient's quality of life. In this review, we have discussed radiation induced changes in the healthy oral tissues, the resulting consequences and the various possibilities to prevent or treat these concerns. As the management therapies of radiotherapy induced oral consequences are being developed and tested, it will become even more critical for dental professionals, as experts of the oral cavity, to be involved in evaluating these modalities and providing better oral care for cancer patients.

Keywords: Management, Oral consequences, Prevention, Radiotherapy

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### INTRODUCTION

Head and neck region is a complex area composed of several dissimilar structures. These structures, mucosal linings, skin coverings, subcutaneous connective tissue, salivary gland tissue, teeth and bone/cartilage, respond differently to cancer therapies which include chemotherapy and radiotherapy.<sup>1</sup> The inclusion of the oral cavity, salivary glands, and jaws in the radiation treatment portals for patients who have head and neck cancer is governed by the location of the primary tumor and lymph node metastases. Acute changes produced by radiotherapy are observed in the oral mucosa

(erythema, pseudomembrane-covered ulcerations), salivary glands (hyposalivation, changed salivary composition), taste buds (decreased acuity), and skin (erythema, desquamation). Late changes can occur in all tissues.<sup>2,3</sup> The resulting oral sequelae may cause substantial problems during and after radiation therapy and are major risk factors in determining patient's quality of life.<sup>4</sup> An adjustment or an interruption of the radiation treatment schedule may be required occasionally in certain conditions like severe mucositis or acute exacerbation of focal infection (periapical and periodontal infection). For all these reasons, oral

complications should be prevented or reduced to a minimum. Most preventive procedures described in the literature<sup>4-6</sup> are based on clinical experience, since there is rather small number of sound clinical trials reported in the literature, and there is a great diversity in supportive care and treatment policies and preventive approach policies in daily practice.

In this review, we have discussed radiation induced changes in the healthy oral tissues, the resulting consequences and the various possibilities to prevent or treat these concerns.

### RADIOTHERAPY IN ORAL CAVITY

Radiotherapy is the treatment of diseases using ionizing radiation. It plays an important role in the management of head and neck cancers, usually squamous cell carcinomas. Radiation therapy for malignant lesions in the oral cavity is usually indicated when the lesion is radiosensitive, advanced, or deeply invasive and cannot be approached surgically. Combined surgical and radiotherapeutic treatment often provides optimal treatment.

Fractionation of the total radiation dose into multiple small doses is done and this provides greater tumor destruction than is possible with a large single dose, allows increased cellular repair of the normal tissues and increases the mean oxygen tension in an irradiated tumor, rendering the tumor cells more radiosensitive.

Typically 2 Gy is delivered daily, bilaterally through 8 x 10 cm fields over the oropharynx, for a weekly exposure of 10 Gy. This continues typically for 6 to 7 weeks until a total of 64 to 70 Gy is administered.<sup>7</sup> Table 1 illustrates the time period of appearance of initial symptoms presented in various tissues and when these tissues are healed following radiotherapy.

### ORAL MUCOSA

Radiation therapy of head and neck region leads to the development of oral mucositis. It is commonly described as the most significant and debilitating acute complication associated with radiation therapy. It usually develops seven to fourteen days after radiation therapy is initiated and results from repeated tissue damage from multiple daily radiation treatments. It begins to manifest at doses of 1000 to 2000 cGy (one or two weeks of therapy) and is limited to the field of radiation. Virtually all radiation patients who receive 5000 cGy or more will develop moderate to severe oral mucositis.

Mucosal whitening due to transient hyperkeratinization may also be seen as the first sign which is then followed by erythema. This further leads to ulceration of the oral mucosa which occurs typically at doses over 3000 cGy. Following the end of radiation treatment, it requires three to six weeks for oral tissues to heal.<sup>8,9</sup>

**Table1:** Appearance of initial symptoms and its healing following radiotherapy in the oral cavity<sup>1,7</sup>

TISSUE IRRADIATED	BEGINNING OF SYMPTOMS	HEALING COMPLETED BY
Oral mucous membrane	At the end of 2 <sup>nd</sup> week of therapy	1-2 months
Taste buds	2 <sup>nd</sup> or 3 <sup>rd</sup> week	60 to 120 days
Salivary glands	1 <sup>st</sup> week	6 – 12 months
Teeth	3 months	Life long
Bone	3 years after radiotherapy	Life long
Musculature	2 months after radiotherapy is complete	Life long

Until recently, radiation therapy-induced oral mucositis was thought to be a process involving the epithelium only. Its pathophysiology includes radiations directly damaging the basal cells of the mucosal epithelium, compromising the capacity of this tissue to regenerate itself. No new cells develop at the basal layer and existing cells migrate to the surface and are exfoliated. As more layers of cells are lost, the epithelium will become thinner and thinner, resulting in erythema initially and eventually ulceration. DNA strand breaks in the basal epithelial cells when radiation is applied to the external surface of the epithelium. Current studies<sup>10</sup> reveal that the process of oral mucositis involves not only the epithelium, but includes the multiple cellular processes of the submucosa as well. Damage to the endothelium of submucosal blood vessels and to connective tissue occur before damage to epithelial cells in irradiated oral mucosa.<sup>8,11</sup> Though radiation damage to oral mucosa is a dynamic process, Sonis<sup>12</sup> has divided it into five stages to simplify its understanding. These stages are initiation, primary damage response, signal amplification, ulceration, and healing and in these ROS, NF $\kappa$ B, TNF $\alpha$ , IL-1 $\beta$ , IL-6 and MMPs play a vital role. With radiation that is applied incrementally over seven weeks, these stages overlap. There are conflicting results for a large number of mucositis management and prevention strategies. Main aim of mucositis management strategy is pain control which is initiated with topical analgesics and is followed by increasingly potent systemic medication. Therapy with the growth factor, KGF1, appears promising, as it is the only medication currently approved by the FDA.<sup>13</sup> The various mucositis prevention therapies are listed in Table 2.<sup>8</sup>

### **TASTE BUDS**

Taste buds are sensitive to radiation. Alteration in taste is an early response to

radiation and often precedes mucositis. Taste sensation decreases by a factor of 1000 to 10,000 with a cumulative dose of about 30 Gy (3 weeks), 2 Gy per fraction, after which it becomes virtually absent.<sup>14</sup> Main cause of taste loss is direct radiation damage to the taste buds or their innervating nerve fibers. Doses in the therapeutic range cause extensive degeneration of normal histologic architecture of taste buds leading to loss of taste acuity during second or third week of radiotherapy. Loss of taste is also due to the reduction in salivary flow rate which decreases transport and solubilization of gustatory stimulants, reduces the ability of saliva to protect the mucosa against bacteria, fungi, and variation in the oral pH, alters the ionic composition of saliva which is important for taste and affects mastication, nutrition, and the hedonic aspects of tasting.<sup>1,15</sup> Bitter and acid flavors are more severely affected when the posterior two thirds of the tongue is irradiated and salt and sweet when the anterior third of the tongue is irradiated.

Loss of taste is usually transient and recovery takes 60 to 120 days and hence, usually requires no treatment. Loss of taste can be prevented by direct shielding of healthy tissue or placement of these tissues outside the radiation field by means of shielding or repositioning prostheses. Recently, a cytoprotection against the loss of taste was reported by the administration of amifostine during a course of radiotherapy but is still questionable.<sup>16</sup> Since weight loss is one of the consequence of taste loss, dietary counseling has to be done as it helps in adapting the patient to the taste of the food. Food intake can be improved by advising food preparations with pleasing taste, color, and smell and by substitution of food aromas for the sense of taste. A basic meal plan including the addition of supplementary feedings should be started at the beginning of therapy and followed, with modifications,

**Table 2: Mucositis prevention therapies<sup>8</sup>**

1. Oral Hygiene	7. Cryotherapy
2. Infection Prevention Antimicrobial Lozenges, Chlorhexidine, Clindamicin, Acyclovir, Valacyclovir, Famcyclovir, Fluconazole, Clotrimazole, Nystatin	8. Glutamine
3. Anti-Inflammatory Agents Dinoprostone, Misoprostol, Prednisone, Pentoxifylline, Benzylamine	9. Coating Agents Sucralfate, Hydroxypropylcellulose Gel, Polyvinylpyrrolidone and Sodium Hyaluronate
4. Reactive Oxygen Species Inhibitors Amifostine, N-acetylcysteine, Manganese Superoxide Dismutase	10. Laser Therapy
5. Salivary Function Modifiers Propantheline, Pilocarpine	11. Growth Factors Epidermal Growth Factor (EGF), Granulocyte Colony Stimulating Factor (GCSF), Granulocyte Macrophage Colony Stimulating Factor (GMCSF), Transforming Growth Factor Beta 3 (TGFb3), Interleukin 11 (IL- 11), Fibroblast Growth Factors (FGFs): Keratinocyte Growth Factor 1 (KGF1, FGF7), Fibroblast Growth Factor 10 (FGF10), Fibroblast Growth Factor 20 (FGF20)
6. Azelastine	

during at least the total period of treatment. Level of hyposalivation should also be checked. In case of patients who are left with residual hypogeusia after radiotherapy, Zinc supplements are reported to be helpful in increasing the taste acuity.<sup>4,17</sup>

### SALIVARY GLANDS

Radiotherapy for cancer in the oral cavity or oropharynx results in unavoidable exposure of major salivary glands leading to changes in quantity and composition of saliva seen during the first few weeks. Depending on the localization of the radiation portals, a rapid decrease of the salivary flow rate is observed during the first week of radiotherapy, after which there is a gradual decrease to less than 10% of the initial flow rate.<sup>18</sup> The extent of reduced flow is dose dependent and reaches to zero flow at 60 Gy. The cause of damage of salivary gland tissue can be direct effects of radiation on the secretory and ductal cells or may be secondary to injury of the fine vascular structures, increased capillary permeability, interstitial edema and inflammatory infiltration. The parenchymal component of the salivary glands is

radiosensitive. Since serous cells are more radiosensitive than mucus cells, the residual saliva is more viscous than usual. The saliva has a pH value of 5.5 in irradiated patients and buffering capacity is reduced by 44%.<sup>7</sup> The salivary electrolyte levels are altered and non-immune and immune antibacterial systems are changed. Decreased salivary secretion causes changes in oral flora, promoting flora associated with the development of dental caries. Radiation-induced hyposalivation may result in dryness of mouth, thirst, difficulties in oral functioning, alterations of soft tissues, difficulties in wearing dentures, shift in oral microflora, nocturnal oral discomfort, radiation caries, mucus accumulation, periodontal disease, burning sensation and taste disturbances.<sup>1</sup>

Treatment of hyposalivation includes stimulation of the residual secretory capacity of the salivary glands, the use of saliva replacements if the result of stimulation of the residual salivary flow is insufficient, or possibly, in future, by gene transfer to repair hypofunctional gland parenchyma or to

produce secretory transgene products. Surgical transposition of the submandibular salivary glands outside the treatment portals has also been described as a successful method for the prevention of hyposalivation), but its indications are limited. Pilocarpine is the most commonly used sialogogue.<sup>4,19</sup> In addition, good oral hygiene practices and symptomatic relief of dryness are also included in the treatment regime. Prevention of radiation damage to salivary glands includes meticulous treatment planning and beam arrangement designed to spare as much of the parotid and submandibular glands as possible. Direct radioprotection is achieved by the systemic administration of amifostine, a radical scavenger during radiation treatment.<sup>20</sup>

#### TEETH

High levels of radiation exposure can markedly affect teeth both directly and indirectly. The extent of the direct effect is dependent on the radiation dose and the stage of tooth development. Children who receive radiation therapy to the jaws may show defects in the permanent dentition such as retarded root development, dwarfed teeth, or failure to form one or more teeth. If the exposure occurs before the calcification, it interferes with odontogenesis and histodifferentiation of tooth formation, the tooth buds may be destroyed whereas exposure after calcification may inhibit cellular differentiation, interfering with morphodifferentiation causing malformations and arrested general growth resulting in retarded or no root formation. The eruptive mechanism of the teeth is relatively radioresistant. Adult teeth show resistance to the direct effects of radiation. There occurs no change in the crystalline structure of enamel, dentin, or cementum, and nor is their solubility increased.<sup>7</sup>

Indirect effects of radiation on dentition lead to rampant form of dental decay characterized by rapid course and widespread

attack, commonly known as radiation caries. This occurs when the major salivary glands are included in radiotherapy leading to the changes in the microflora of the oral cavity rendering it more acidogenic in the plaque and saliva. The levels of *Streptococcus mutans*, *Lactobacillus* and *Candida* are increased. This along with other changes in the saliva ie., reduced flow, decreased pH, reduced buffering capacity, increased viscosity and decreased concentration of  $Ca^{2+}$  result in greater solubility of tooth structure and reduced remineralization therefore, leading to rampant caries.<sup>7</sup>

Clinically, three types of radiation caries can be seen.<sup>21</sup> The first type is the widespread superficial lesions attacking buccal, occlusal, incisal, and palatal surfaces and is the most common type. The second type involves primarily the cementum and dentin in the cervical region and may progress around teeth circumferentially resulting in the loss of the entire crown. The third type appears as a dark pigmentation of the entire crown in which incisal edges may be markedly worn. Combinations of the three may also develop in some patients. The histologic features of the lesions are similar to those of typical carious lesions. The best method to reduce radiation caries is application of viscous topical 1% neutral sodium fluoride gel in custom-made applicator trays for 5 minutes daily. In addition, comprehensive preventive measures have been recommended for head and neck cancer patients before, during, and after radiotherapy which include rigorous oral hygiene, daily self-application of topical fluoride, limitation of cariogenic foods, remineralizing mouthrinse solutions, and artificial saliva preparations. A combination of restorative dental procedures, excellent oral hygiene, diet restricted in cariogenic foods, and topical application of sodium fluoride yields the best results. Teeth with gross caries or periodontal involvement are often extracted before irradiation.<sup>4,22</sup>

## **PERIODONTIUM**

Irradiation of the oral cavity results in decreased vascularity and acellularity of the periodontal membrane with rupturing, thickening, and disorientation of Sharpey's fibers and widening of the periodontal space. Widening of the periodontal ligament spaces and destruction of bony trabeculae are found to be the early radiographic changes.<sup>23</sup> The cementum appears completely acellular, and its capacity for repair and regeneration is severely compromised. The changes in cementum and periodontal ligament may predispose individuals to periodontal infection, the risk of which is also increased due to radiation-induced hyposalivation, the concomitant increased plaque accumulation and shift in oral microflora. Periodontal attachment loss and tooth loss occur due to direct and indirect effects of high-dose radiotherapy on the periodontium. The periodontal status should be thoroughly evaluated before, during, and after radiation treatment. The use of mechanical oral hygiene procedures (calculus removal, root planing, soft tissue curettage, tooth surface polishing, and daily plaque removal) help to remove the local etiologic factors of inflammatory diseases of the periodontium. Optimal oral and periodontal hygiene must be maintained indefinitely, due to the lowered biological potential for healing of the periodontium (alveolar bone, periodontal ligament, cementum) after radiotherapy. Maintenance of good oral hygiene and topical fluoride applications greatly reduce the risk of developing periodontal disease and, osteoradionecrosis consequently.<sup>4,6</sup>

## **BONE**

Changes in the bone matrix as a result of radiotherapy in the oral region develop relatively slowly. The primary damage to mature bone results from radiation-induced damage to the vasculature of the periosteum and cortical bone, which are normally already sparse. Initial changes result from

injury to the osteocytes, osteoblasts, and osteoclasts, osteoblasts being more radiosensitive than osteoclasts leading to a relative increase in the lytic activity.<sup>24</sup> Radiation injury to the fine vasculature of bone and its surrounding tissues leads to hyperemia, followed by endarteritis, thrombosis, and a progressive occlusion and obliteration of small vessels. Subsequently, normal marrow may be replaced with fatty marrow and fibrous connective tissue. With time, the marrow tissue becomes hypovascular, hypocellular, and hypoxic.<sup>7</sup> Hypovascularity and fibrosis are commonly found to be the end-stage of irradiation-induced tissue injury. Subsequently, these changes become severe leading to dead bone formation and its exposure. This condition is known as osteoradionecrosis and is the most serious clinical complication that occurs in bone after irradiation.

By definition, osteoradionecrosis is bone death secondary to radiotherapy.<sup>24</sup> A higher incidence of osteoradionecrosis is observed after cumulative radiation doses to the bone exceed 65 Gy.<sup>1,25</sup> Mandible is affected more commonly than the maxilla, because of the richer vascular supply of the maxilla and the fact that the mandible is more frequently irradiated. The potential risk factors for osteoradionecrosis include radiation therapy, dental extraction, infectious disease, dental trauma, concomitant therapy with corticosteroids, and chemotherapy. Any of these causes may lead to weakening of the oral mucous membrane with its subsequent breakdown, therefore providing portal for the entry of microorganisms from the oral cavity into the bone. The decreased vascularity of the bone as a result of radiation therapy renders it easily infected by the microorganisms and this infection may cause a nonhealing wound in irradiated bone that is difficult to treat. Objective signs that may occur before frank clinical presentation of

osteoradionecrosis include a sudden change in the health of periodontal or mucosal tissues, failure of the oral mucosa to heal, undiagnosed oral pain, loose teeth, or soft-tissue infection.<sup>7</sup> The clinical presentation of osteoradionecrosis represents a spectrum of symptoms, signs, and severities, from relatively asymptomatic to more severe lesions.

The main goal of the treatment of osteoradionecrosis is the elimination of the necrotic bone and improvement in the vascularity of the remaining radiation-damaged tissues. The basic step in the treatment of osteoradionecrosis is debridement of all necrotic bone, thus eliminating any nidus for continued infection and inflammation. But this does not improve the vascularity of the adjacent tissue bed and the remaining vascularized bone. To combat this major obstacle, Marx<sup>26</sup> developed a protocol that aimed to improve the healing of radiation-injured tissue as well as to increase their vascularity permanently. Marx protocol<sup>26</sup> combines antibiotic therapy, hyperbaric oxygen therapy (HBO) and debridement. According to the Marx protocol<sup>26</sup>, bone exposures of the mandible are initially treated by local debridement and HBO (stage I treatment). Smaller defects frequently close with this management. Defects that do not fully respond are treated by marginal mandibulectomy of the involved region, followed by additional HBO treatment exposures (stage II). In case of failure of stage II management, initial defects that involve the inferior border of the mandible, defects having an oro-cutaneous fistula, or pathologic fractures are managed by resection of the involved portion of the mandible down to a margin of healthy bone and stabilization of the defect by extra-oral fixation (stage III). Since osteoradionecrosis is a result of hypovascularity and not necessarily an infection, antibiotic therapy is considered adjunctive.

For a dental surgeon, the primary goal should be to optimize the condition of the patient's dentition, so that high-risk procedures, such as extraction of teeth, apicoectomies, etc., will not have to be performed in the post-irradiation period. All teeth with questionable prognosis must be extracted before radiotherapy and the extractions should be performed as atraumatically as possible and with primary closure. When there is a 21 day or greater time period between extraction and initiation of radiotherapy, the risk of development of osteoradionecrosis is reduced to zero. Antibiotic coverage should necessarily be provided. There is some evidence that HBO treatment is more beneficial than conventional antibiotic prophylaxis in preventing osteoradionecrosis (5% incidence of osteoradionecrosis vs. 30%, respectively). HBO therapy stimulates angiogenesis, increases neovascularization, optimizes cellular levels of oxygen for osteoblast and fibroblast proliferation, stimulates collagen formation, and supports blood vessels, all of which enhances the healing potential in irradiated compromised tissues. If extensive wounding or extraction in radiation portals is necessary, then HBO treatment should be used both prior to surgery and after wounding occurs.<sup>1,4</sup>

#### **MUSCLES AND JOINTS**

Trismus, or limited jaw opening, may develop due to tumor invasion of the masticatory muscles and/or the temporomandibular joint (TMJ), or be the result of radiotherapy if masticatory muscles and/or the TMJ is included in the field of radiation, or a combination of both.<sup>7</sup> This is discomforting to the patient and interferes with oral hygiene, speech, nutritional intake, examination of the oropharynx, and dental treatment. Masseter and pterygoid muscles are most commonly involved. Restriction in mouth opening usually starts about 2 months after radiotherapy is completed and

frequently becomes a lifelong problem. It occurs due to muscle fibrosis and scarring in response to radiation injury as well as to fibrosis of the ligaments around the TMJ and scarring of the pterygomandibular raphe. The severity of trismus is dependent on the tumor growth, surgical procedures, configuration of the radiation field (unilateral or bilateral), the radiation source, and the radiation dose. Some authors<sup>27</sup> report that trismus develops after high radiation doses to the TMJ only, while other authors<sup>28</sup> reported that trismus may already develop after low doses and increases with increasing doses. The most decisive factor which determines whether trismus will develop is probably the inclusion of the pterygoid muscles in the treatment portals.

Main aim is the prevention of the trismus rather than its treatment. The clinician should measure the maximum mouth opening (inter-arch or inter-incisal distance) before radiotherapy is started as well as during radiotherapy to ensure its maintenance. Patients at risk of trismus should be put on home exercises to maintain maximum opening and jaw mobility as soon as radiotherapy begins and also use tongue blades or rubber stops in these exercises to increase the size of mandibular opening. In patients in whom trismus has developed, exercise program combined with physiotherapy help to regain the lost inter-arch distance.<sup>29</sup> Prosthetic appliances (dynamic bite openers) containing springs and bands designed to re-stretch the muscles have been helpful in some patients.<sup>4</sup>

### CONCLUSION

Evidence based studies have shown that the process of radiotherapy induced changes in the oral cavity involves far more than just the overlying epithelium, but includes multiple cellular processes of the submucosal structures and other soft and hard tissues. These oral sequelae may be dose limiting and have a tremendous impact on the patient's

quality of life. As the management therapies of radiotherapy induced oral consequences are being developed and tested, it will become even more critical for dental professionals, as experts of the oral cavity, to be involved in evaluating these modalities and providing better oral care for cancer patients.

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