

REVIEW ARTICLE



Adverse effects of radiotherapy on oral tissues: A review

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Abstract

Oral cancer is a major health problem in developing countries like India that is attributed mainly due to tobacco chewing habit. Oral squamous cell carcinoma (OSCC) accounts to about 90% of all oral cancers and holds 3rd place in South Central Asia. OSCC is managed by surgery, radiotherapy, or chemotherapy, or a combination of any of these modalities. Radiotherapy is a part of cancer treatment where high doses of radiation are delivered to large areas of oral cavity that includes the lesional areas as well as surrounding structures. This may result in several undesired reactions that manifest during or after the completion of therapy. The acute and chronic effects of radiation on oral tissues are discussed in detail here. The irreversible damage caused to the oral tissues is related to the dosage of radiation, the field of irradiation, the degree of hypovascularity/hypocellularity of tissues, the age of the patient, and the wound healing capacity. Majority of the patients undergoing treatment have a compromised quality of life as a side effect of radiation therapy. Hence, in-depth knowledge of radiation exposure, adequate dosage, modality, general state, and prognosis of each case is essential to evaluate personalized treatment plan. The severity of the complications can be minimized by implementing oral care protocols before, during, and after radiation therapy. A multidisciplinary treatment plan with dental surgeons, radiotherapists, speech therapists, nutritionists, and psychologists is required for patient management.

Keywords: Mucositis, oral cancer, osteoradionecrosis, taste dysfunction, trismus, xerostomia

Introduction

Radiotherapy is a curative medical intervention in cancer therapeutics. High doses of radiation used to destroy cancer cells can cause side effects because radiation can damage healthy cells and tissues near the zone of radiation. Total body irradiation and irradiation to the head and neck cause several adverse effects that manifest during or after the course of treatment. Today, major advances in radiotherapy have made it more precise with fewer side effects. The multidisciplinary management of oral cancer is essential to minimize effects of ionizing radiation on oral tissues. This paper reviews the adverse effects of radiation therapy on oral tissues.

Rationale of Radiotherapy of Oral Cavity

Radiation therapy is part of the oral cancer treatment. Most of the aggressive oral cancers require radiotherapy either as a primary mode of treatment, pre-surgery/post-surgery, part of radiochemotherapy, or as palliative therapy.^[1] The radiation dose is assessed by tumor variables such as size, location, invasion, histological diagnosis, radiosensitivity, and invasion into adjacent structures.^[2] Radiation therapy is indicated when

the lesion is radiosensitive, advanced or deeply invasive, and cannot be approached surgically.^[3]

Classification of Effects of Radiation Therapy on Oral Cavity

The effects of radiation on oral tissues can be classified as acute and chronic as given in Table 1.

Acute effects

Mucositis

Radiotherapy induced mucositis is an inflammatory reaction of the mucous membrane of the oral/oropharyngeal area during radiation therapy.^[4] The basal mucosal layer is composed of rapidly dividing radiosensitive cells that begin to show areas of redness and inflammation (mucositis). Radiation mucositis is considered to be an inevitable but transient side effect of therapeutic head and neck irradiation.^[5]

Clinical presentation

The earliest signs and symptoms of oral mucositis include erythema and edema, burning sensation and increased

sensitivity to hot and spicy food.^[6] As the therapy continues the irradiated mucous membrane shows redness, inflammation, it begins to break down, with the formation of white to yellow pseudomembrane (the desquamated epithelial layer). Thus erythematous areas may develop into elevated white desquamative patches and subsequently into painful ulcers which becomes secondarily infected. This impairs the nutrition and fluid intake, resulting in malnutrition and dehydration.^[6]

Scales developed by the National Cancer Institute and the World Health Organization,^[7] based on common toxicity criteria [Table 2].

Pathophysiology

The acute mucosal response to radiotherapy is due to basal cell death of the mucosal epithelium, compromising its capacity to regenerate itself thus leading to thinning of epithelium and ulcerations.^[8] It also damages the endothelium of the blood vessels.^[9]

Histopathology

It shows atrophy of epithelium, absence of vascular damage, and juxtaepithelial dense inflammatory infiltrate. Degenerative changes such as homogenization of the collagen and mucoid degeneration are seen. The submucosa will gradually increase in collagen content and become less vascular and more fibrotic.^[10]

Table 1: Classification of effects of radiation therapy on oral cavity

Acute effects	Chronic effects
Oral mucositis	Dental alterations Teeth Effect on odontogenesis Dental caries Periodontal problems Pulpal changes
Salivary gland dysfunction	Osteoradionecrosis
Taste dysfunction	Dysgeusia
Infections	Trismus Soft tissue necrosis and fibrosis

Table 2: Systems for rating mucositis severity

Score	National Cancer Institute rating	WHO rating
0	None	No symptoms
1	Painless ulcers, erythema, or mild soreness	Sore mouth, no ulcers
2	Painful erythema, edema, or ulcers; however patient can eat solid food	Sore mouth with ulcers but able to eat normally
3	Painful erythema, edema, or ulcers; patient cannot eat solid food	Liquid diet only
4	Requires parenteral or enteral support (such as gastric feeding tube) to provide nutrition	Unable to eat or drink

Salivary gland pathoses

Parenchymal component (salivary acini) is radiosensitive. Serous cells are more radio-sensitive than mucous cells thus parotid glands are more sensitive than submandibular or sublingual glands. Radiation thus tends to affect the parotid gland earlier to the other major salivary glands and therefore residual saliva is more viscous.

Initial radiation induced changes include degeneration or destruction of acinar tissue with subsequent inflammation and marked loss of salivary secretion (hyposalivation) in first few weeks. Months after irradiation inflammatory response becomes more chronic and glands demonstrate progressive fibrosis, adiposis, loss of fine vasculature, and concomitant parenchymal degeneration, thus accounting for xerostomia. There is usually difficult and painful swallowing due to loss of lubricating properties of residual saliva. Low concentration of Ca^{+2} in individuals with xerostomia leads to greater solubility of tooth structure and reduced remineralization.^[3,4]

Hyposalivation

The first few weeks after the initiation of radiotherapy, a marked and progressive loss of salivary secretion is seen. The mouth becomes dry and tender. Swallowing is difficult and painful as saliva also loses its normal lubricating properties. Four phases of loss of salivary gland function induced by radiation in rat parotid gland were observed by Coppes *et al.* They are as follows:^[3,4]

- The first phase (0-10 days): Characterized by decrease in salivary flow rate without any changes in amylase secretion or cell number of acini
- The second phase (10-60 days): Decrease in amylase secretion and acinar cell loss
- The third phase (60-120 days): Salivary flow rate, amylase secretion with no change in acinar cell numbers
- The fourth phase (120-240 days): Deterioration of salivary gland function with poor tissue morphology but increase in number of acinar cells.

The final degree of radiation-induced hyposalivation depends on patient characteristics, such as patient age, gender, and pre-irradiation salivary gland function.^[11,12]

Rating scales can be used to describe the degree of xerostomia. The Radiation Therapy Oncology Group uses two scales: One for acute reactions; the other for late or delayed reactions^[13] as shown in Table 3.

Alterations in composition of saliva

Change in salivary composition makes it very viscous. The salivary pH, buffering capacity reduces, electrolyte levels are altered and changes are seen in immune/non-immune antibacterial systems. The average pH decreases from 7 to 5 which can initiate the decalcification of normal enamel. Since the overall immunity is compromised, alterations are seen in the oral microbial flora of the patients undergoing radiotherapy.^[14]

Histopathology

Initial changes include the degeneration or destruction of acinar tissue with subsequent inflammation. Chronic exposure leads

to fibrosis, adiposis, loss of fine vasculature, and concomitant parenchymal degeneration.^[15]

Dry mouth/xerostomia, burning sensation, increased thirst, taste alterations, difficulties in oral functioning and wearing dentures, soft tissue alterations, disturbances in oral microflora, oral discomfort at night, radiation induced caries, mucus accumulation, and gingival/periodontal disease are the consequences of radiation-induced hyposalivation in the oral cavity.^[16]

Taste dysfunction

Taste could be defined as a chemical sensation related to specialized receptors, selectively stimulated by molecules and ions of solutions in contact with them.^[4] Taste buds are radiosensitive and gets almost completely destroyed during therapy.^[17]

Ionizing radiations cause extensive degeneration of normal architecture of salivary glands and taste buds leading to taste alterations during 2nd and 3rd week of radiotherapy. With irradiation of the posterior 2/3rd of tongue, bitter and acid flavors are more severely affected, while irradiation of the anterior 1/3rd of tongue affects salt and sweet flavors. Recovery of taste buds to near normal level takes some 60-120 days after irradiation.^[18]

Scoring systems

Multiple systems have been developed for grading the adverse effects of cancer treatment and several classifications have been used for describing the radiation-induced alterations. A subjective total taste acuity (STTA) scale, modified from the late effects of normal tissues/subjective, objective, management, analytic scoring system, is used to evaluate, in a specific way, the STTA^[19] as given in Table 4.

People with cancer who lose 10% or more of their normal body weight do not live as long as those with similar cancers at similar stages who remain well nourished. The multiple oral complications caused by stomatitis, xerostomia, and taste changes, maintaining adequate appetite, and nutrition is a challenge.^[18]

Infections

The reduction in salivation from radiotherapy coincides with a shift in the oral microflora, with a prominence of cariogenic microorganisms. This shift shows an increase in *Streptococcus mutans*, *Lactobacillus*, and *Candida albicans*, with a decrease in *Streptococcus sanguinis*, *Neisseria*, and *Fusobacterium*.^[14] This increase in oral Gram-negative enterobacteria and *Pseudomonas* is an aggravating factor for developing oral mucositis. Candidiasis is the most common infection affecting the oral cavity during radiotherapy.^[20]

Bacterial infections may also occur early in the course of head/neck radiation. Herpes virus infections may also occur in patients who are seropositive prior to head and neck radiation due to virus re-activation.^[21]

Table 3: Radiation Therapy Oncology Group radiation morbidity scoring criteria for xerostomia

Acute reactions	
0:	No change over baseline
1:	Mild mouth dryness/slightly thickened saliva/may have slightly altered taste, such as metallic taste/changes are not reflected by alteration in baseline feeding
2:	Moderate to complete dryness/thick, sticky saliva/markedly altered taste
3:	Not used
4:	Acute salivary gland necrosis
Late reactions	
0:	No change over baseline
1:	Slight dryness of mouth/good response on stimulation
2:	Moderate dryness of mouth/poor response on stimulation
3:	Complete dryness of mouth/no response on stimulation
4:	Fibrosis

Table 4: Scale of STTA

Grade 0	Same taste acuity as before treatment
Grade 1	Mild loss of taste acuity, but not inconvenient in daily life
Grade 2	Moderate loss of taste acuity, and sometimes inconvenient in daily life
Grade 3	Severe loss of taste acuity, and frequently inconvenient in daily life
Grade 4	Almost complete loss of taste acuity

STTA: Subjective total taste acuity

Late effects

Dental alterations

During the course of radiotherapy, increased dental sensitivity is experienced by many patients to temperature and taste variations due to loss of protective layer of saliva.^[4]

Effects on teeth

Retardation of growth of teeth is seen when the oral cavity of the child is irradiated during the developing years. Before calcification, radiation leads to the destruction of the tooth bud while irradiation after calcification causes inhibition of cellular differentiation, causing malformations and arrest in general growth. However, the structure of enamel, dentin, or cementum does not alter. Solubility of the teeth does not increase due to radiotherapy. Pulpal tissue demonstrates long-term fibroatrophy after irradiation. The eruptive mechanism of teeth is relatively resistant to radiation effects and the irradiated teeth with alterations in root structure still erupt into the oral cavity.^[22]

Effects on odontogenesis

The extent of retardation of tooth growth depends on the radiation dosage and the stage of tooth development.

Odontogenic cells are more radiosensitive in the pre-formative and differentiation phases than cells in the secretory/mature stage. Kaste *et al.* stated that the maturing ameloblasts may be permanently damaged with as little as 10 Gy, and ameloblastic activity ceases after exposure to 30 Gy.^[23]

Radiation caries

Radiation caries is rampant, may occur in individuals who receive a course of radiotherapy that includes exposure to salivary glands. It causes rapid destruction of tooth structures.^[24]

Clinically, three types of radiation caries exist which may occur in combinations in some patients. They are as follows:

1. Widespread superficial lesions attacking buccal, occlusal, incisal, and palatal surfaces – Most common
2. Lesions involving primarily cementum and dentin in cervical region. These lesions may progress around the teeth circumferentially and result in loss of the crown
3. Dark pigmentation of entire crown and wearing away of the incisal edges.^[25]

Pathogenesis

Radiation caries could be a direct or indirect effect of radiotherapy. Several studies claim that radiation caries occurs due to the presence of main salivary glands within the radiation field causing hyposalivation. This change in the salivary flow rate brings changes in the normal microbial flora and immunologic factors, thus increasing the caries incidence in irradiated patients.^[24,25]

Periodontal problems

Post irradiation, decrease in the vascularity and acellularity of the periodontal membrane is seen. Disorientation and rupture of Sharpey's fibers, thickening, and widening of the periodontal space have been reported. The cementum gets acellular, and its repair and regeneration capacity is severely reduced.^[22]

These changes that occur in the periodontal ligament and cementum may predispose individuals to radiation-induced hyposalivation, increased plaque accumulation, shift in oral microflora, which may lead to infection. The potential of the periodontium to regenerate following surgery will be reduced.^[22,26]

Pulpal defects

Pulpal tissue will demonstrate long-term fibroatrophy after irradiation. Patients may exhibit hypersensitivity, pulpal pain, and necrosis.^[25]

Osteoradionecrosis

Marx and Johnson in 1987 and Constantino *et al.*, 1995, defined osteoradionecrosis as "bone death secondary to radiotherapy." The incidence of osteoradionecrosis is more common in mandible.^[27]

Osteoradionecrosis of the jaws occurs due to radiation, followed by trauma, and then infection.^[4] Portal of entry for oral

bacteria into the underlying bone occurs due to trauma. Due to compromised vascularity and minimal regenerative abilities, the infection rapidly progresses and spreads throughout the bone. The primary damage to mature bone results from radiation-induced damage to the vasculature of the periosteum and cortical bone, which is normally already sparse.^[27,28]

Marx (1983) described the following steps in the development of osteoradionecrosis. They are as follows:^[29]

- Hypoxic-hypovascular-hypocellular tissue: Bone loses its ability to replace normal collagen
- Tissue breakdown: Synthesis and cellular replication is exceeded by collagen lysis and cell death
- Chronic non-healing wounds: Occurs due to increase in energy, oxygen, and metabolic demands that exceeds the supply.

Non-healing wound in irradiated bone occurs in the oral cavity due to decreased vascularity of the mandible and increased infection. It is more common in mandible than maxilla, probably because of the richer vascular supply to the maxilla and also due to the fact that mandible is more frequently irradiated. As the radiation dose absorbed by the bone is increased, the risk of osteoradionecrosis is also increased.^[28,29]

Histopathology

The initial changes in the bone components - Osteocytes, osteoblasts, and osteoclasts result from injury or damage to the remodeling system. There is decrease in the formation and increase in the lytic activity because osteoclasts tend to be more radioresistant than osteoblasts. Radiation injury affects the bone vascularity and tissues in the vicinity. This leads to hyperemia, followed by endarteritis and thrombosis. Ultimately, this leads to obliteration of small vessels and fatty degeneration. Atrophy of endosteum occurs with loss of active osteoblasts.^[27,28]

Trismus

During radiotherapy, if masticatory muscles and/or the temporomandibular joint (TMJ) comes in the path of radiation, trismus can occur. Muscle fibrosis/scarring, fibrosis of the TMJ ligaments, pterygo-mandibular raphes can scar in response to radiation injury. Oral hygiene, speech, nutritional intake of the patient is compromised due to limited jaw opening interferes. Trismus develops in most patients within 3-6 months after radiotherapy and frequently becomes a long lasting problem.^[30]

Soft tissue necrosis and fibrosis

Soft tissue necrosis can be defined as an ulcer located in the radiation tissue, without the presence of residual malignancy. The primary etiologies for this type of chronic complication are due to excessive doses delivered to the tissues via interstitial implants or secondary to soft tissue irritation from an inadequate fitting prosthesis. Besides, ulceration and necrosis, soft tissues may suffer from fibrosis after radiotherapy. It can appear pale, thin, and without flexibility. This may interfere with eating and dental care.^[31]

Conclusion

Radiation therapy plays a significant role in cancer therapy. As a result, various changes are induced in oral tissues. The resulting sequelae cause substantial problems and may affect the patient's quality of life. Larger prospective trials that include the prevention and treatment of radiation-induced damage to oral tissues are needed to improve management and enhance better prognosis.

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