Review Article

Oral Adverse effects of Radiotherapy: A Review

Palkin Mehta¹, Ankur Bhagat², Vikas Sharma³, Lavina Arya⁴

¹Senior Lecturer, Dept. of Oral Medicine and Radiology, Saraswati Dental College and Hospital, Lucknow, U.P., India
²Senior Lecturer, Dept. of Oral Medicine and Radiology, Rayat Bahra Dental College and hospital, Mohali, Punjab
³Senior lecturer, Dept. of Oral and Maxillofacial Pathology, Desh Bhagat Dental College and hospital, Mandi Gobindgarh, Punjab, India
⁴Professor, Dept. of Oral Medicine and Radiology, Faculty of Dental Sciences, S.G.T. Dental College, Hospital & Research Institute, Gurugram (Haryana), India

ABSTRACT
Oral cancer now-a-days is a major health issue in developing countries like India which is caused mainly due to tobacco dependence. It is among the 10 most common cancers worldwide, and is especially seen in disadvantaged elderly males. Treatment of Oral Cancer plays a vital role in dentistry which includes Radiotherapy, chemotherapy, surgery or a combination of any of these treatment modalities. Radiotherapy is the use of a certain type of energy called ionizing radiation to kill cancer cells and shrink tumors. Radiotherapy may result in several adverse effects that manifest either during or after the treatment which includes Xerostomia, dental caries, mucositis, Dysgeusia, ageusia, osteoradionecrosis, infection, and trismus. These effects can be eradicated or controlled with proper treatment. This paper aims to review the effects of ionizing radiation on the oral cavity.

Key words: Radiotherapy, mucositis, ageusia, osteoradionecrosis.

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Corresponding author: Dr. Palkin Mehta, Senior Lecturer, Dept. of Oral Medicine and Radiology, Saraswati Dental College and Hospital, Lucknow, U.P., India


Introduction
Radiotherapy alone or in combination of other treatment modalities plays a vital role in the treatment of Oral Cancer. It is the use of a certain type of ionizing radiation to kill cancer cells and shrink tumors. Radiation injuries or destroys cells in the area being treated (the “target tissue”) by damaging their genetic material, making it impossible for these cells to continue to grow and divide. Although radiation damages both cancer cells and normal cells, most normal cells can recover from the effects of radiation and function properly.¹

High-energy radiation damages genetic material (deoxyribonucleic acid, DNA) of cells and thus blocking their ability to divide and proliferate further.² Although radiation damages both normal cells as well as cancer cells, the goal of radiation therapy is to maximize the radiation dose to abnormal cancer cells while minimizing exposure to normal cells, which is adjacent to cancer cells or in the path of radiation. Normal cells usually can repair themselves at a faster rate and retain its normal function status than the cancer cells. Cancer cells in general are not as efficient as normal cells in repairing the damage caused by radiation treatment resulting in differential cancer cell killing. Various adverse effects are caused by the ionizing radiations. These effects are related to the dose, the age of the patient, dose of radiation, the field of irradiation, the degree of hypovascularity or hypocellularity of tissues.³

Classification of Adverse Effects
Based on the time of occurrence and the amount of effect caused the adverse effects can be divided into early and late effects. Early effects are the one noticed during or shortly after treatment mostly affecting the oral mucosa, taste buds and salivary glands and late effects are developed at the end or years after the treatment, affecting dentition, bone, muscles and skin⁴ as explained in the Table 1
Mucositis
Radiotherapy induced Mucositis is the most common early adverse effect experienced by patients undergoing treatment of Oral Cancer. Decreased cell renewal in the epithelium causes damage to the oral mucous membrane leading mucosal atrophy and ulcers.\textsuperscript{1,5} Sings & symptoms of oral mucositis includes burning sensation, inflammation, erythema, sloughing, mucosal atrophy, ulcers, infections. This is accompanied by pain, burning and discomfort, which are greatly aggravated by contact with highly spicy foods. When the irradiation field involves the pharyngeal mucosa, it may produce difficulties in swallowing and speech.\textsuperscript{6}
Scales have been given for assessing the severity of Mucositis by National Cancer Institute and the World Health Organization\textsuperscript{7}

Table 1: Adverse effects of Radiotherapy

<table>
<thead>
<tr>
<th>Early effects</th>
<th>Late effects</th>
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<tbody>
<tr>
<td>Mucositis</td>
<td>Dentition</td>
</tr>
<tr>
<td>Taste dysfunction</td>
<td>Soft tissue necrosis</td>
</tr>
<tr>
<td>Bacterial, Viral &amp; Fungal Infections</td>
<td>Osteoradionecrosis</td>
</tr>
<tr>
<td>Salivary gland dysfunction</td>
<td>Mucosal fibrosis and Atrophy</td>
</tr>
<tr>
<td></td>
<td>Trismus</td>
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Salivary gland dysfunction
Radiotherapy leads to the damage to the salivary glands, either by changing the salivary composition or by altering the salivary flow rate. After radiotherapy many mechanisms leads to the salivary gland dysfunction.\textsuperscript{8}
Early changes result from damage to the plasma membrane of acinar cells or disturbances in intracellular signalling; late damage results due to lack of proper cell renewal because of damage to the DNA of progenitor cells and stem cells. The extent of salivary gland dysfunction depends on the dose of radiation, the volume of irradiated gland tissue.\textsuperscript{9,10} Radiotherapy also leads to the changes in the composition of saliva, alterations in the buffering capacity, concentration of electrolytes, making it more viscous and changing its nonimmune and immune antibacterial systems.\textsuperscript{8,11,12} Several salivary substitutes are advised to increase the salivary flow rate and overcome the discomfort caused due to salivary dysfunction.\textsuperscript{13}

Taste Buds dysfunction
Taste buds are extremely sensitive to radiation. Doses in the therapeutic range cause extensive degeneration of the normal histology and architecture of taste buds. Dysgeusia, hypogeusia or ageusia is often noticed by the patient during the second or third week of radiotherapy. 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. Taste acuity usually decreases by a factor of 1000 to 10,000 during the course of radiotherapy. Alterations in the saliva may account for this reduction, which may proceed to a state of virtual insensitivity, with recovery to near-normal levels some 60 to 120 days after irradiation.\textsuperscript{10,15} These alterations can lead to reduction in the intake of food and nutritional deficits, resulting in weight loss and, in severe cases, weakness, cachexia, malnutrition and susceptibility to infection

Infections
The decrease in salivary flow rate due to radiotherapy further results in a shift in the oral microflora, with a increase of cariogenic microorganisms. \textit{Streptococcus mutans, Lactobacillus,} \textit{and Candida albicans} are increased whereas, \textit{Streptococcus sanguinis, Neisseria,} and \textit{Fusobacterium} are decreased. This shift in oral microflora is an aggravating factor for developing oral mucositis. Candidiasis is the most common infection affecting the oral cavity during radiotherapy.\textsuperscript{16,17} Bacterial infections may occur during the initial stages of radiotherapy. Herpes virus infections may also occur in patients who are seropositive prior to Oral cancer treatment by radiation due to virus re-activation.

Late effects
During the radiotherapy, increased sensitivity to all the hot and cold food is experienced by the patients due to loss of protective layer of saliva.\textsuperscript{18}

Radiation Caries
Changes in the chemical composition of saliva and increased amounts of cariogenic oral bacteria result in rapid decalcification of dental enamel. Radiation caries is not caused directly by irradiation, but results from the sequelae of xerostomia: decrease of pH, decreased buffering capacity, and increased viscosity.\textsuperscript{19} Clinically it’s a form of rampant caries, and tends to spread to all the surfaces of teeth, altering the color. As a result of this decay, friability is increased leading to the breakdown of tooth structure.\textsuperscript{20}

Osteoradionecrosis
Osteoradionecrosis, is one of the most serious adverse effect of radiotherapy. It is an inflammatory condition resultant of the bone ionizing radiation. Radiation

Table 2: Scale for rating mucositis severity

<table>
<thead>
<tr>
<th>Grades</th>
<th>WHO Criteria</th>
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<tbody>
<tr>
<td>0</td>
<td>No symptoms</td>
</tr>
<tr>
<td>1</td>
<td>No ulcers or asymptomatic ulcers, erythema or Sore mouth</td>
</tr>
<tr>
<td>3</td>
<td>Painful erythema, edema or ulcers; patient cannot eat solid food Liquid diet only</td>
</tr>
<tr>
<td>4</td>
<td>Patient is unable to eat or drink; Requires parenteral or enteral support (such as gastric feeding tube) to provide nutrition</td>
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damages the osteocytes and the microvascular system, with a progressive decrease of the microvascularization. The tissue becomes hypovascular, hypocellular and hypoxic. All these features avoid the bone healing, and it can proceed to a necrosis with or without infection. These changes in bone result from injury to there modeling system, causing atrophy, osteoradionecrosis and pathological fractures\(^3,21\). The mandible is much more susceptible to osteoradionecrosis than the maxilla, because its vascularization is poor and bone density is high. This adverse effect usually occurs within one year of therapy. Radiologic features include ill-defined cortical destruction with or without sequestration\(^5\). Clinical features may include pain, oral fistulas, exposed necrotic bone, pathologic fracture and suppuration. The patient may presents clinical signs and symptoms of ulceration or necrosis on the mucosa, with exposure of necrotic bone for longer than 3 months. Radiographically, irregular bone destruction is observed and the mandible is most frequently involved. The progression of this process can lead to pathologic fracture and intraoral or extraoral fistula\(^23\).

**Trismus**

During radiotherapy, if masticatory muscles or the temporomandibular joint (TMJ) comes in the path of radiation, trismus can occur. Muscular fibrosis or TMJ ligaments fibrosis, 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 interferences. Trismus develops in most patients within 3–6 months after radiotherapy and frequently becomes a long lasting problem.\(^24\)

**Conclusion**

Radiotherapy plays a major role in treatment of Oral cancer. As a result of which it causes various adverse effects on oral cavity and hence affects the patients quality of life. Larger prospective trials that include the treatment of ionizing radiation-induced damage to oral tissues are needed to improve management and enhance better prognosis.

**References**