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OBSERVATIONS ON ALTERATION IN ORAL FLORA AMONG ORAL CANCER PATIENTS UNDERGOING CHEMO-RADIOTHERAPY- A REVIEW

YADAV P[1], MAURYA R[2*], SINGH N[3] AND YADAV PK[4]

1: PhD, Department of General Pathology and Microbiology, Chandra Dental College and Hospital Barabanki, India

2: Molecular Biologist (Non-Medical Research Scientist), Maharshi Vashisht Autonomous State Medical College, Basti Uttar Pradesh, India

3: PhD Scholar, Department of Biotechnology, DAV University, Jalandhar, Punjab-144012, India

4: MDS, Chandra Dental College and Hospital Barabanki India

***Corresponding Author: Dr. Reeta Maurya: E Mail: reeta1707maurya@gmail.com**

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ABSTRACT

The oral microbiota is drastically changed by radiation therapy for oral cancer, which may result in side effects such xerostomia, mucositis, and infections. Chemoradiotherapy, which is frequently used to treat oral cancer, alters the mouth environment, causing microbial imbalances and harming good tissue. This might raise the risk of oral health problems including infections and dry mouth while decreasing good bacteria and increasing dangerous microbes. Healthcare professionals can improve oral health management both before and after treatment, improving patient outcomes and lowering treatment-related problems, by having a better grasp of these microbial alterations. In order to determine how these changes impact oral health, this study will compare the microbiological changes in patients with oral cancer before and after radiation therapy.

Keywords: oral microbiota, Oral microbial profile, oral squamous cell carcinoma, radiotherapy

INTRODUCTION

The sixth most prevalent type of cancer worldwide is head and neck cancer. Every year, this disease claims the lives of over 350,000 people globally and causes the diagnosis of over 600,000 new cases **[1]**. Oral cancer is becoming more common,

which is a serious worldwide health issue. Geographically, the incidence rate of oral cancer varies, with France and India having the highest rates. In addition to alcohol and tobacco use, poor oral hygiene is linked to an increased risk of oral cancer **[1, 2]**. The oral mucosa's microbial flora appears to vary between malignant and healthy locations. It is generally recognized that certain bacterial infections can cause or contribute to cancer **[3]**.

Figure 1: Oral cancer

Helicobacter pylori has been linked to stomach cancer as well as various malignancies of the colon, gallbladder, prostate, and lung **[4]**. Microbes, which are ten times more numerous than the cells in the human body, live in a rich and diverse community on exposed surfaces including the mouth, skin, and stomach. Chronic periodontitis, a risk factor for oral cancer, is linked to changes in the makeup of microorganisms and the expansion of specific pathogens. Due to swallowing difficulties, hyposalivation, and variations in the quality, quantity, and complexity of oral microbes, which cause an imbalance in the oral ecosystem, patients' local and systemic immunity decreased even though there were several effective treatment options available, including surgery, radiation, chemotherapy, or a combination of these for oral cancer **[5, 6]**. Both cancer and precancerous diseases have been linked to elevated levels and altered compositions of oral cavity microorganisms. Proteobacteria, Bacteroidetes, Actinobacteria, Fusobacteria, and Firmicutes are the most common and prevalent phyla linked to oral cancer **[7, 8]**. Streptococcus species are the most commonly found oral microbe in healthy people, while Prevotella, Veillonella, Neisseria, and Haemophilus are less common. Certain bacteria and Candida species can proliferate and overwhelm other resident microorganisms when the balance between bacterial load and compromised

immunological state is upset, leading to infections **[8]**. Oral cancer treated with radiation therapy alters the oral microbiota, which can result in the establishment of a possible pathogen and other systemic issues. The patient may develop drug-resistant opportunistic infections from changed oral microorganisms following radiation therapy, which could result in significant morbidity and systemic consequences. In order to accurately determine the presence or absence of specific microorganisms and their effects on immunocompromised patients, there is a need to investigate the precise function that oral microbes play and how they affect cancer treatment both before and after it has been completed **[9, 10]**.

Changes in microbial Diversity

Disease, therapy, and environmental variables are some of the major causes of changes in microbial diversity, especially within the oral microbiome. The range of distinct species of bacteria, fungi, viruses, and other microorganisms found in a given environment is referred to as microbial diversity. In terms of oral health, preserving dental homeostasis and halting the proliferation of harmful microbes depend on a diversified and balanced microbial community. However, illnesses including mouth cancer, chemotherapy, radiation therapy, and the use of antibiotics can all significantly change the oral microbiome, which frequently results in a decrease in microbial diversity **[11, 12, 13]**.

Radiation therapy, for example, can affect the salivary glands, resulting in xerostomia, or decreased saliva production, which inhibits the oral cavity's capacity to eliminate pathogens. Microbial diversity is further diminished as a result of the favorable conditions this decreased clearance provides for the growth of harmful bacteria. In a similar vein, chemotherapy, which targets cells that divide quickly, can also impact healthy oral mucosal and microbial cells in addition to cancer cells, causing an imbalance. These therapies may cause harmful pathogens like Candida, Streptococcus mutans, and Fusobacterium, which are known to contribute to oral diseases, to proliferate while decreasing the number of good bacteria, such as Lactobacillus and Streptococcus, which guard against oral infections and dental caries **[14, 15]**. In cancer patients receiving radiation and chemotherapy, oral infections, mucositis, and dry mouth are frequent side effects that might be exacerbated by a more homogeneous microbial community dominated by pathogens. Furthermore, the oral cavity's natural defenses are disrupted when microbial diversity declines, increasing the cavity's susceptibility to illness. For example, opportunistic pathogens may flourish if the ecological

balance of the oral microbiome is upset and the beneficial microorganisms that generate antibiotic compounds are reduced **[16]**.

In order to improve oral health and overall quality of life for cancer patients receiving treatment, it can be helpful to restore microbial diversity and encourage the growth of beneficial microorganisms through interventions such as probiotics, antimicrobial treatments, or oral hygiene techniques. For the purpose of creating focused strategies to preserve oral health and avoid difficulties in patient groups who are at risk, it is essential to comprehend these changes in microbial communities.

Normal Oral Microbiota: Composition and Function

Bacterial Flora- 1-2 paragraph

Fungal Flora

Viral and Protozoal Components

Oral Cancer and Microbial DysbiosisOral Health Issues observed due to Changed Flora

Many serious and frequently incapacitating oral health issues can result from altered oral flora brought on by chemotherapy, radiation therapy, and other medical procedures. Oral mucositis, a painful disorder marked by inflammation and ulceration of the mucous membranes inside the mouth, is one of the most frequent side effects.

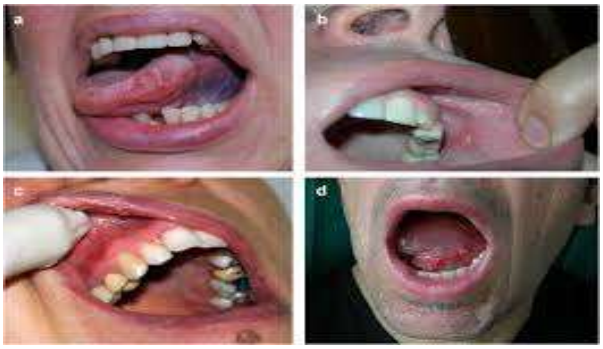
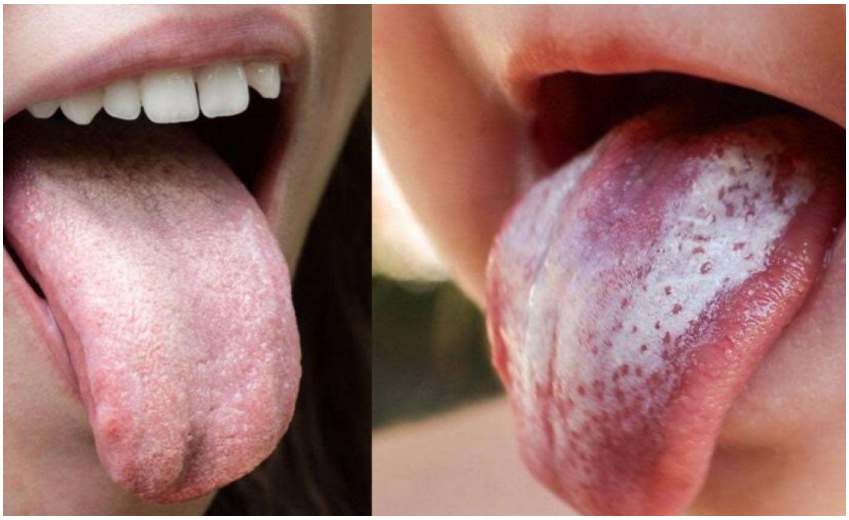


Figure 2: Oral mucositis

This happens when the fast-dividing oral cavity epithelial cells are harmed by chemotherapy or radiation therapy, increasing their susceptibility to infection by harmful microbes. Treatment-induced microbial changes have the potential to worsen mucositis, extending its course and intensifying its intensity **[17]**. Dry mouth, or xerostomia, is another common side effect that frequently arises following radiation treatment that targets the head and neck. Saliva production may be significantly reduced as a result of radiation damage to the salivary glands. Because it neutralizes acids, washes away food particles, and inhibits bacteria growth, saliva is essential for maintaining dental health. Dental caries (tooth decay) and infections are more likely

to occur when saliva production declines because it fosters the growth of dangerous bacteria and fungus **[18]**.

An overabundance of the common fungal infection Candida albicans can cause oral thrush, which manifests as white spots in the throat and mouth. Patients whose immune systems have been damaged by cancer therapies are especially likely to experience this. Furthermore, alterations in the oral microbiota may lead to a rise in periodontal disease, a disorder that damages the gums and the tissues that support the teeth. When the microbial balance is upset, pathogenic bacteria such as Porphyromonas gingivalis and Fusobacterium nucleatum can multiply and cause gingivitis, gum recession, tooth mobility, and possibly tooth loss. Halitosis, or bad breath, can also result from an imbalance in the oral microbiome because harmful bacteria release sulfur compounds that are volatile and give off offensive odors.



Furthermore, cariogenic bacteria like Streptococcus mutans may become more prevalent if there are less helpful bacteria like Streptococcus and Lactobacillus species, which aid in preventing oral illnesses **[19]**. Dental caries results from the demineralization of tooth enamel caused by the acids produced by these bacteria. In conclusion, a variety of oral health problems, including as mucositis, xerostomia, infections, periodontal disease, caries, and foul breath, might result from the disturbance of the oral microbiome brought on by cancer treatment and other causes. A patient's quality of life may be greatly impacted by these issues, thus maintaining oral health both before and after treatment is crucial to lowering the chance of serious consequences and enhancing general wellbeing **[20, 21]**.

Impact of Chemo-Radiotherapy on Oral Flora and Oral Cancer

Malignancies that arise in the tissues of the mouth, lips, tongue, cheeks, gums, floor of the mouth, and hard palate are referred to as oral cancer, a subtype of head and neck cancer. Human papillomavirus (HPV) infection, alcohol intake, tobacco use, and poor dental hygiene are risk factors for this cancer, which is among the most prevalent in the world. Although many occurrences of oral cancer are discovered at an advanced stage, which makes treatment more difficult, early detection can result in better treatment outcomes **[22, 23]**.

Depending on the tumor's stage and location, chemotherapy, radiation therapy, and surgery are frequently used in combination as the conventional treatment for oral cancer **[24]**. The initial line of treatment is usually surgery, which entails removing the tumor along with a margin of healthy tissue to guarantee total excision. Reconstructive surgery could also be required in certain situations to restore the appearance and function of the mouth. Radiation therapy is frequently used as the principal treatment for inoperable tumors or to eradicate any cancer cells that may have remained after surgery. Radiation therapy prevents cancer cells from growing and dividing by altering their DNA, but it also damages good oral tissues, causing side effects such mucositis, xerostomia, difficulties swallowing, and dental problems. When surgery is not an option or the cancer is advanced, chemotherapy may be given in addition to radiation therapy. Chemotherapy kills quickly dividing cancer cells with strong medications, but it also affects healthy cells and can cause side effects like fatigue, nausea, and immunological suppression **[25]**.

The patient's oral health and quality of life may be drastically changed by the combination of these treatments, even though they are helpful in managing and curing oral cancer. Comprehensive oral care is a crucial part of cancer treatment because it includes modifications to the oral microbiota, which can raise the risk of infections, oral mucositis, and other problems. Multidisciplinary care including oncologists, surgeons, dentists, and other medical professionals is essential to improving patient outcomes and reducing treatment-related problems because oral cancer is an aggressive disease **[26]**.

Radiation induced changes on the Oral Microbiome and oral cancer

One of the main treatments for oral cancer, chemotherapy and radiation, has a significant effect on the oral microbiome because it upsets the delicate balance of the microbial communities in the oral cavity. The combination of chemotherapy and radiation causes the oral environment to change significantly, mostly by damaging

healthy oral tissues including the salivary glands and mucosa **[27]**. These procedures not only weaken the mouth cavity's structural integrity but also change the makeup of the microbes, which significantly reduces their diversity. Beneficial, healthy germs like Lactobacillus and Streptococcus are frequently reduced, but harmful bacteria like Fusobacterium, Streptococcus mutans, and Candida may multiply. This imbalance makes one more vulnerable to a variety of oral health issues, such as xerostomia (dry mouth), dental caries, mucositis, and oral infections. Additionally, these problems are made worse by the decrease in protective saliva brought on by radiation-induced injury to the salivary glands, since saliva is essential for preserving oral hygiene and destroying dangerous bacteria **[28]**.

These microbial changes may have systemic effects in addition to local oral health issues since they may lead to opportunistic infections, especially in people with impaired immune systems. The damaged oral environment could operate as a haven for harmful germs, which could result in more issues and have a detrimental effect on the prognosis as a whole. Healthcare professionals can better customize interventions, such as probiotics, antimicrobial therapy, and better oral hygiene practices, to reduce treatment-related complications and enhance patient outcomes both during and after chemo-radiotherapy by knowing these radiation-induced changes in the oral microbiome **[29, 30]**.

Chemotherapy-Induced Immunosuppression

Combined Effects

Patterns of Microbial Alteration during Chemo-Radiotherapy

Therapeutic and Preventive Strategies

1. **Oral Hygiene and Antimicrobial Management**
2. **Probiotics and Microbiome Modulation**
3. **Salivary Substitutes and Cytoprotective Agents**
4. **Personalized Microbiome-Based Interventions**

Managing and preventing oral health issues brought on by changes in oral microbiota, especially in cancer patients receiving radiation and chemotherapy, calls for an all-encompassing strategy. Regular and comprehensive dental hygiene procedures are the first step in preventive treatment since they help to lessen the buildup of dangerous microbes. It is recommended that patients use a soft-bristled toothbrush and fluoride toothpaste to brush their teeth at least twice a day in order to protect delicate oral tissues **[31]**.

Using an antibiotic mouthwash can also help lower the bacterial load and avoid illnesses

like periodontitis or oral thrush. Saliva replacements or oral moisturizers can help relieve dry mouth and increase patient comfort for those who suffer from xerostomia. Lozenges that increase saliva production or sugar-free chewing gum might also be suggested. Patients should be urged to drink lots of water throughout the day because it's equally vital to stay hydrated. It's crucial to see an oncology-focused dentist on a regular basis since they can keep an eye on oral health and see any early warning indicators of problems like mucositis, infections, or dental decay **[32]**.

Mucosal protectants and pain relievers (such benzydamine mouthwash) are topical treatments that can be used to ease irritation and discomfort in cases of oral mucositis. In addition to using fluoride toothpaste with a greater fluoride concentration than ordinary products, dental professionals may apply fluoride varnishes or gels to patients in order to prevent dental cavities. Systemic treatments like antifungal medications (such nystatin or fluconazole) are frequently required in addition to local oral hygiene to prevent or treat oral thrush brought on by Candida overgrowth. Because they may encourage the growth of good bacteria while inhibiting dangerous infections, probiotics are being investigated as a possible tactic to reestablish a healthy microbial balance in the oral cavity **[33, 34]**.

Dietary changes can also help manage oral health, with a focus on avoiding sugary or acidic foods that can worsen tooth decay and keeping a balanced, nutrient-rich diet to boost the immune system. Use of fluoride trays or personalized mouth guards are examples of protective measures that can help patients receiving radiation therapy avoid tooth damage and lower their risk of radiation-induced dental decay. Enhancing patients' quality of life requires effective pain treatment, and options range from over-the-counter painkillers to more potent drugs that doctors prescribe. Finally, for the best possible care of oral health both during and after cancer treatment, strong coordination between oncologists, dentists, and other medical professionals is crucial **[35]**.

Future Perspectives and Research Gaps

Anyplace in the oral tissues, such as the tongue, palate, gingival, buccal mucosa, floor of the mouth, or lip, OSCC can be found. Most squamous cell carcinomas result from normal-looking epithelium and previous "potentially malignant" lesions or abnormalities. While the origins of OSCC may be complex, tobacco or its products, both smoke and smokeless, are the most common etiology. In India, rising tobacco use has expanded into a complex issue that poses a risk to young people's health.

Males are more likely than girls to develop oral cancer (72.9%), according to a study by

Anjali *et al*. [10] Most OSCC patients were between the ages of five and six. These results are consistent with research conducted by other groups. Even while it is known that oral cancer is more common in older adults, new data trends show that the disease is more common in younger people, and the current study found a similar association. According to numerous recent research, the frequency of oral cancer in younger people under 40 years of age is between 4% and 6%. In this investigation, eight OSCC cases under 40 years old were found, including four tongue cases. In addition, a review by **Sarkaria and Harari [36]** found 14 reports with three or more patients under 40 years old with OSCC of the tongue, supporting the findings previously reported by **Selvamani *et al*., [37]** who reported that the prevalence of tongue cancers in the Indian population was 12% in the age group of 31–40 years. As the most prevalent location seen in female patients and the major site for OSCC in smokeless tobacco users, we found that the buccal mucosa was involved in 50% of female cases in this investigation. Smoking and alcohol use were linked to 47.14% of instances in this investigation, while **Ajay *et al*. [38]** found a similar correlation in 28.1% of patients.

There are around 100 trillion microbial cells that coexist with their host in the human body. It has long been thought that microorganisms in specific bodily locations have a role in immunological regulation, the advancement of disease, and maintaining health. Several of these microbes have been linked to oral conditions like periodontitis and dental cavities, which are among the most prevalent bacterial infections in people. The endotoxins (lipopolysaccharides), enzymes (proteases, collagenases, fibrinolysin, and phospholipase), and metabolic byproducts (hydrogen sulfide, ammonia, and fatty acids) that microorganisms and their products produce are harmful to host cells and can cause direct mutations or change signaling pathways that may impact epithelial cell survival and/or proliferation. It is commonly known that bacterial infections can contribute to the development or progression of cancer. Helicobacter pylori has been linked to stomach cancer, and specific bacterial infections have also been linked to malignancies of the gallbladder, colon, lung, and prostate. Therefore, it is unclear if changes in the normal oral flora's makeup and/or persistent microbial infections can contribute to or cause oral cancer **[10, 39, 40]**.

According to **Binder Gallimidi *et al*., [41]** mice with a persistent infection of *Porphyromonas gingivalis* and *Fusobacterium nucleatum* are more likely to

develop chemically induced OSCC. Alcohol dehydrogenase activity and the production of acetaldehyde, a recognized carcinogen produced from alcohol, by *Streptococcus thermophiles* and *Streptococcus mitis* concealed in deep periodontal pockets point to one possible reason for the pathophysiology of oral cancer. These results are consistent with the current study, which found that nearly all patients had *Staphylococcus, Streptococcus,* and *Enterococcus.*

According to a study salivary bacteria connected to oral malignancies, patients who had radiation therapy had considerably greater levels of *Prevotella melaninogenica, Leptotrichia buccalis, Capnocytophaga gingivalis, Eubacterium saburreum,* and *S. mitis* than controls. The pH of dental plaque and microorganisms during hyposalivation in ten patients following three to five years of radiation therapy with equal controls were examined by **Eliasson *et al*. [42]** They found that the irradiated group had higher levels of Lactobacilli and Candida species than their controls because of their saliva's decreased buffering capacity.

CONCLUSION

In conclusion, individuals with oral cancer may experience serious difficulties if their oral microbiota is disrupted by therapies like chemotherapy and radiation therapy. The oral microflora is essential for preserving oral health. Oral mucositis, xerostomia, dental cavities, infections, periodontal disease, and poor breath are among the problems caused by these treatments, which alter the microbial variety and frequently decrease helpful bacteria while encouraging the proliferation of harmful microbes. These issues can have a substantial impact on a patient's quality of life and general well-being in addition to their oral health. Numerous problems can be lessened, nevertheless, with the right management and prevention techniques. Key strategies include practicing good dental hygiene, treating dry mouth with saliva substitutes, preventing cavities with fluoride treatments, and treating infections with antimicrobial medicines. The restoration of microbial balance and improvement of oral health can be further supported by probiotics, dietary changes, and routine dental checkups. Interdisciplinary care including oncologists, dentists, and other experts is crucial for patients with severe difficulties in order to provide the best possible treatment outcomes by monitoring and addressing problems early. Healthcare practitioners can enhance patient comfort, avoid difficulties, and promote the general health and recuperation of cancer patients by comprehending how chemo-radiotherapy affects the oral microbiome and putting beneficial techniques into practice.

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Authors' Contribution: PY drafted the manuscript, compiled information from the literature, Figures and the manuscript and gathered information from the literature. RM supervised and reviewed the manuscript.

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