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## Review Article

# Stomatological complications and comprehensive oral care of post-menopausal patients undergoing breast cancer treatment

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## ABSTRACT

Breast cancer is one of the widespread diseases all over the world. Breast cancer is the leading variant of cancer among females. Oral diseases are potentially thought to be relevant to systemic disease. Surgical approaches lumpectomy, partial mastectomy along with post surgical radiotherapy (RT) or chemotherapy (CT) is the mainstream gold standard treatment of breast cancer. But unfortunately RT/CT comes with some unavoidable stomatological complications especially in post menopausal age. There are many studies found some definite oral complications during the treatment periods of breast cancer therapy like sore mouth, mucositis, salivary gland dysfunctions, dysgeusia, dysesthesia, cervical caries, periodontitis, alveolar bone loss, opportunistic infections, and osteoradionecrosis etc. Obtained from present knowledge available, different oral complications are discussed like proper oral hygiene (both professional and domiciliary), pretreatment prophylaxis, appropriate diet, periodontal check up, fluoride varnish, salivary substitutes which minimize the chance to develop complications. Certain measures are to be taken at pretreatment and post treatment sessions in order to prevent possible complications. We will try to discuss the possible oral complications and way outs in the article.

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## 1. Introduction

Oral health is the mirror of the systemic wellness of human being. Oral diseases are proven to be associated with systemic diseases. Different microbial organisms reside in oral cavity. Some of the organisms can cause dental caries, periodontal mucosal infections and opportunistic infections in immunocompromised patients. Post-menopausal women are more susceptible to periodontal problems. Periodontal problems are Decline in estrogen levels can cause erosion in spine, hip and jaw bones. Periodontal problems are chronic inflammatory conditions which worsen in immunocompromised conditions. Several studies have shown definite relevance between chronic inflammatory conditions and oncogenic diseases.<sup>1</sup> Breast cancer is

one of the leading cancers now a day. Post surgical chemotherapy and radiotherapy have some pernicious impact on oral mucosal and dental health. Cancer chemotherapy causes acute toxicity that generally resolves after the discontinuation of therapy and there is auto recovery of damaged tissue. But radiation therapy can cause not only acute oral toxicities, but can induce permanent tissue damage, resulting in lifelong risk for the patients. This will lead to myriads of undesired situations like hyposalivation, xerostomia, radiation caries, oral thrush, loss of taste, burning mouth syndrome, oral sores, progressive periodontal bone loss, periodontal abscess, glossitis, salivary gland infections, cracked tooth syndrome, trismus, lichenoid reactions, mucositis, dysphagia, osteoradionecrosis etc.<sup>2-4</sup> So, it is quite important to take some preventive measures in pre treatment and post treatment planning sessions to escape the radio and

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chemotherapy associated oral health hazards.

## 2. Prevalence of Breast Cancer

Breast cancer ranked one among Indian females with age adjusted rate as high as 25.8 per 100,000 women and mortality 12.7 per 100,000 women. Breast cancer is one of the most common cancers in United States. Near about 30% of all new female cancers each year. In 2023, an estimated 297,790 women in the U.S are expected to be diagnosed with invasive breast cancer and 55,720 women will be diagnosed with in situ breast cancer. Breast cancer is more prevalent in post- menopausal women and the median age at diagnosis is 61 years. The etiological factors of most of the breast cancers are still under research.<sup>3</sup> However some risk factors have been proven like age, family history, late menopause, early menarche, ethnicity and genetic factors. In recent years, for the advancements in treatment modalities and screening programs the mortality rate of breast cancer has been decreased which gives a hope for prognosis and survival. Periodontal issue is very much relevant to the post menopausal age due to fall in serum estrogen level.<sup>4</sup> It is a chronic progressive situation. Findings supported the factor that, those who suffered from chronic periodontitis, had two to three times higher odds of developing breast cancer. Due to immunocompromisation at the post surgical therapy, there is a trigger for the virulence of the periodontal and cariogenic microorganisms which create the oral complications.<sup>4,5</sup>

### 2.1. Impact on Alveolar and Jaw Bone Mineral Density (BMD)

Breast cancer therapies have an impact on bone mineral density (BMD). Aromatase inhibitors (AI), Anti-estrogen therapies are associated with bone loss and Vitamin D deficiency. There is definite interference in osteoblastic activity and Vitamin D absorption is reported. AIs are notorious for incident fragility fractures leading to a well known condition - cancer treatment induced bone loss (CTIBL). A study by Reid et al. it was found that in postmenopausal women, the aromatase inhibitors elevates bone turnover and induces annual bone loss at an average rate of 1-3% leading to an increase in fracture incidence compared to that seen during tamoxifen use.<sup>5</sup> Estrogen plays a pivotal role in homeostasis of minerals of bone and oral tissue. Drugs, those declines the production of estrogen or interfere the binding of estrogen to its receptors adversely affect the health of hard and soft tissue of oral cavity as well. In postmenopausal women Tamoxifen has been shown to decrease the BMD and bone mass also. In postmenopausal age, women face the estrogen deficiency problem which is a risk factor for periodontal bone loss which worsens by anti estrogen therapy. Several studies have found that use of tamoxifen for more than one

year was associated with greater tooth loss among breast cancer survivors. However, ovarian ablation along with chemotherapy is known to cause the highest bone loss.<sup>6</sup> To mitigate the bone loss of chemotherapy Bisphosphonates are prescribed which has a detrimental effect on jaw bone as during the Bisphosphonate therapy any invasive dental procedures like alveoloplasty, flap surgery, tooth extraction and implants are absolute contraindications to escape the fatal consequence of osteoradionecrosis (ORN). Bone vitality is hampered secondary to injury to osteoblasts, osteocytes and osteoclasts or from a relative hypoxia due to lack of blood supply.<sup>7</sup> Mandibular bone is more susceptible to the situation which may lead to ORN. So, dental care is very much challenging in this stage. Endodontic therapy under medical supervision is permissible to combat the toothache at this stage. For progressive bone loss of denture foundation, dentures are relined frequently. Fixed partial dentures (FPD) are not suitable to replace the missing one as the abutments are at the risk of radiation caries and there is unfavorable crown root ratio for advancement of alveolar bone loss. So removable partial dentures (RPD) is the only option remained.

## 3. Progressive Periodontitis

Periodontitis is a chronic inflammatory disease affecting the periodontium and is characterized by local tissue destruction initiated by the exposure to bacterial plaque and their metabolic bioproducts. There is a strong correlation between periodontitis and post surgical therapy of BC. The AIs, which are used as adjuvant endocrine therapy to prevent the recurrence of BC is suspected for degradation of periodontal health. The manifestations are bleeding gums, loss of attachments, increased pocket depth, horizontal and vertical pattern of alveolar bone destruction, triggering of periodontal pathogens causes periodontal abscess etc. This leads to the stage 4 of advanced periodontal diseases.<sup>8</sup> The post tumor therapy hyposalivation causes the adherence of biofilm and plaque in the periodontal tissue, which triggers the primary and secondary co-aggregation.

Amodio et al. unlike conducted a case-control study in which they assessed the prevalence of periodontal disease in 48 post BC treatment postmenopausal patients, compared to 48 controls without cancer. They found a high prevalence of periodontitis in postmenopausal survivors: 98% in breast cancer survivors and 87% in controls.<sup>9</sup>

Vargas-Villafuerte et al evaluated the influence of cancer therapy on periodontal treatment and prognosis. They found an interesting fact that patient undergone tumor therapies respond poor in non surgical conventional periodontal therapy compared to normal individuals who respond favorably in conventional prophylaxis at same baseline periodontitis stage. They also observed that even after minimal invasive periodontal therapy the bone loss is progressive in tumor therapy patients which lead to gradual

loosening of teeth.<sup>10</sup>

So to avoid such consequences, pre chemo/radio therapy session is very important. Non surgical or surgical periodontal therapies, curettage should be completed 2 weeks before the radiotherapy session. During tumor therapy periodical periodontal checkups, professional non surgical prophylaxis along with personal brushing flossing is the remedy. Recently induced Periochips are of great help in reducing the periodontal pathogens which can be utilized in such conditions. Table 1

#### 4. Salivary Gland Dysfunction

One of the most common complication of head and neck cancer radiotherapy is salivary gland dysfunction (SGD). SGD is an umbrella is an umbrella terminology which encompasses hyposalivation and Xerostomia. Dry mouth in tumor patients create serious problem in normal functions like eating, speaking, swallowing. There is increased risk of dental caries, opportunistic candidal infections which leaves a negative impact o nutritional and psychological status of patients which in turn compromises the quality of life. Saliva stimulants like chewing of sugar free gum or candy, use of saliva substitutes (carboxymethylcellulose), medicines lik Pilocarpine (Salagen), Cevimeline (Exovac) can solve the problems. Acupuncture following the radiation therapy, low voltage TENS (Transcutaneous electric nerve stimulation) are proposed to be possible treatment modalities to stimulate salivation.<sup>12</sup>

#### 5. Oral Mucositis, Burning Mouth Syndrome (BMS)

Oral mucositis is defined as ulceration and inflammation of mucosa with pseudomembrane formation. Patient complains about severe burning sensation and inability to take hot and spicy foods. Situations sometimes worsen so much that patient can't take even normal food. It was estimated that 60% patients undergoing chemo or radiotherapy suffer from mucositis. There are two possibilities are postulated to cause oral mucositis; direct and indirect.<sup>13,14</sup>

Direct mucositis is directly caused by toxicity. Because of having high turnover rate of oral mucosa they are susceptible to the cytotoxic effect of radiotherapy (RT) and chemotherapy (CT). Indirect mucositis is caused by myelosuppression due to tumor therapy which favors the invasion of fungal and bacterial species due to neutropenia. Tumor therapy changes the microflora, turnover rate of oral mucosa, epithelial maturation and flow of saliva. The combined factorial change gives the way of opportunistic lesions. To avoid consequences, all possible causes of mucosal breaching like ill fitting denture and sharp edges of teeth or restoration should be corrected. The treatment is to provide symptomatic relief. Use of topical analgesics and anesthetic gels provides enough

comfort. Vitmain A and Lycopene supplements along with metronidazole or doxycycline hypothetically have a role to minimize the discomfort. Single-agent oral elixirs (Magic mouthwash) containing dexamethasone, diphenhydramine, benzydamine, or doxepin have been used to alleviate oral mucositis.<sup>15</sup>

BMS is a painful condition characterized by burning, scalding or tingling sensation in oral mucosa which can even occur daily specially in post menopausal women. Etiology is still unclear but it is thought that fall of estrogen level probably cause the problem. During the RT and CT the exacerbation is more severe due to hyposalivation or xerostomia. Symptomatic relief with use of saliva substitute, assurance and Tricyclic antidepressants (TCA) thought to be beneficial to prevent such conditions.<sup>16</sup>

#### 6. Glossitis, Oral Thrush and Oral sores

Myelosuppression can cause anemia, susceptibility to infectio due to neutropenia, compromise of local/systemic immunity and there is chance of bleeding from gums due to thrombocytopenia. So, different types of tongue problems are observed after Chemo or radio sessions. Atrophic glossitis (Hunter glossitis), dysguesia, smooth glossy burning tongue (due to deficiency of vitamins), red beefy tongue, swollen tongue (due to anemia), sore and tender tongue, hairy tongue (after long term CT/RT, Candida infection) are the commonest findings of post menopausal women undergoing treatment or at post treatment stage.<sup>17</sup> Proper diet counseling, supplements of vitamins, maintenance of good oral hygiene, use of topical/systemic antifungals are must during the sessions and even after the treatment completion.

Due to immunocompromisation, different oral opportunistic infections can take place. Viral infections such as Herpes labialis, Herpes gingivostomatitis or Varicella Zoster infection sometimes occur which require antiviral therapy. Different fungal infections like angular chellitis, oral thrush, median rhomboid glossitis and erythema candidiasis are treated with topical or systemic antifungls depending upon prognosis and extension.<sup>18</sup>

#### 7. Dysguesia and Ageusia

Dysguesia is referred as the alteration or reduction of taste sensation. Ageusia is the complete obliteration of taste sensation. This type of taste disorder is one of the more frequent complaints of patients during chemotherapy. The cause behind the disorder can be explained as neurological interference in 7, 9 and 10th cranial nerves and alteration and inflammation of taste bud and tongue mucosa. According to the case control study by Ishikawa., et al. 43.8% of the patients participated in the study undergoing cancer chemotherapy raised the complaint of dysguesia.<sup>19</sup>

**Table 1:** List of chemotherapy drugs and their oral complication<sup>11</sup>

<b>Chemotherapy</b>	
Doxorubicin	Oral mucositis, xerostomia, lip sores
Epirubicin	Bleeding, redness, or ulcers in the mouth or throat; sores, ulcers, or white spots in the mouth or on the lips
Paclitaxel	Ulcers, sores, or white spots in the mouth; cracked lips
Docetaxel	Bleeding gingiva; sores, ulcers, or white spots on the lips or tongue or inside the mouth; xerostomia
5-Fluorouracil	Oral mucositis, xerostomia, lip sores
Capecitabine	Pain, redness, swelling, sores, or ulcers in the mouth or, bleeding gingiva; sores, ulcers, or white spots on the lips or in the mouth; white patches in the mouth or throat, or on the tongue
Cyclophosphamide	Sores in the mouth and on the lips, xerostomia, swollen lips
Carboplatin	Sores in mouth and on lips
Albumin-bound paclitaxel	Sore mouth, tongue, or throat; ulcers, sores, or white spots in the mouth; cracked lips
Cisplatin	Loss of taste; sores in mouth and on lips
Vinorelbine	Bleeding gingiva; sores, ulcers, or white spots on the lips or in the mouth
Gemcitabine	Bleeding gingiva; sores, ulcers, or white spots on the lips or in the mouth
Ixabepilone	Sores, ulcers, or white spots on the lips, tongue, or inside the mouth; xerostomia; cracked lips
Eribulin	Xerostomia; ulcers, sores, or white spots in the mouth; cracked lips; sores, ulcers, or white spots on the lips, tongue, or inside the mouth; swelling or inflammation of the mouth
<b>Selective Estrogen Receptor Modulators</b>	
Tamoxifen	Sores, ulcers, or white spots in the mouth or on the lips
Raloxifene	Dryness/soreness of throat
Toremifene	Dry mouth or metallic taste
<b>Aromatase Inhibitors</b>	
Exemestane	Sore throat
Anastrozole	Sore throat
Letrozole	Sore throat or sores, ulcers, or white spots on the lips or in the mouth
<b>Monoclonal Antibody</b>	
Trastuzumab	Bleeding gingiva; cracked lips; dry mouth; sore throat; or sores, ulcers, or white spots on the lips or in the mouth
Signal Transduction Inhibitor	Inhibitor
Lapatinib	Sores, ulcers, or white spots on the lips or in the mouth
Selective Estrogen Receptor Degrader	Receptor Degrader
Fulvestrant	Bleeding gingiva; sore throat; tender/swollen glands in the neck; sores, ulcers, or white spots on the lips or in the mouth
<b>Luteinizing Hormone</b>	
Goserelin	None known
Leuprolide	Sore throat

## 8. Dental Neurotoxicity

Perineural invasion is a complication due to tumor progression at metastatic site. Dysesthesia, paresthesia, neuralgic pain, tingling sensation and numbness are usually found in these patients. Certain types of CT drugs (Vinca alkaloids) can cause dental neurotoxicity, which is usually manifested as persistent deep aching pain, dull pain, and throbbing pain or burning pain in tooth or jaw region where definite origin can't be detected.<sup>20</sup>

## 9. Trismus, Dysphagia

Radiation therapy can produce trismus. There are chances of fibrosis, scar tissue formation, muscle atrophy, inflammation and hypoxia, trigeminal nerve invasion (PNI) and neurotoxicity which usually affect the muscles

of mastication, TMJ, jaw elevator and depressor muscles. Post menopausal women with multiple missing teeth and osteoporosis most often suffer from TMJ problem. Post tumor treatment period is more challenging to them. Regular active jaw stretching exercises, moist hot compress, physiotherapy (Therabite, tongue blade, dynamic bite opener), analgesics and muscle relaxants are commonly used to maintain optimum mouth opening.<sup>21</sup>

Radiation induced aerodigestive tract is less common complication. Laryngeal and pharyngeal muscle stiffens due to radiation exposure or there is scar formation. This affects the function of swallowing.

## 10. Cervical caries (Radiation caries) and Cracked tooth Syndrome

Different studies have shown that a cumulative dose with 30 and 60 Gy results in a morphological changes in the enamel and dentine structure. It is an aggressive and extensive caries characterized by rapid decalcification of enamel which is catalyzed by increased amount of cariogenic bacteria and hyposalivation. It starts from labial surface of incisor and canine which rapidly progresses inwardly to the cervical region followed by complete amputation of crown. The loss of crown is less common in molar teeth where brownish or black discoloration of crown which spreads palatally and occlusally.<sup>22</sup>

Pre treatment dental assessment is necessary to calculate the DMFT index (Decayed, missing and filled tooth), periodontal status, Oral hygiene score, and sites of possible dental infection. All decayed, broken, abscessed and periodontally weak teeth should be assessed before radiation sessions. Many of the post menopausal women are usually detected with unsatisfactory periodontal health, plaque deposits and multiple carious teeth. All decayed, broken teeth should be restored and unrestorable teeth must be extracted 4 weeks before RT. Periodontally weak teeth should be removed also because during the RT session extraction can lead to ORN. Fluoride application is mandatory in Pre and post RT sessions where caries index is expected to be high. Professional prophylaxis should be carried out before RT. Patients should be educated to maintain personal oral hygiene and usage of cleaning aids (floss, water jet) during the sessions. Use of chlorhexidine mouthwash and sodium lauryl sulfate prevents plaque formation and improves the periodontal health. Alcohol containing mouthwashes are contraindicated in dry mouth patient, it may cause burning sensations. Because hyposalivation, there is of fall in pH which elevates the chance of radiation caries. So, sodium bicarbonate mouthwash is also advocated to maintain the salivary pH.

## 11. Conclusion

Whilst undergoing the breast cancer treatment it is equally important to maintain proper oral care. In our country, in the post menopausal age dental health is one of the most neglected parts among the women. So, consequences and professional care limitation during CT/RT should be explained properly before the sessions. Pre treatment assessment is necessary to rule out further complications and care should be taken to minimize the secondary and unavoidable damage to oral hard and soft tissue. A small negligence can trigger various serious issues during the RT/CT phase or recovery period. So, a good coordination with consultant oncologist and regular dental checkups at pre treatment and post treatment phases are the prime need to improve the quality of life in the post therapy period.

## 12. Conflict of Interest

None.

## 13. Source of Funding

None.


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