Keywords Chemotherapy, oral mucositis, periodontitis, prosthodontics, restorative dentistry,oral microbiome

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Oral Mucosal and Periodontal Alterations in Breast Cancer Patients: Implications for Restorative and Prosthodontic Care

Abstract
One of the most common modalities of breast cancer treatment is chemotherapy; it is also often linked to oral cavity adverse effects. The purpose of this study was to test the changes in the oral mucosa, periodontal tissues, oral microbiota and bone status induced by chemotherapy and to examine the implications of these changes on the prosthodontics and restorative dental treatment. Between 2021 and 2023, 703 women aged 55-65 years were studied with breast cancer, and 154 subjects were controls. The Oral Mucosal Grading Scale (OMGS) was used to clinically assess oral mucosa. Microbiological examination was done to assess the alteration of oral microflora and radiographic examination to assess alveolar bone resorption and bone density index through orthopantomography. Correlation analysis and Fisher exact test ($p < 0.05$) were used to perform statistical analysis. The findings revealed that oral mucositis was highly prevalent with moderate to severe inflammation in chemotherapy patients. Major changes in the oral microbiota were observed with a greater number of opportunistic pathogens. Radiographic results showed that bone density was significantly decreased and moderate to severe chronic periodontitis was highly prevalent. It was observed that these changes were highly linked with chemotherapy regimens. Clinically, these changes bear significant significance on prosthodontic and restorative dentistry. Inflammatory responses of the mucosa and xerostomia can impair denture tolerance, and periodontal destruction and bone loss can impair the location of implants and the stability of prostheses. Also, the microbiological modifications can predispose to the biofilm formation and adversely impact the durability of restorative materials.

Introduction:
The occurrence and severity of complications have been widely investigated by Russian and international researchers, who categorize these influencing factors into systemic and local determinants [1,2]. Systemic factors include the type of chemotherapy agents immunosuppression, lifestyle-related habits such as chronic alcohol consumption and tobacco use, as well as underlying systemic conditions including diabetes mellitus, HIV infection, cardiovascular disorders, and renal diseases [2,3]. Among chemotherapeutic agents, particular attention has been given to 5-fluorouracil, methotrexate, and doxorubicin due to their strong association with oral tissue complications [4,5]. Among chemotherapeutic agents, particular attention has been given to 5-fluorouracil, methotrexate, and doxorubicin due to their strong association with oral tissue complications [6]. However, its cytotoxic mechanism also contributes to significant adverse effects in the oral mucosa, making it a key focus in studies investigating chemotherapy-induced oral complications.The study of the pathogenesis of the action of 5-fluoruracil in mice revealed that the drug causes the atrophy of the oral mucosa, which is characterized by the slowdown of proliferation, the increase of death of cells, the detachment of inflammatory factors and the loss of protective properties of the oral mucosa [1]. Genetic

factors may play a role in the occurrence of oral mucositis as a result of 5-fluoruracil administration. Gene chemotherapeutic agents can affect
metabolizing enzymes. Thus, the dihydropyrimidine dihydrogenase deficiency may contribute to the potentially toxic action of 5-fluoruracil. Methotrexate is a cytostatic agent belonging to the family of antimetabolites - antagonists of folic acid. The drug inhibits the synthesis of tetrahydrofolate, which disrupts DNA synthesis, thus blocking cell proliferation. The World Health Organization considers methotrexate as an essential drug; it is applied to treat acute Lymphoblast leukoses, nervous system edema, osteosarcoma and some autoimmune conditions [4]. Doscorubicin is a cytotoxic anthracycline antibiotic that causes a change in the nucleotide base structure, thinning the nucleotide and DNA - and RNA - polymerase replication. It is this that leads to the development of toxic effects on various organs [7].

Doxorubicin is applied for the treatment of breast cancer, oesophagal cancer, gastric cancer, malignant tumors of the brain and neck regions, ovarian cancer, cervical cancer and several other cancers [7,8]. The oral cavity has various microorganisms: according to recent studies, the number of microorganisms is more than 700. This makes the oral cavity the richest part of the human body in terms of post-intestinal microorganisms [9]. In the flora, 50-200 species are selected, these are common, present in almost all people.

They are divided into microorganisms that fertilise the tooth surfaces (above the gums) and microorganisms that are under the gums.ms. These are Actinomyces, Campilobacter, Capnocytophaga, Corynebacterium, Fusobacterium, Granulicatella, Neisseria, Prevotella, Streptococcus, Veilonella.

The latter include Filifactor, Fusobacterium, Parvimonas, Porphyromonas, Prevotella, Tannerella, Treponema. Anaerobic streptococci (S. mutans, S. mitis, S. sanguis) represented by peptostreptococci make up almost half of the normal microflora of the oral cavity. The oral microbiota is involved in the use of specific and non-specific, humoral and cellular immunity. Bifidobacteria have a beneficial effect on the maturation of the lymphoid system and induce the formation of a protective barrier, increase the level of properdin protein, lysosym enzyme, prevent the occurrence of bacteremia and sepsis [10].

Chemotherapy-related changes in the oral environment play an important role in prosthodontic and restorative dentistry [11]. Oral mucositis and inflammation can decrease tolerance to removable prostheses and make clinical practices difficult [9,12]. Systemic therapy-induced periodontal tissue destruction may result in tooth loss, requiring prosthetic replacement [3]. Chemotherapy-induced bone density loss may also impact implant stability and osseointegration [13,14]. This study aims to evaluate the impact of chemotherapy on oral mucosal health, periodontal status, oral microbiota, and alveolar bone condition in breast cancer patients, using clinical (OMGS), microbiological, and radiographic assessments. Additionally, it seeks to analyze the association between different chemotherapy regimens and the severity of oral complications, and to determine how these alterations influence prosthodontic and restorative dental treatment outcomes.

Materials and Methods

Study Design and Setting

The study was conducted between 2021 and 2023 at the Bukhara branch of the Republican Specialized Scientific Practical Medical Center of Oncology and Radiology and the Dental Scientific Practical Center of the Bukhara State Medical Institute.

Study Population

A total of 703 patients were examined, of which 154 patients served as the control group. The study included women aged 55–65 years with moderate to severe chronic diffuse periodontitis and a history of at least 5 years of post menopause.

Clinical Assessment of Oral Mucosa

Clinical evaluation of the oral mucosa was performed using the Oral Mucosal Grading Scale (OMGS), which was used to assess the severity of mucosal inflammation during chemotherapy.

Microbiological analysis of oral samples was conducted to evaluate changes in oral microflora before and after chemotherapy. The presence of key microorganisms was assessed and compared between groups.

Radiographic and Bone Assessment

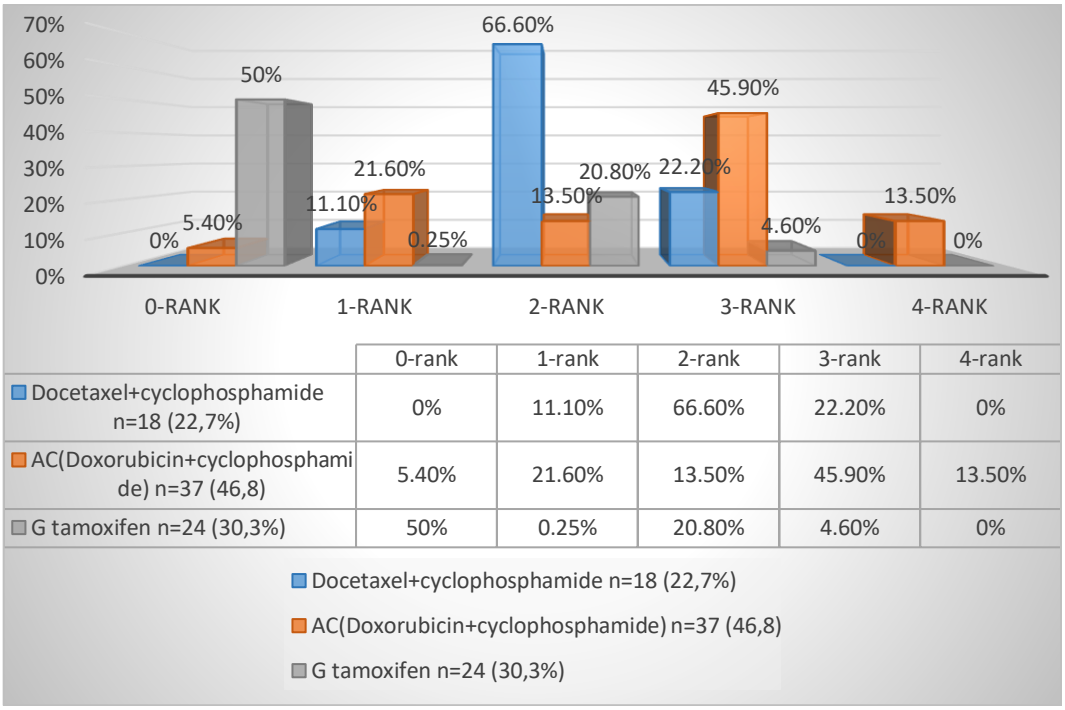
Radiographic assessment was performed using orthopantomography to evaluate alveolar bone resorption. Bone status was analyzed using the Fuchs index and mandibular cortical index (MCI).

Statistical analysis was performed using correlation analysis and Fisher’s exact test to determine the significance of observed differences between groups. A p-value < 0.05 was considered statistically significant.

Results

Oral Mucosal Changes Associated with Chemotherapy

To determine the effect of a special mixture of drugs used for chemotherapy on the mucous membrane of the oral cavity, a correlation analysis was carried out between the values of the scale for assessing the severity of the oral mucosa and the drugs used in the patients included in the study. The average values of the measurement scale of the oral mucosa during treatment with different chemotherapy drugs and different chemotherapy regimens. As shown in **Figure 1**, patients receiving doxorubicin-based regimens exhibited higher rates of Grade III–IV mucositis.



	0-rank	1-rank	2-rank	3-rank	4-rank
Docetaxel+cyclophosphamide n=18 (22,7%)	0%	11.10%	66.60%	22.20%	0%
AC(Doxorubicin+cyclophosphamide) n=37 (46,8)	5.40%	21.60%	13.50%	45.90%	13.50%
G tamoxifen n=24 (30,3%)	50%	0.25%	20.80%	4.60%	0%

Figure 1. Luminal Group A OMGS-oral mucosal scale values and different chemotherapy complication rates

The possible complications from chemotherapy drugs in the group of vaginal A in women with mammary cancer are as follows: - dosetaxel+cyclofosmid Grade II 66.6% swelling redness, pain when speaking, Grade III 22.2% redness and swelling on the oral mucosa are clearly manifested, pains, Grade I 11.1% jaroxat slight redness, discomfort, at levels 0 - III we can see that the indicator is zero. - in drugs of the doxorubicin+cyclofosmide group, 45.9% of the III degree were clearly manifested redness and swelling of the oral mucosa, pains, IV-degree 13.5% severe pain, constant bleeding of the mucous membrane, inflammation from the mucous membrane to the hard tissue, II-degree 13.5% swelling redness, pain when speaking, 0-degree 5.40% during the incubation period, it was observed - tamoxifen was observed to have caraches on the 50% mucosa of Level 0, Level II was 20.8%, Level III was 4.6%, level I was 0.25% higher (Figure 1). These findings suggest potential challenges in denture tolerance and patient comfort during prosthodontic rehabilitation.

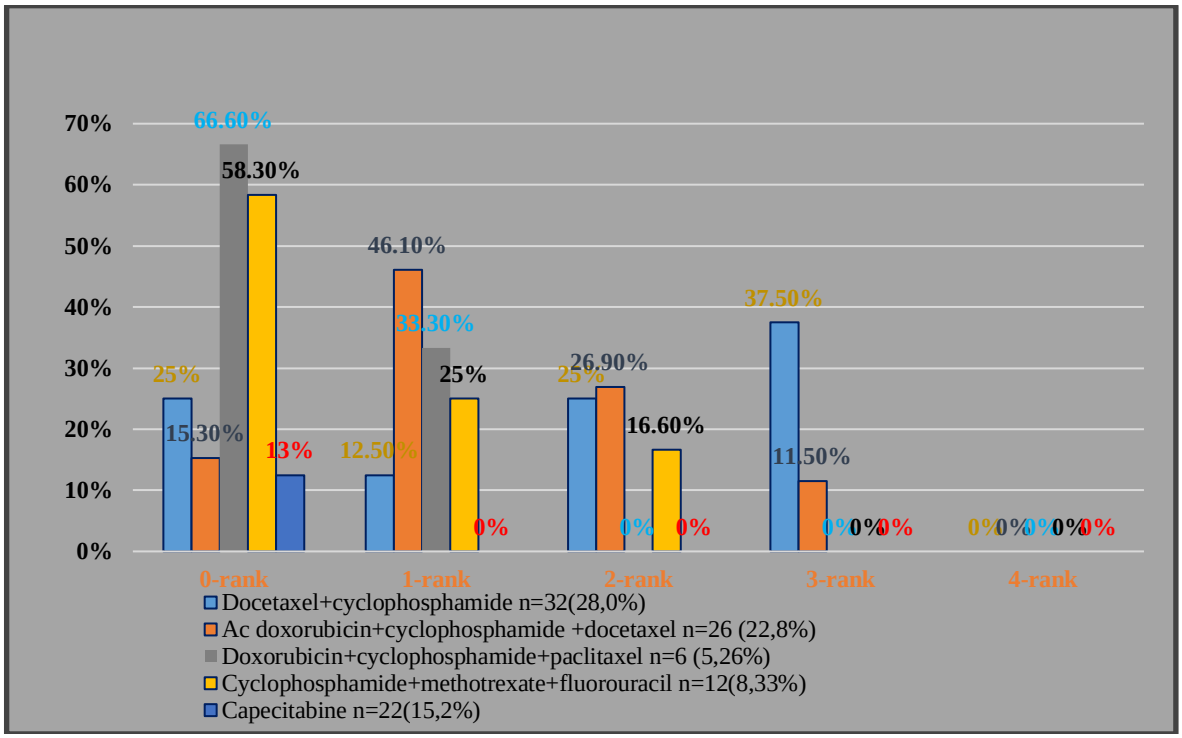


Figure 2. Luminal V HER2 OMGS in the negative Group-scale values of the oral mucosa and the level of complications of various chemotherapy

The distribution of mucosal complications in HER2-negative patients across different chemotherapy protocols is illustrated in **Figure 2**. Also mammary cancer luminal V HER2 possible complications from the negative group of chemotherapy drugs are as follows: - Dosetaxel+cyclofosmid - Level III 37.5% of redness and swelling on the oral mucosa is evident, pains, Level II 25% swelling redness, pain when speaking, Level 0 25% in the incubation period karash mucous covering the top, level I 11.1% jaroxat slight redness, levels IV can be seen as equal to 0%. - AS doxorubicin+cyclofosmide+dosetaxel - I-level 46.1% mild redness, Level II 26.9% swelling redness, Level 0 15.3 in the incubation period, karash mucous covering the top, level III 11.5% redness and swelling on the oral mucosa are evident, Level IV are 0% equal. doxorubicin+cyclophosmide+paclitaxel - level 0 - 66.6% has been seen to cover the carash mucosa UST during the incubation period, level I-level 33.3% swelling redness, Level II - III-IV 0%. Cyclofosmide + methotrexate + fluoruracil has been shown to cover the carash mucosa UST during the level 0 incubation period of 58.3%, level I-25% jaroxate slight redness, Level II 16.6% swelling redness, when speaking pain is 0% at levels III - IV. - capesitabine, Grade I-81.8% mild redness, grade 0 - 9.09% was seen to cover the carash mucous UST during the incubation period, Grade II - 9.09% swelling redness, Level III-IV-0%. Olaparib - level 0 was seen to cover the carash mucosa UST during the 37.5% incubation period, Level II 50.0% swelling redness, pain I-level 12.5% mild redness when speaking, and Level III - IV 0%. Increased severity of mucosal inflammation may further compromise the clinical feasibility of removable prostheses. As demonstrated in **Figure 3**, most patients exhibited mild to moderate mucosal changes, with no cases of severe mucositis.

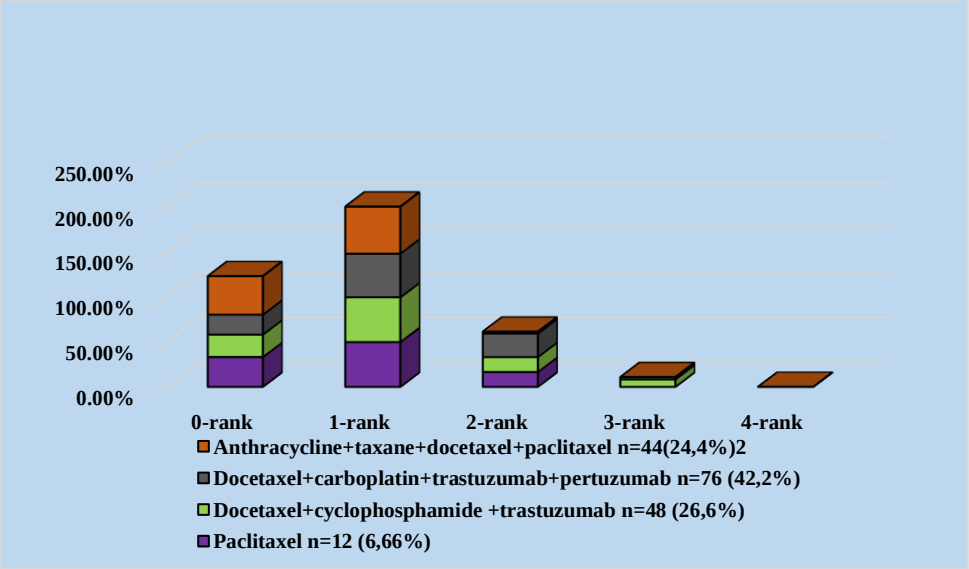


Figure 3. Luminal V HER2 positive group OMGS - oral mucosal scale values and different chemotherapy complication rates

As a result of the studies carried out, it is determined that: - Inflammation of the oral mucosa with paclitaxel medication I-level 50% jaroxat slight redness, level 0 33.3% during the incubation period, with a mucous covering the top, level II 16.6% swelling redness, pain when speaking, Level III-IV was seen to be 0%. - Docetaxel + cyclophosphamide + Trastuzumab effects have been studied.

Microbiological Findings

Absolute values of the number of people with non-zero growth and their share in the group are given. CT-chemotherapy. The event level was analyzed using Fisher's specific criterion. The Streptococcus oralis in the protocol group remained the same as the non-zero growth percentage and fell from 14.3% to zero in the comparison group. As shown in Table 1, there was a significant increase in opportunistic microorganisms such as Candida albicans and Streptococcus mitis following chemotherapy.

Table 1. The degree of occurrence of microorganisms under study in patient groups

The microorganism being examined	**The guru who used the protocol (n = 17)**	**Guruh who did not use the minutes (n = 14)**	p
Candida albicans KT before	2 (11,7%)	6 (42,9%)	0,1
Candida albicans KT then	4 (23%)	12 (85,7%)	0,001
Streptococcus salivarius KT before	4 (23%)	0 (0%)	0,1
Streptococcus salivarius KT then	4 (23%)	0 (0%)	0,1
Streptococcus mitis KT before	2 (11,7%)	6 (42,9%)	0,1
Streptococcus mitis KT then	2 (11,7%)	12 (85,7%)	0,0001

Klebsiella pneumoniae KT before	0 (0%)	12 (85,7%)	0,0001
Klebsiella pneumoniae KT then	0 (0%)	4 (28,6%)	0,037
Neisseria subflavaKT before	2 (11,7%)	4 (28,6%)	0,38
Neisseria subflavaKT then	2 (11,7%)	6 (42,9%)	0,1
Enterobacter cloacae KT before	0 (0%)	4 (28,6%)	0,037
Enterobacter cloacae KT then	0 (0%)	10 (71,4%)	< 0,0001
Streptococcus parasanguisKT before	8 (47%)	0 (0%)	0,003
Streptococcus parasanguis KT then	8 (47%)	0 (0%)	0,003
Streptococcus oralis KT before	12 (70%)	2 (14,3%)	0,001
Streptococcus oralis KT then	12 (70%)	0 (0%)	< 0,0001

Radiographic and Periodontal Findings

According to the WHO, tooth loss as a result of periodontal diseases functional disorders of the tooth-jaw system, develop five barovars faster than complications of caries and is the second most common among all dental diseases in terms of prevalence. Orthopantomography was used for X-ray examination of the gums in patients with mammary cancer. It assesses the degree of resorption of the alveolar barrier relative to the length of the tooth root according to the Fuchsa - 4-score index: 4 - lack of resorption in the alveolar tumor; 3-score resorption up to 1/3 of the root length of the bone; 2-score resorption up to 2/3 of the root length of the bone; 1-score resorption; 0-complete resorption of the alveolar bone resulting from periodont pathology. The calculation of the Fuchsia index is carried out according to the following formula. As illustrated in **Figure 4**, moderate to severe periodontitis was highly prevalent among patients with osteoporosis and osteopenia.

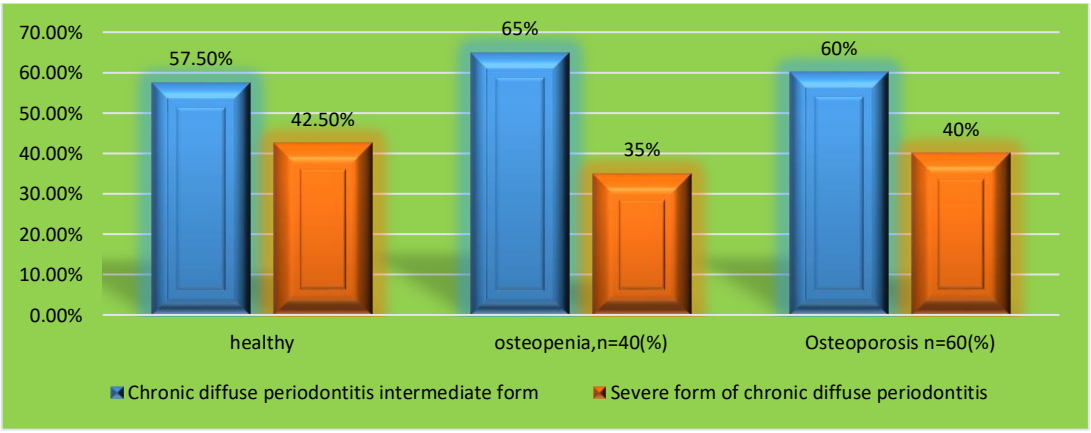


Figure 4. Chronic diffuse periodontitis in patients with breast cancer (%)

Index of characterization of the cortical layer of the lower jaw Clemetti E. and was increased to AML based on the MCI index by others. It was evaluated according to the morphological characteristics of the bone. Depending on its morphological characteristics, 3 types of it were distinguished: S1 - normal cortical layer with a clear inner border, cortical area without a bilinear unknown change. S2-one side of the cortical plate is crescent-shaped and significantly damaged. The S3-cortical margin is uneven, the cortical plate is multilayered with many defect areas. The initial orthopantomograms were also analyzed 2 years after treatment. Chronic diffuse periodontitis (%) in patients with breast cancer. Among patients with chronic diffuse parodontitis and postmenopausal osteoporosis, 60% had moderate-grade parodontitis, and 40% had severe-grade parodontitis, based on clinical and radiological data.Among the patients examined, STP 65% median periodontitis against the background of osteopenia was diagnosed with 35% severe periodontitis. It has a significant difference in statistical comparison of patients by group. These findings collectively indicate that chemotherapy-induced oral and bone changes significantly influence dental treatment planning and prosthodontic outcomes.

Discussion

The analysis of oral microflora provides valuable insights into the early prediction and progression of mucosal diseases and their associated complications. Oral dysbiosis may increase the risk of biofilm formation on dental prostheses and restorations, potentially affecting their longevity and hygiene maintenance [15,16]. In women with breast cancer, light and chemistry are the main causes of the occurrence of chronic diffuse periodontitis after the exception of therapy oral mucosa [17,18]. Early menopause in women after chemotherapy and light is an important factor in the development of the disease [8]. It is a chronic hypoxia in the microcirculation of parodont tissue, with impaired nutrition contributing to the destruction of parodont tissue. Microcirculation, on the other hand, is primarily due to the inflammation of the tissues of their endothelial walls, ischemia and excessive

damage in others, which eliminates the protective barrier, helping the periodontium to become one of the pathomechanisms of the disease [15]. During the long-term treatment of patients with mammary gland cancer, large and small pain syndromes of the spine and bones appear, and joint pain that irritates and does not stop for a long time has been observed in dispensary control. The developmental pathogenesis of pain syndrome in patients is often caused by osteoporosis (op) in SBS [19]. Chemotherapy and hormone therapy are factors that have a great influence on the metabolic process of bone structure.

Chemotherapy also affects the mineral density of the bone by affecting ovarian dysfunction with bone tissue against the background of cytotic therapy, which in due time causes the rapid development of early menopause and osteoporosis [20]. In mammary gland cancer (SBS), drugs that affect tumors that occur in a hormone-dependent manner affect the patient's menstrual cycle and at the same time a change in bone density occurs.Tamoxifen or gonadotropin-releasing hormone antagonists are used to treat aduvant breast cancer,causing up to 7% bone loss during one year of treatment. Also surgery leads to artificial menopause according to the indications of an ovariectomy, which increases the risk of fractures characteristic of osteoporosis [21]. Thus, changes in bones caused by the use of endocrine therapy chemotherapy and surgical methods in the treatment of mammary cancer are currently a pressing problem. Osteoporosis has been negatively affecting patients with this cancer, leading to unpleasant symptoms [19]. Solving the problem of spreading periodontal tissue diseases is one of the most important and urgent tasks of modern dentistry. A healthy periodontal in 12% of the population.In people over 35 years of age, the proportion of initial changes in parodont gradually decreased by 26-15%, while an increase in moderate to severe changes was observed to be as high as 75%. This in turn leads to the appearance of functional disorders in the dentition [16].

Periodontal destruction and decreased bone density may adversely affect the success of implant-supported prostheses and prosthodontic treatment. Chemotherapy-associated oral alterations have a direct impact on prosthodontic and restorative care [4]. Inflammation and ulceration of the mucosal tissues may decrease the tolerance to removable prostheses, causing pain and discomfort [22]. Moreover, periodontal bone destruction and the incidence of periodontitis may lead to tooth loss, requiring prosthodontic treatment [23]. Chemotherapy and hormone therapy-induced bone density loss can impact the placement and osseointegration of implants, reducing the potential for successful implant-supported prostheses in cancer patients. Moreover, changes in salivary and bacterial flora may contribute to biofilm formation on prostheses and reduce the durability of dental materials [10,24]. These observations underline the need for coordinated dental care within the management of oncological patients to enhance prosthodontic rehabilitation [25].

Chemotherapy patients may have sensitive mucosa, dry mouth, and poor periodontal support, which impact prosthodontic management. Irritation and discomfort from removable prostheses can lead to poor patient acceptance. Moreover, bone loss and loss of periodontal attachment may restrict the use of fixed prostheses and dental implants [23]. Thus, treatment planning with the use of soft liners, conservative prostheses, and delayed implant placement is crucial for this patient population [26].

Salivary flow rates and composition changes during chemotherapy may influence the physical and chemical properties of dental materials. Diminished salivary flow may affect the retention of removable prostheses, while changes in pH and microbiota may affect the degradation and wear of restorative materials. These should be taken into account when choosing materials for prosthodontic and restorative rehabilitation of cancer patients. These changes could also affect the behaviour of modern adhesive systems, denture base materials and implant surface interactions.

Conclusion

Chemotherapy causes considerable changes in the oral mucosa, periodontal tissues, oral microbiota and bone metabolism of breast cancer patients. These modifications lead to mucositis, periodontal disease, and reduction of bone density, which altogether affects oral health and functioning. Clinically speaking, these changes have significant implications in terms of planning prosthodontic and restorative treatments. Mucosal inflammation and xerostomia can decrease the removable prosthesis tolerance, and periodontal destruction and bone loss can restrict the viability and success of the implant-supported restorations. Also, dysbiosis induced by chemotherapy can contribute to the risk of biofilm formation and negatively impact the survival of restorative materials. That is why the management of oncology patients undergoing chemotherapy should include the comprehensive dental assessment and the individual approach to treatment planning. To maximize the results of oral rehabilitation and enhance the quality of life of patients, it is necessary to engage in preventive measures, routine monitoring, and the correct choice of the material.

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