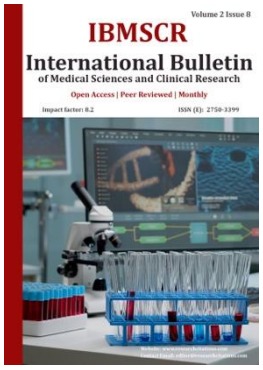

ORAL HEALTH STATUS IN PATIENTS DIAGNOSED WITH MALIGNANT NEOPLASMS

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Abstract Cancer treatment, particularly cytotoxic chemotherapy and targeted therapy, is associated with a high incidence of oral complications such as mucositis, xerostomia, stomatitis, periodontal inflammation, and taste alterations. These complications can significantly impact patients' quality of life and interfere with oncological treatment protocols.

Keywords: oral mucositis, chemotherapy, cancer patients, periodontal disease, mucosal immunity, supportive care, photobiomodulation, cryotherapy, dental screening

Introduction

Cancer therapy, particularly chemotherapy and targeted treatment, frequently induces various oral complications, among which oral mucositis and periodontal disease are the most prevalent and clinically significant. The oral cavity, as an active immunological barrier and microbiological environment, is highly susceptible to cytotoxic damage due to its rapid cell turnover and direct exposure to systemic medications. Complications such as mucositis, xerostomia, stomatitis, taste disorders, and secondary infections not only reduce the patient's quality of life but can also interfere with the planned oncological treatment, requiring dose adjustments or interruptions.

In recent years, growing attention has been paid to the pathophysiological mechanisms underlying oral mucosal damage in cancer patients, including inflammation, microbial imbalance, and local immune suppression. Modern research emphasizes the importance of the mucosal immune system and non-specific defense mechanisms of the oral cavity in counteracting these processes. Specific salivary components such as immunoglobulin A (IgA), lysozyme, and lactoferrin play a pivotal role in maintaining local homeostasis. However, chemotherapy-related myelosuppression, mucosal injury, and dysbiosis frequently compromise these defenses, resulting in a high risk of bacterial, fungal, and viral infections.

Despite international recommendations from associations such as MASCC/ISOO and ESMO, which advocate for pre-treatment oral screening and preventive dental protocols, the integration of oral care into routine oncology practice remains inconsistent. Furthermore, specific data on periodontal complications and their systemic implications in immunocompromised patients are still limited, especially in regions with unique epidemiological and environmental conditions.

This study aims to provide a comprehensive analysis of oral and periodontal complications among cancer patients receiving chemotherapy, evaluate current methods of prevention and management, and highlight the significance of maintaining oral health to improve therapeutic outcomes. By addressing both the local immune response and clinical aspects of oral care, this work seeks to contribute to the optimization of supportive oncology protocols.

The growing incidence of oncological diseases makes the impact of neoplastic pathology on the overall condition of the body an increasingly relevant issue. Cancer ranks second in mortality worldwide after cardiovascular diseases [9, 25]. In developed countries, malignant neoplasms account for up to 13% of total mortality, with a persistent upward trend [2]. The proportion of patients with malignant tumors may reach 1.4% of the national population [9, 15]. Overall morbidity and mortality from cancer are increasing [18, 26], although advancements in diagnostics and treatment have been achieved for certain tumor types [22]. Most countries have established mandatory cancer patient registries, enabling comprehensive epidemiological analysis and reliable statistics [22].

In dentistry, one of the key areas of focus is the diagnosis and treatment of oral mucosal diseases [39, 16]. The prevalence of oral mucosal conditions, according to various sources, ranges from 3% to 20% [12, 21]. In many cases, clinical signs in the oral cavity may serve as predictors of underlying systemic diseases [35, 40, 36, 37, 38, 44]. Therefore, dental examination and oral diagnostics may contribute to the early detection of systemic pathologies [8, 18].

Between 2016 and 2018, the dental status—specifically, the condition of the oral mucosa and periodontal tissues—was examined in 526 patients with malignancies of various localizations at the Nizhny Novgorod Regional Oncology Dispensary (Russia). The findings revealed that all oncology patients, regardless of cancer site, had decompensated dental caries.

The highest prevalence of periodontal disease was observed in patients with skin cancer, and the lowest in those with cancers of the laryngopharynx and esophagus. In addition to these oral mucosal conditions, atrophic papillae of the tongue, candidiasis, oral leukoplakia and lichen planus, lingual papillomas, and cheilitis were also identified.

Some studies suggest that pre-existing oral diseases may increase the risk of developing dental complications during chemotherapy. Up to 75% of the general population is affected by chronic periodontal diseases [5]. Poor oral hygiene, caries-associated periapical pathology, and periodontitis have been causally linked to increased risk of stomatotoxicity during cancer treatment [57]. Younger patients appear more susceptible to chemotherapy-induced stomatitis, possibly due to higher epithelial mitotic rates. Other factors modulating the severity of stomatitis include nutritional status, specific treatment protocols, quality of oral hygiene during therapy, pre-treatment neutrophil count, use of hematopoietic growth factor support, and variations in the oral microbiome [9, 17, 23]. Genetic predisposition is considered a possible factor, though not yet definitively proven [6, 14, 16].

Clinically, cytotoxic agents typically exert direct stomatotoxic effects, often beginning on day 7 of treatment and peaking between days 10 and 14. Initial manifestations include erythema of the buccal or palatal mucosa, accompanied by a burning sensation in the mouth. This may be followed by the development of isolated, slightly painful, white desquamative patches. With progression, epithelial detachment leads to multiple shallow pseudomembranous ulcers, which may coalesce into large painful erosions causing dysphagia and reduced food intake.

The severity of mucositis ranges from mild oral discomfort with minimal clinical manifestations to severe erosive mucositis accompanied by intense pain and an inability to eat or drink. Severe pseudomembranous or erosive mucositis can lead to secondary infections or sepsis, particularly in the presence of concurrent neutropenia, and may necessitate the use of

parenteral nutrition and/or opioid analgesics. Additionally, if the patient develops thrombocytopenia, bleeding from the oral cavity or gums may occur. In some cases, pain may precede visible mucosal changes.

Oral Cavity Condition During Systemic Therapy in Cancer Patients

Currently, targeted agents are among the widely used methods in cancer treatment. These drugs are pathogenetically justified, offer high therapeutic efficacy, and exhibit lower overall toxicity [11]. Nevertheless, targeted therapy can also cause toxic effects on the gastrointestinal tract, particularly on the oral mucosa [5], significantly reducing the patient's quality of life.

One Russian study conducted at the Oncology Research Institute of the Tomsk National Research Medical Center examined dental status and oral mucosal lesions in cancer patients receiving targeted therapy, specifically vascular endothelial growth factor inhibitors (bevacizumab) and IL-6R inhibitors (tocilizumab) [1]. In 87.98% of cases in the main group, various oral mucosal lesions were diagnosed, including mucositis, different forms of oral lichen planus, and combinations of multiple types of leukoplakia. In the control group (patients who had not received targeted therapy during or prior to the study), no oral mucosal lesions were detected.

Among the most common oral complications caused by systemic anticancer therapy—often leading to significant discomfort and nutritional impairment—are: mucositis, salivary alterations, oral pain, mucosal dysesthesia/hypersensitivity, dysgeusia, dysphagia, xerostomia, aphthous ulcers [27], infections, and gingival bleeding [8, 11]. The spectrum of gastrointestinal-related symptoms includes oral ulceration, dysphagia, odynophagia, esophagitis, gastritis, diarrhea, and malabsorption. The precise mechanisms behind some of these complications remain unclear, though they may be associated with impaired healing of microtrauma. Disruptions in the integrity of the oral and gastrointestinal mucosa present a particular challenge in oncological patients.

Dental Complications in Oncology Patients Undergoing Treatment

Mucositis is a common but transient side effect of chemotherapy. On average, 20–40% of patients undergoing standard-dose cytotoxic chemotherapy develop oral complications [153, 152, 69]. This incidence rises to 80% in patients undergoing hematopoietic stem cell transplantation (HSCT), especially those preconditioned with radiation-based regimens or methotrexate.

The pathological processes underlying damage to the oral mucosal barrier are complex. In patients receiving traditional cytotoxic chemotherapy, several stages can be identified [12, 15, 17]:

Initiation: radiation and chemotherapy induce direct and indirect DNA and non-DNA damage via reactive oxygen species;

Upregulation and message generation: the initial damage activates transcription factors such as nuclear factor kappa B, leading to the production of biologically active proteins, including pro-inflammatory cytokines;

Signal amplification: as these cytokines accumulate, they damage surrounding tissues and amplify inflammation through feedback loops. This precedes the visible clinical phase of mucositis;

Ulceration and inflammation: breakdown of mucosal integrity leads to painful lesions and promotes secondary bacterial colonization;

Healing: mucositis typically resolves spontaneously once tissue damage subsides and regeneration begins.

Evaluation of Oral and Gastrointestinal Mucosal Toxicity Associated with Targeted Therapy in Oncology Patients

The Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) conducted an assessment of the risk and severity of mucosal damage in the oral cavity and gastrointestinal tract associated with selected targeted agents. A meta-analysis incorporating data from 85 studies comparing targeted agents to conventional treatment regimens revealed that oral mucositis was significantly more frequent in patients treated with bevacizumab, erlotinib, sorafenib, and sunitinib. However, these differences were largely limited to low-grade mucositis. The clinical significance of these findings remains uncertain, given the generally low incidence and mild severity. In contrast, diarrhea occurred significantly more often in patients treated with most targeted agents, with adjusted relative risks ranging from 1.5 to 4.5. Statistically, for every 3–5 patients receiving targeted therapy instead of standard regimens, one additional patient developed diarrhea.

The severity and extent of oral mucositis in oncology patients are influenced by numerous factors, including the specific drug used, dosage, route and frequency of administration, patient tolerance, genetic polymorphisms in drug metabolism pathways, immune response, and mechanisms of cellular injury and repair [16]. Among these, dosimetric parameters have been most reliably confirmed as key predictors of mucositis risk.

Generally, cell cycle-specific DNA-targeting agents—such as bleomycin, fluorouracil (5-FU), and methotrexate—are more toxic to the oral mucosa compared to non-cell cycle-specific agents like cyclophosphamide, cisplatin, and anthracyclines [13]. Some agents, such as methotrexate and etoposide, are secreted in saliva, which may increase the likelihood of stomatotoxicity. Common cytotoxic agents associated with mucositis include cytarabine, doxorubicin, high-dose etoposide, high-dose melphalan, bolus-scheduled fluorouracil, and methotrexate.

The reported incidence of stomatitis in patients receiving molecularly targeted agents varies widely depending on drug class. Oral mucositis has been observed in 30–40% of patients treated with orally active tyrosine kinase inhibitors (e.g., sunitinib, sorafenib, lenvatinib, regorafenib), which target, among others, vascular endothelial growth factor receptors (VEGFR); 25% of patients receiving the CDK4/6 inhibitor palbociclib; 20% of those treated with the PARP inhibitor niraparib; and 10–46% of patients receiving epidermal growth factor receptor (EGFR) inhibitors (e.g., cetuximab, erlotinib, dacomitinib, mobocertinib). In most cases, mucositis presents with mild to moderate clinical severity [6, 8, 17]. Higher rates of stomatitis (72% overall, with 9% being grade 3 or higher) have been reported with afatinib and fibroblast growth factor receptor (FGFR) inhibitors (56% overall, 9% grade ≥3) [14, 16, 18]. However, the majority of cases associated with these agents are mild.

Additionally, oral mucosal lesions—including typical ulcerations due to barrier disruption and aphthous-like inflammatory elements—have been observed in 73% of patients treated with mammalian target of rapamycin (mTOR) inhibitors [16, 26, 28]. According to review data, mTOR inhibitor-associated stomatitis is the most frequent adverse event (73%),

accounting for nearly 30% of dose reductions and representing the most common dose-limiting toxicity (53%) [112].

Mucosal Toxicity Associated with Immune Checkpoint Inhibitors

Mucosal toxicity associated with the use of immune checkpoint inhibitors includes periodontal disease and stomatitis, as well as oral lichen planus, xerostomia, and, in rare cases, Sjögren's-like syndromes affecting the salivary glands and pemphigoid-like mucosal lesions [14, 19].

Mucositis is typically a self-limiting condition. Following conventional cytotoxic chemotherapy—usually administered in intermittent cycles—oral mucosal lesions tend to resolve spontaneously within several days and generally heal completely within 10 to 14 days of onset, often coinciding with neutrophil recovery [85]. Severe symptoms (grade 3 or 4) may necessitate dose reductions in subsequent treatment cycles. However, treatment is rarely discontinued due to mucosal toxicity alone. Oral mucositis associated with molecularly targeted agents is generally less severe than that caused by traditional cytotoxic drugs [16, 18].

When administered intermittently, as in the case of certain mTOR inhibitors (e.g., cetuximab), mucositis tends to resolve spontaneously. In contrast, tyrosine kinase inhibitors, which are administered continuously on a daily basis, may cause persistent mucositis. However, symptoms may diminish over time or after several weeks of treatment interruption, depending on the specific agent. Clinically, this form of mucositis typically presents as well-defined aphthous stomatitis.

Mucositis associated with immune checkpoint inhibitors displays a distinct clinical pattern, frequently manifesting as lichenoid reactions. Oral lichenoid lesions usually appear as reticulated white striations (Wickham's striae) or as erosive lesions. While potentially severe, immune-related mucositis typically presents with low-grade clinical manifestations.

Assessment of Oral Mucositis Severity, Infectious and Other Complications, and Periodontal Status in Oncology Patients

A number of assessment systems are currently used to evaluate the severity of mucositis, incorporating both subjective and objective criteria. The most commonly applied grading tool is the Common Terminology Criteria for Adverse Events (CTCAE) developed by the National Cancer Institute, which grades mucositis severity on a scale from 1 to 5 based on clinical findings and patient-reported symptoms.

The World Health Organization (WHO) offers the following grading scale:

Grade 0 – No signs of oral mucositis
Grade 1 – Erythema and soreness
Grade 2 – Presence of ulceration; able to eat solid food
Grade 3 – Ulceration; patient can ingest only liquids due to mucositis
Grade 4 – Ulceration; oral intake is not possible due to mucositis

For recipients of high-dose chemotherapy, the Oral Assessment Guide (OAG) developed by the University of Nebraska is frequently used. This tool scores eight clinical parameters with a possible total score ranging from 8 to 24. Patients with higher peak mucositis scores (≥18 vs. <18) demonstrated significantly higher rates of positive blood cultures (60% vs. 30%) and elevated transplant-related mortality (24% vs. 4%).

An intact oral mucosal surface serves as a physical barrier to pathogens and facilitates the removal of adhered microorganisms through continuous desquamation of surface epithelium

[15]. Disruption of this barrier predisposes patients to bacterial, fungal (especially Candida albicans), and viral superinfections, particularly during chemotherapy-induced neutropenia. The risk and severity of infectious complications increase when the absolute neutrophil count falls below 1000/μL. A compromised mucosal barrier may become a portal of entry for translocation of various pathogens—including viruses, fungi, and bacteria—into the bloodstream [15].

The link between mucositis and systemic bacteremia has been demonstrated in a study of 69 patients who underwent autologous hematopoietic stem cell transplantation (HSCT). Among those who developed alpha-hemolytic streptococcal bacteremia (n = 24), ulcerative mucositis was significantly more frequent (62% vs. 36%). Furthermore, the presence of ulcerative mucositis increased the likelihood of developing bacteremia by threefold.

As noted earlier, fungal infections, especially with Candida albicans, are the most common superinfections in chemotherapy-induced mucositis. Many oncology patients are already at increased risk of developing superficial oral candidiasis due to immune suppression from progressive malignancy. Mucositis further exacerbates the risk of local infection and dissemination [17]. For instance, in a cohort of patients undergoing high-dose chemotherapy for acute leukemia, systemic fungemia occurred almost exclusively in those with preceding oropharyngeal candidiasis.

Superficial oropharyngeal candidiasis can often be treated with topical agents such as clotrimazole lozenges or nystatin suspension. Systemic therapy with oral fluconazole is generally unnecessary unless the patient is intolerant to topical treatments. Refractory infections may require oral or intravenous fluconazole or parenteral amphotericin B.

Chemotherapy is also associated with an increased risk of viral reactivation. Antiviral prophylaxis is therefore recommended for herpes simplex virus (HSV)-seropositive patients undergoing induction chemotherapy (e.g., for acute leukemia) or receiving high-dose conditioning regimens prior to HSCT.

Viral Infections, Xerostomia, and Bleeding Complications in Chemotherapy Patients

In the absence of antiviral prophylaxis, the oral cavity can be affected by viral pathogens. The most common is reactivation of herpes simplex virus type 1 (HSV-1), which occurs in over 60%—and in some studies up to 90%—of HSV-seropositive patients receiving high-dose chemotherapy followed by hematopoietic cell transplantation (HCT). HSV infection should be considered in the differential diagnosis of any patient who develops vesicular lesions or unusually painful oral ulcers following chemotherapy, particularly when candidiasis is not clinically evident. Compared to mucositis-related oral lesions, HSV-induced erosions are more atypical, irregular in shape, and superficial.

In patients with HSV-1 seropositivity and moderate-to-severe mucositis, empirical antiviral therapy—either intravenous or oral acyclovir or valacyclovir—can be initiated while awaiting culture results. Clinical trials in immunocompromised patients with mucocutaneous HSV infections (including those undergoing chemotherapy) have shown that a one-week course of intravenous acyclovir significantly reduces viral shedding, accelerates lesion healing, and alleviates pain.

Although salivary gland dysfunction is most often associated with radiation therapy, chemotherapy can also cause salivary hypofunction [13]. Reduced salivation may also result from the use of anticholinergic agents prescribed for nausea or diarrhea associated with

anticancer therapy. The clinical presentation of xerostomia varies: some patients report varying degrees of dry mouth, while others paradoxically experience excessive salivation and drooling due to dysphagia or odynophagia. Primary symptoms of xerostomia include mucosal dryness, discomfort, and thick, sticky saliva, which may interfere with speech and swallowing. Patients may also report dysgeusia (altered taste) [13].

Chemotherapy-induced xerostomia is typically reversible and resolves spontaneously after the end of treatment. Although this form of xerostomia may exacerbate other complications such as mucositis, it generally does not have a long-term impact on oral health.

Thrombocytopenia, particularly when platelet counts drop below 15,000/μL, may result in spontaneous gingival bleeding. This risk increases with poor oral hygiene or minor mucosal trauma, such as from ill-fitting dentures or aggressive toothbrushing. If toothbrushing causes unacceptable tissue trauma or pain, plaque control may be maintained using regular chlorhexidine mouth rinses. Gingival bleeding has also been reported in patients treated with bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor (VEGF), though such events are rare [2, 7].

Taste and Smell Alterations, Osteoradionecrosis, Trismus, and Secondary Malignancies in the Oral Cavity of Cancer Patients

Transient alterations in taste and smell are frequently observed in patients undergoing chemotherapy and may contribute to reduced appetite and weight loss [17, 19, 20, 25]. In two prospective series involving cancer patients undergoing chemotherapy for various malignancies, taste changes were reported in 70% and 67% of cases, respectively [1, 6]. In one report, 49% of patients experienced changes in olfaction during chemotherapy [6]. Among a cohort of 87 women undergoing chemotherapy for breast or gynecologic malignancies, significant decreases in olfactory and gustatory function during treatment nearly completely recovered to baseline levels within three months post-chemotherapy [155]. Olfactory dysfunction was more pronounced in elderly patients than in younger ones [9, 12, 18].

Chemotherapy and targeted therapies may influence taste either through direct stimulation of taste receptors (due to drug secretion in saliva or gingival crevicular fluid—patients often describe a metallic or chemical taste during chemotherapy) or by altering signaling pathways involved in taste perception [163]. In some cases, taste disturbances may persist after drug elimination, possibly due to direct damage to taste receptor cells [6, 26].

Osteoradionecrosis (ORN) is a potential complication of radiation therapy, defined as exposed necrotic bone in a previously irradiated area in the absence of tumor recurrence. It is often triggered by trauma to hypoxic bone tissue, such as tooth extractions, poor dental eruption, surgery, or infection. Symptoms of ORN may include pain, halitosis, dysgeusia, dysesthesia or anesthesia, trismus, difficulty chewing or swallowing, speech impairment, fistula formation, pathological fractures, and secondary infections. ORN may be diagnosed shortly after the completion of radiotherapy or may manifest years later [4].

The mandible is most frequently affected, particularly in patients receiving high-dose radiation for head and neck cancers. Maxillary ORN is less common and typically occurs after radiotherapy for nasopharyngeal carcinoma [7]. In any patient with ORN and exposed mandibular or maxillary bone, tumor recurrence must always be considered in the differential diagnosis.

Trismus, defined as the inability to fully open the mouth, is a common complication of head and neck cancer treatment [8]. It can impair nutrition due to difficulty chewing, compromise oral hygiene, cause pain and muscle spasms, and significantly reduce quality of life [80, 60]. Management often requires lifelong physiotherapy [8, 9, 12, 15].

The risk of developing new oral malignancies is associated with the type of prior cancer, treatments received, and individual risk factors such as tobacco use or family history [71, 158]. Patients with squamous cell carcinoma of the head and neck, those with graft-versus-host disease (GVHD), and those previously treated with high-dose chemotherapy are particularly at risk for developing new primary tumors and oral cancer recurrence [9, 12].

Metastatic cancer to the oral cavity from distant solid tumors is rare, accounting for approximately 1–2% of all oral malignancies [99]. The most common primary sites metastasizing to the oral cavity are: lung (22.5%), breast (18%), kidney (12%), and liver (8.6%) [13]. Metastatic spread may occur via arterial, venous, or lymphatic routes and can involve both soft tissues and bone [14]. Treatment strategies depend on the primary tumor type, whether the oral lesion is the sole site of metastasis, and the patient's symptoms.

Specific and Non-Specific Defense Mechanisms of the Oral Cavity: Status of Local Immunity

Within the body's system of "external barriers," the oral mucosa plays a critical frontline role in antigen–antibody interactions that may lead to both primary and secondary damage. It serves as the first line of defense against pathogenic agents [4, 17, 23].

The mucosal immune defense mechanisms and the resistance of the oral mucosa to microbial and viral insults are ensured by several components: epithelial barrier function, interactions among immunocompetent cells, mechanisms of foreign antigen recognition and immune tolerance, as well as the production of immunoglobulin A (IgA) and secretory IgA (sIgA). These immunoglobulins neutralize antigens and disrupt immune complexes independently of the complement system [23, 24].

Local oral immunity maintains mucosal homeostasis through the tightly integrated action of both non-specific and specific defense mechanisms, developed through evolutionary processes [9, 13, 21]. Currently, the concept of local mucosal immunity encompasses the activity of all lymphoid-derived immune cells residing in the mucosa, including macrophages, neutrophils, eosinophils, mast cells, as well as connective tissue and epithelial cells [2].

In inflammatory conditions of the oral cavity—such as caries, gingivitis, and stomatitis—mixed infections are frequently encountered, involving associations of bacteria, spirochetes, fungi, and viruses. As a result, specific antigens—derived from animal, plant, or bacterial sources—can be found in saliva, dental tissues, dental plaque, and the epithelium of the tongue and cheeks. Additionally, ABO blood group antigens have been identified in the epithelium of the cheeks, tongue, and esophagus. However, the majority of antigens are microbial in origin [28].

Despite this antigenic burden, the oral mucosa provides protection from chemical, thermal, mechanical, and infectious insults through the action of superficial epithelial cells [28].

Non-specific immune protection of the oral cavity is largely mediated by the antimicrobial properties of saliva, which contains lysozyme, lactoferrin, lactoperoxidase, amylase, transferrin, and other biologically active molecules [20, 11]. These salivary enzymes perform

local lysis and neutralization of pathogenic agents (e.g., lysozyme, lactoperoxidase, α-amylase, mucin) [2, 13, 15].

Another important protective component is the complement system proteins, which acquire immunological activity upon activation by other immune mechanisms [11, 10]. Additional humoral factors of non-specific defense in the oral cavity include circulating interferons, which enhance cellular resistance to viral infections and inhibit viral replication, and C-reactive protein, which activates both the complement cascade and immune effector cells (e.g., phagocytes) [42].

Non-Specific and Specific Defense Mechanisms of the Oral Cavity: Role of Local Immunity

Both humoral and cellular mechanisms contribute to the non-specific immune defense of the oral cavity, with key involvement from polymorphonuclear neutrophils and macrophages (monocytes) [6]. Among the non-specific protective factors, phagocytes play a central role. In clinically healthy gingiva, these cells can constitute over 60% of the total immune cell population. Macrophages are active participants in both innate and adaptive immunity [3, 13], due to their phagocytic abilities and the synthesis of biologically active substances with bactericidal properties (e.g., pro-inflammatory mediators, chemotactic factors such as interleukin-1, leukotrienes, reactive oxygen species, etc.).

Neutrophils initiate oxidative stress cascades that result in the presence of superoxide anions, hydroxyl radicals, and atomic oxygen in the saliva—leading to the destruction of pathogens engulfed by phagocytes. However, this oxidative response may also exacerbate local inflammation, due to the damaging effects of reactive oxygen species on the cell membranes of gingival and periodontal tissues [30, 33]. In addition, connective tissue cells of the oral mucosa, including fibroblasts and resident tissue macrophages, play an important role in maintaining mucosal immune defense [24].

The specific immune defense of the oral cavity is primarily mediated by humoral factors, including interleukins and immunoglobulins. A pivotal role in maintaining mucosal immunity is attributed to secretory immunoglobulin A (sIgA), which is produced by plasma cells located in the stroma of salivary glands and mucosal tissues. In healthy individuals, sIgA is the dominant immunoglobulin found in saliva—its concentration far exceeds that of IgG. For instance, in parotid saliva, the IgA/IgG ratio is 400 times higher than in blood serum [14, 27, 19].

Secretory IgA performs several key immune functions, including:

Inhibition of viral and bacterial adhesion to the epithelial surface;

Neutralization of viruses and prevention of oral viral infections, as well as clearance of neutralized viral particles;

Prevention of antigen and allergen absorption: sIgA forms immune complexes with foreign antigens and allergens, which are subsequently cleared by non-specific mechanisms (e.g., macrophages and the complement system);

Regulation of immune responses by enhancing the antibacterial activity of phagocytes;

Inhibition of dental caries development [3, 4, 27].

The effectiveness of sIgA in the oral cavity is influenced by the composition of the colonizing microbiota and the presence of antimicrobial substances in secretions, such as lactoferrin, lactoperoxidase, lysozyme, and others [17]. IgM and IgG are either produced locally by plasma cells or derived from the bloodstream. Through activation of the complement

cascade, these immunoglobulins increase vascular permeability (via complement factor C1), enhance chemotaxis of polymorphonuclear leukocytes, and facilitate phagocytosis of pathogens, thereby interacting with other immune effectors [4].

IgM is capable of neutralizing foreign particles, promoting agglutination and lysis of cells. Although it is generally considered less effective than IgG in antigen binding, it plays a vital role in stimulating the local lymphatic system [4, 12, 28,].

In conclusion, oral immunity is maintained by a balanced interplay of multiple defense factors, both specific and non-specific, ensuring protection against a wide range of pathogens and preserving mucosal homeostasis.

1.3. Preventive Dental Measures in Cancer Patients Before and During Treatment

The Multinational Association of Supportive Care in Cancer (MASCC), the International Society of Oral Oncology (ISOO), and the European Society for Medical Oncology (ESMO) [10, 8, 13] recommend that patients undergoing systemic cancer therapy undergo comprehensive oral evaluation prior to treatment initiation. Although data on the benefit of oral mucositis prevention are limited, intensive oral care protocols have shown to reduce the frequency of oral complications related to chemotherapy [4, 8, 17, 23].

A small randomized controlled trial involving 169 women with metastatic breast cancer receiving everolimus demonstrated the benefit of weekly professional oral care (tooth brushing, dental scaling, and tongue cleaning). In the intervention group, fewer patients developed grade ≥2 oral mucositis (34% vs. 54%), and fewer experienced dose reductions due to stomatitis (22% vs. 32%) [3]. However, most studies assessing the preventive effect of oral hygiene protocols suffer from significant methodological limitations. A 2019 systematic review by MASCC/ISOO concluded that there is currently no high-level evidence to recommend professional oral care specifically for mucositis prevention in patients receiving systemic anti-cancer therapy [100].

Nevertheless, expert panels agree that pre-treatment dental examination and management are advisable, aiming to reduce the risk of both local and systemic infections from odontogenic sources [3]. Oral hygiene protocols prior to therapy should include dental scaling, root planing, and caries management. In cases of advanced odontogenic pathology, tooth extraction may be necessary. Incidentally detected asymptomatic periapical radiolucencies generally do not warrant intervention before chemotherapy. Dental or endodontic therapy is recommended only for patients showing clinical or radiological signs of acute periapical infection [7].

A controlled trial of 166 oncology patients compared limited vs. intensive oral hygiene during high-dose therapy and hematopoietic stem cell transplantation (HSCT). The group receiving intensive oral care had statistically significant, although modest, reductions in the incidence (85% vs. 93%) and duration (17 vs. 19 days) of moderate-to-severe mucositis.

In a prospective controlled study involving 96 children (aged 1 to 16 years) with acute lymphoblastic leukemia, the effectiveness of a preventive oral care protocol was evaluated [12]. Compared to the control group, which received only treatment for oral complications and no prophylaxis, the preventive care group showed improved oral hygiene and reduced incidence of mucositis and oral candidiasis.

On the other hand, a retrospective review of 58 patients who underwent allogeneic or autologous hematopoietic cell transplantation (HCT) for various malignancies found no

significant differences in infection rates, mucositis, or post-transplant survival between the group that underwent intensive pre-transplant dental examination and treatment (n=36) and those who did not [129]. A prospective pilot study conducted at the University of Chicago evaluated 48 consecutive adults with hematologic or solid malignancies for periodontal health prior to chemotherapy. Patients with chronic dental disease did not undergo preemptive dental intervention. Among 21 patients with severe chronic periodontal disease, only two developed acute periodontal infections following chemotherapy, both managed successfully with antibiotics. No cases led to interruptions in chemotherapy or adversely affected oncologic outcomes. The authors concluded that patients with chronic dental conditions may safely proceed with chemotherapy without pre-treatment dental intervention, as acute exacerbations of chronic oral disease during chemotherapy are infrequent.

If oral infections occur, dental treatment is often feasible without interrupting oncologic therapy, except in patients receiving additional immunosuppressive therapy, where the risks are elevated. Prior to transplantation, all efforts should be made to address active dental issues. Chronic periodontitis, associated with significant microbial load in periodontal pockets, should be considered a potential infection source in patients with febrile neutropenia [17]. Although invasive manipulation of soft tissues prior to chemotherapy does not appear to worsen fever or bacteremia outcomes, such procedures should be avoided during neutropenic periods.

Patients with advanced periodontal disease, non-restorable or necrotic teeth, teeth with untreatable periapical infections, or partially erupted third molars should undergo tooth extraction prior to oncologic treatment [13]. Tooth extractions can be performed safely before therapy with minimal risk of post-extraction complications [88], but current guidelines recommend completing extractions at least 10 days prior to chemotherapy, minimizing tissue trauma during surgery, and ensuring primary wound closure without using hemostatic agents. Platelet transfusion should be considered prior to extraction if platelet counts are below 50,000/μL [8].

Several strategies have been explored for the prevention or reduction of chemotherapy-induced mucositis [15]. Although evidence quality from randomized trials remains limited [17], updated evidence-based clinical practice guidelines developed by MASCC/ISOO support the use of oral cryotherapy, palifermin, and photobiomodulation in selected clinical settings [8]. For patients developing grade ≥3 mucositis during fluorouracil- or doxorubicin-based chemotherapy, dose reduction in subsequent cycles is preferred over prophylactic intravenous palifermin administration. The U.S. Food and Drug Administration (FDA) has approved palifermin to reduce the incidence and severity of severe oral mucositis in patients with hematologic malignancies receiving myelotoxic therapy supported by autologous hematopoietic stem cell transplantation, particularly when the conditioning regimen is expected to cause grade ≥3 mucositis in the majority of patients.

For patients receiving bolus chemotherapy containing fluorouracil [15, 18, , 26, 28] and high-dose melphalan-based regimens used as conditioning for autologous hematopoietic cell transplantation (HCT) [5, 15, 20, 24, , 25, 27], oral cryotherapy is commonly recommended. Most patients achieve mucosal cooling by placing ice chips in the oral cavity during chemotherapy administration. This method is cost-effective and clinically validated. An alternative approach is the use of a more complex and expensive intraoral cooling system, Cooral [16].

The use of photobiomodulation therapy (PBMT)—low-level laser therapy—to prevent oral mucositis in patients undergoing high-dose chemotherapy with HCT has demonstrated efficacy and is recommended in updated MASCC/ISOO guidelines. However, in most countries, PBMT remains underutilized in clinical practice due to the high cost of equipment and the need for operator training, limiting its use to specialized centers.

Several controlled studies have shown that pre-treatment with helium–neon laser (He-Ne laser), a form of low-intensity laser irradiation, reduces the severity of mucositis in patients undergoing myeloablative chemotherapy [17]. In one study, 38 oncology patients were randomized to either PBMT or a control group [5]. A significantly higher proportion of patients in the PBMT group developed mucositis of grade ≥2 (95% vs. 32%), and fewer developed large ulcerative lesions (≥9.1–18 cm^2) (5% vs. 32%). In another study, 70 patients received laser therapy to the oral mucosa and tongue surfaces using two different lasers (visible red at 650 nm and infrared at 780 nm) or placebo [14]. The 650 nm wavelength was associated with significantly lower mucositis severity and reduced pain intensity. PBMT was well tolerated, with no reported adverse events. Current consensus guidelines from MASCC/ISOO and ESMO recommend PBMT to reduce the incidence of oral mucositis in patients undergoing conditioning regimens for HCT and in head and neck cancer patients receiving radiotherapy, with or without chemotherapy [83, 136, 174]. Due to the infrastructure and training requirements, its clinical use remains limited.

Thus, current medical evidence clearly supports a relationship between dental pathology and various neoplasms, as well as the negative impact of anticancer therapies on oro-dental health. In light of the above, timely diagnosis and prevention of periodontal diseases in cancer patients—particularly considering the influence of regional climatic and social factors—remains a pressing issue. Although international dental society guidelines have proven effective in reducing the incidence of mucositis in oncology patients, the implementation of dental screening focusing on periodontal involvement is still insufficiently explored.

Conflict of interest

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

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