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Open Access Journal of Dental Sciences
ISSN: 2573-8771

Effect of Radiotherapy on the Susceptibility and Progression of Periodontal Disease

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Research Article

Volume 11 Issue 3

Received Date: July 31, 2026

Published Date: August 19, 2026

DOI: 10.23880/oajds-16000424

Abstract

Introduction: Cancer represents a growing global health problem, and radiotherapy is one of the most widely used treatment options. Its main objective is the elimination of malignant cells through the use of ionizing radiation; however, it is also associated with side effects. Among these, there is evidence suggesting a possible relationship between the use of radiotherapy and the onset or exacerbation of periodontal disease, which is considered the eleventh most prevalent chronic non-communicable disease worldwide.

Objective: To evaluate the best available published evidence regarding the effect of radiotherapy on the susceptibility to and progression of periodontal disease.

Methods: An electronic search was performed in the PubMed database using the following search strategy: (((radiotherapy) AND (periodont* OR periodontitis)) AND cancer) NOT chemotherapy. A manual search was also conducted in the same database.

Results: Based on the search strategy and manual search, a total of 26 articles were selected that addressed a possible relationship between periodontal deterioration and radiotherapy in patients receiving treatment. This deterioration is characterized by an increase in proinflammatory cytokines, matrix metalloproteinases, and clinical attachment loss.

Discussion: Studies suggest a possible positive correlation between radiotherapy and the worsening of periodontal condition in affected patients; however, the available evidence remains limited in terms of sample size, longitudinal design, and the establishment of causality.

Conclusions: The available evidence suggests that radiotherapy may promote the onset or progression of periodontal disease by altering the immunoinflammatory homeostasis of patients undergoing this treatment.

Keywords: Radiotherapy; Cancer; Periodontal Disease; Periodontitis; Inflammation; Cytokines; Matrix Metalloproteinases; Clinical Attachment Loss

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Introduction

Cancer is a broad term that encompasses a group of diseases that can affect any part of the body. It is characterized by the rapid proliferation of abnormal cells that can invade surrounding tissues and spread to distant organs. Cancer is a prevalent disease, affecting more than 22 million people worldwide each year [1]. Various treatment modalities are available for the management of these neoplastic conditions, including surgery, chemotherapy, radiation therapy, immunotherapy, and transplantation, among others. Among these, radiation therapy is one of the most commonly used approaches.

Radiation therapy uses ionizing radiation to manage and treat cancer and, in some cases, certain benign conditions. It aims to deliver high doses of radiation to eliminate abnormal or malignant cells through external beam radiation or brachytherapy by inducing DNA damage and disrupting cellular function, ultimately leading to cell death [2]. It has been reported that radiation therapy exerts immunosuppressive effects, as it can reduce the number of circulating T lymphocytes and affect the precursors of monocytes, granulocytes, and natural killer (NK) cells. Following irradiation, cells may release immunosuppressive or immunostimulatory factors, thereby modulating the host immune response, which may become impaired [3].

Advances in technology have enabled the development of more precise treatment modalities that minimize the irradiation of healthy tissues. However, ionizing radiation may still produce systemic effects through the activation of molecular signaling pathways [4]. Therefore, radiation therapy could have undesirable effects in patients with chronic diseases, such as periodontitis.

According to the Global Burden of Disease study, periodontal diseases are the eleventh most prevalent noncommunicable diseases (NCDs) worldwide [5]. Periodontitis is defined as a disease associated with microbiological aggression and mediated by the host immune response, leading to the loss of clinical attachment level of periodontal tissues and, ultimately, tooth loss.

Some authors have suggested that radiotherapy may exacerbate pre-existing periodontal disease. Therefore, the objective of this literature review is to evaluate the best available evidence regarding the effect of radiotherapy on the susceptibility to and/or progression of periodontal disease.

Methods

A search strategy was conducted in the PubMed database using the following terms: (((radiotherapy) AND (periodont* OR periodontitis)) AND cancer) NOT chemotherapy. This search yielded 297 articles, of which 91 were excluded due to publication dates prior to 2005. Subsequently, after screening titles and abstracts, 195 articles were excluded, as most focused on complications such as osteoradionecrosis, which are beyond the scope of this review. A total of 11 articles met the inclusion criteria, comprising four literature reviews, three pilot studies, three observational studies, and one case report. Additionally, a manual search was performed, identifying 15 further relevant articles. The article selection process is presented in Figure 1.

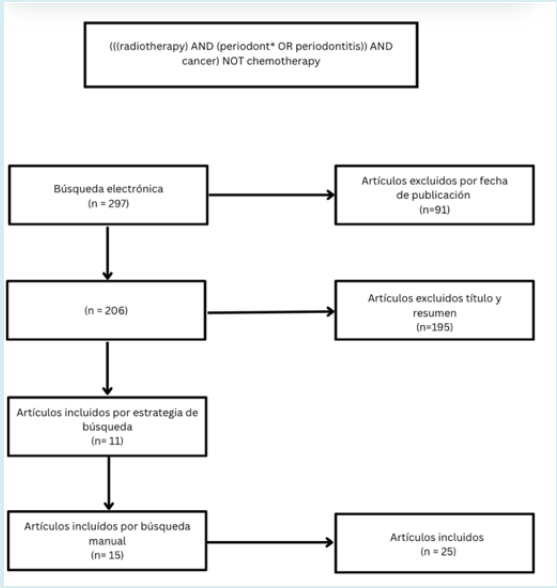


Figure 1: Flowchart.

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Generalities of Radiotherapy

Radiation therapy, as previously mentioned, is a medical branch that uses ionizing radiation for therapeutic purposes. This treatment modality has been in use since the late 19th century, following the discovery of X-rays. The principles of radiation therapy are based on the increased sensitivity of rapidly proliferating cells, such as cancer cells, to ionizing radiation, which deposits energy within tissues, inducing DNA damage and disrupting molecular bonds, thereby impairing cellular replication. However, radiation therapy does not selectively target malignant cells; both healthy and cancerous cells may be affected. The required doses to induce damage are similar for both cell types, but normal cells generally have a greater capacity for DNA repair and recovery following radiation exposure [6]. Therefore, the effectiveness of radiation therapy relies on delivering an optimal dose to achieve tumor control while minimizing damage to surrounding healthy tissues. This balance is known as the therapeutic index [6].

Currently, several radiotherapy modalities are available (Figure 2), among which external beam radiotherapy (EBRT) is the most widely used, accounting for approximately 90% of radiation treatments. This modality employs electromagnetic or particulate radiation generated by linear accelerators or radioisotopes. Depending on the energy of the radiation, EBRT can be classified into kilovoltage and megavoltage therapy [6].

Kilovoltage therapy was the earliest modality, delivering energies of up to 200 kV, and was primarily used to treat superficial skin tumors. In contrast, megavoltage therapy began to develop in 1932; later, isocentric cobalt units were developed in 1950. Cobalt-60, a radioactive isotope, emits gamma rays as it undergoes radioactive decay, which are used for therapeutic purposes [6].

Subsequently, in 1956, the first linear accelerator was introduced. This device generates electrons that are injected using radiofrequency waves produced by a magnetron, reaching high velocities and producing either X-ray photons or electron beams. Linear accelerators have largely replaced cobalt units due to their ability to precisely modulate radiation doses, perform multiple treatment functions, and integrate with advanced technologies such as computerized treatment planning systems, simulators, computed tomography (CT), magnetic resonance imaging (MRI), and other imaging modalities [6].

The biological effectiveness of radiation depends on energy transfer, total dose, and the radiosensitivity of the target cells or tissues. Although radiation is directed toward the tumor intended for elimination, inevitably, surrounding non-involved tissues are also affected due to the energy deposited in the irradiated area [7].

Brachytherapy represents another important treatment modality. The term was first introduced by Dr. Frosell in 1931. It involves the placement of encapsulated radioactive sources to deliver gamma or beta radiation directly to the tumor site, either superficially, intracavitarily, or interstitially. Radioisotopes enclosed in biocompatible materials, such as stainless steel or platinum, are used and can be delivered in the form of needles, wires, or seeds. Commonly used isotopes include radium, cesium, iridium, and iodine. This modality offers several advantages, including the delivery of high radiation doses directly to the tumor with reduced exposure time and limited irradiation of surrounding tissues. However, its use is restricted to specific clinical indications and anatomically accessible sites. Brachytherapy can be classified into different types. Interstitial brachytherapy involves the placement of radioactive sources directly within the tumor tissue, typically through a surgical procedure, and is commonly used for tumors of the tongue or oral mucosa. Surface mold brachytherapy consists of positioning radioactive isotopes within a customized applicator or mold, which is placed over the patient's skin or mucosal surface; this technique is particularly suitable for superficial lesions, such as those affecting the hard palate or skin. Finally, intracavitary brachytherapy involves placing radioactive sources within a body cavity, such as in the treatment of nasopharyngeal, cervical, or esophageal cancers [6].

Finally, radioactive isotope therapy or targeted radionuclide therapy is similar to brachytherapy, with the main difference being that, in this type of treatment, the radioactive material is administered orally or intravenously [6].

Figure 2 Overview of the different types of radiotherapy: (A) external beam radiotherapy; (B1–B3) internal radiotherapy modalities, including (B1) schematic representation of a patient with thyroid cancer treated with radioactive iodine, (B2) placement of radioactive sources near or within tumors (breast, skin, gynecological, and prostate cancers), and (B3) delivery of radioactive seeds to liver and lung tumors via catheter [8].

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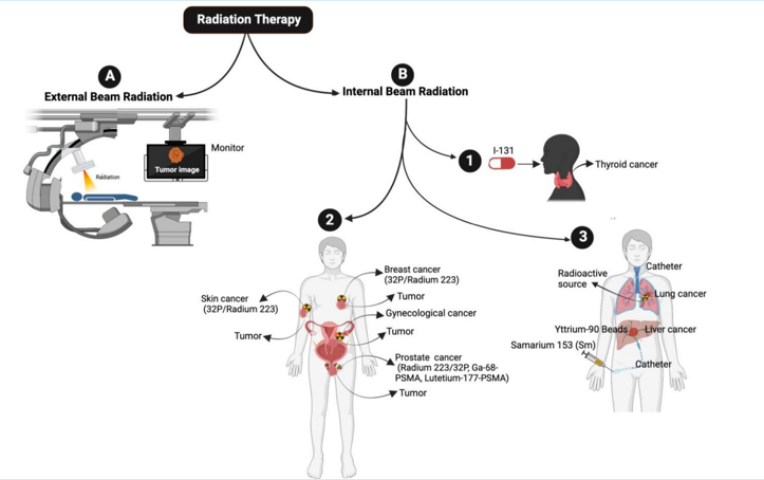


Figure 2: Overview of Different Types of Radiation Therapy: (A) The diagram depicts external beam radiation therapy. (B 1–3) The cartoon presents different models of internal beam radiation therapy: (B 1) Schematics show a thyroid patient being treated with radioactive iodine-131 medication. (B 2) Indicated radioactive capsules are embedded near or inside the tumor in breast, skin, gynecological and prostate cancer. (B 3) Cartoon shows the delivery of indicated radioactive beads/seeds in liver and lung cancers via a catheter.

Effect of Radiotherapy on the Immune System

The effects of radiation on biological tissues occur through the absorption of energy from X-rays and gamma rays, as well as through the ionization of atoms and molecules, initiating a cascade of events that ultimately results in biological damage. DNA is the primary target of radiation, and its lethal effects on cells are mainly due to direct damage to this critical structure. However, radiation can also exert indirect effects through interactions with other molecules or atoms, leading to the generation of free radicals. These reactive species can induce chemical reactions, ultimately resulting in cell death [4].

Radiotherapy may also induce a form of tumor-specific immunity, enabling the immune system to target both the primary tumor and metastatic lesions. This concept, described by Galluzzi, et al. [9] explains how irradiation of a primary tumor can trigger an immune response. Tumor-associated antigens are released and captured by dendritic cells, which subsequently activate T lymphocytes capable of inhibiting metastatic spread [9]. These findings suggest that radiotherapy can generate systemic effects beyond the irradiated field, representing a potential complementary therapeutic mechanism. However, despite being a localized treatment, radiotherapy inevitably exposes surrounding tissues to radiation, inducing cellular stress and systemic effects mediated by molecular and microenvironmental signaling pathways [9].

Following exposure to ionizing radiation, cells may undergo three main types of cell death. The first is apoptosis, also known as programmed cell death, which is characterized by cell shrinkage, chromatin condensation, nuclear fragmentation, membrane blebbing, and the formation of apoptotic bodies. This is one of the most relevant forms of radiation-induced cell death and involves the activation of caspase-dependent pathways [4].

Another mechanism is autophagic cell death, which should be clearly distinguished from autophagy. Autophagy is a cellular regulatory process in which the cell uses lysosomes to remove damaged components and maintain homeostasis. In contrast, autophagic cell death occurs when this process becomes dysregulated and excessive [4].

Finally, cells may undergo necrosis or necroptosis. Necrosis is characterized by cellular and organelle swelling, loss of membrane integrity, and eventual cell lysis with the release of intracellular contents. Necroptosis, on the other hand, is a regulated form of necrosis [4].

Radiation dose has been associated with distinct biological effects. Low doses of less than 0.5 Gy (the unit of measurement for the absorbed dose of ionizing radiation) are generally considered to have a limited impact on inducing cell death. At these levels, irradiated cells release oxygen and nitrogen free radicals, which can play a role in activating the innate immune system and initiating the cascade of defense responses, including the release of macrophages and cytokines [9]. However, it has been reported that these doses may also induce cell death through apoptosis [4]. When these molecules are released, genetic and environmental conditions play an important role, because depending on

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these conditions, a chronic inflammatory process can be generated, which may result in genetic alterations leading to cell damage. When radiation doses are higher or sufficiently strong, they can induce cell death through necrosis and trigger alarm signals detected by the innate immune system, leading to the activation of the adaptive immune system [4,9].

Therefore, the immunomodulatory effects of radiation depend on the radiation dose, the signals generated by both irradiated and non-irradiated cells, and the activation of innate immune pathways [9].

Through in vivo experiments, it has been shown that immune system cells can be activated by radiation, producing pro-inflammatory mediators in response to radiation-induced genomic destabilization. Radiation generates signals that trigger inflammatory processes, and the host response depends on the individual's immune competence. The outcome of this inflammatory response may be either beneficial or detrimental, depending on the patient's condition [9], as observed in individuals with periodontitis.

As previously described, the effects of radiotherapy extend beyond the irradiated tumor to its surrounding microenvironment. Lymphocytes are the most radiosensitive cells, followed by monocytes, macrophages, and antigen-presenting cells. Radiation-induced cell death leads to the release of proinflammatory cytokines, tumor antigens, and other danger signals, which can stimulate both innate and adaptive immune responses outside the irradiated field; this effect is known as the abscopal effect [4].

This response is primarily mediated by T lymphocytes. Following cell death, damage-associated molecular patterns (DAMPs) are released, including reactive oxygen and nitrogen species, TNF-α, TGF-β, and heat shock proteins, among others. These molecules activate Toll-like receptors on dendritic cells and promote antigen presentation. However, radiation also exerts immunosuppressive effects, such as the inactivation of natural killer (NK) cells and alterations in macrophage phenotype [4], leading to a process known as sterile inflammation [8].

Immunopathogenesis of Periodontal Disease

Since 1997, Page and Kornman described periodontal disease as the result of an interaction between microorganisms, the biofilm, and the host response. However, it is now recognized that although a microbial challenge is necessary, it is not sufficient to cause the disease [10]. Initially, periodontal disease presents as gingivitis, which is clinically characterized by gingival inflammation, bleeding, and, in some cases, pain. If this early stage is not adequately treated, it may progress to periodontitis. While periodontitis shares clinical features with gingivitis, it represents a more advanced condition characterized by irreversible loss of clinical attachment and alveolar bone, potentially leading to tooth loss [11]. The prevalence of periodontal disease in Latin America has not been extensively reported; however, in Colombia, gingivitis has been reported in up to 99.6% of the population, and periodontitis in 61.8% of adults [12]. Periodontal disease may exhibit periods of exacerbation and, although it is primarily a localized condition affecting the oral cavity, it can contribute to systemic inflammation [13]. Ultimately, microbial challenge, together with a dysregulated host response, is responsible for the onset and progression of periodontal disease [14].

The periodontium is constantly exposed to different physical and chemical stimuli generated by mastication and respiration; therefore, there is a fine line of balance between the patient's immune response and their microbiome in healthy conditions [15].

When a pathogen enters the body, the innate immune response acts as the host's first line of defense, limiting its invasion. If the innate immune system is insufficient to control the pathogen, the adaptive immune response is subsequently activated. Once engaged, the adaptive immune system generates immunological memory, enabling a more efficient response upon subsequent exposures to the same microorganism. However, if this response is also unable to eliminate the pathogen, a chronic infection may develop. In the case of periodontitis, the accumulation of biofilm with a high presence of periodontopathogenic microorganisms triggers a cascade of immune responses characterized by the secretion of pro-inflammatory mediators. These not only defend the host against microbial aggression but also promote the destruction of periodontal tissues [16].

When a patient presents with dysbiosis, an altered inflammatory state occurs, which may vary between individuals. Several factors can contribute to host susceptibility, including demographic and environmental conditions, systemic diseases, and genetic polymorphisms [14].

The presence of microorganisms from the red complex described by Sigmund Socransky includes bacteria such as Porphyromonas gingivalis, Tannerella forsythia, and Treponema denticola. These bacteria exhibit lipopolysaccharide, which is described as an important virulence factor capable of stimulating macrophages and other inflammatory cells, leading to the production and secretion of proinflammatory mediators such as TNF-α, IL-1β, and PGE2 [17].

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As mentioned previously, the progression of periodontal disease requires the presence of various immune system cells, molecules, and inflammatory mediators [10]. The initial challenge arises from the interaction between an imbalanced microbiome and epithelial cells, gingival fibroblasts, and other immune cells. This interaction triggers the initial release of cytokines such as IL-1, IL-6, and TNF [15].

IL-1 is a family of cytokines first described approximately 40 years ago, comprising 11 molecules and 10 associated receptors, including IL-1α, IL-1β, IL-18, IL-33, IL-36, IL-37, and IL-38. This cytokine family is involved in both innate and adaptive immunity and has been associated with inflammatory and autoimmune responses, as well as systemic diseases such as cardiovascular conditions and cancer [15].

The presence of these molecules primarily activates polymorphonuclear neutrophils, which in turn express various receptors on their surface that recognize chemotactic signals. This subsequently triggers a signaling cascade that leads to different cellular events, responses [10], and differentiation processes [15]. It has been described in the literature that patients with periodontitis exhibit a delayed neutrophil response; their activity is not sufficiently effective in eliminating invading microorganisms, thereby increasing the risk of collateral tissue damage. Neutrophils not only secrete molecules that promote phagocytosis and the elimination of microorganisms, but they can also release enzymes that degrade host tissues, such as elastases and proteinases like collagenase, which break down collagen in the periodontal ligament fibers, thereby promoting disease progression [10].

However, neutrophils are not the only cells involved in the periodontal destruction process; in recent years, evidence has shown that NK cells, T cells, and B cells also play a significant role in tissue destruction [10, 18,19]. Lymphocytes are the main cells involved in the adaptive immune response; the primary function of B cells is antibody production. T cells, on the other hand, are divided into several subsets, including helper T cells, suppressor T cells, regulatory T cells, and cytotoxic T cells. The first two groups regulate the immune response by secreting cytokines, whereas cytotoxic T cells can attack and eliminate target cells through direct interactions [19]. IL-1 and IL-33 have similar structures, and the literature has shown that genetic polymorphisms in their receptors are associated with increased susceptibility to developing periodontitis. IL-1β induces the activation and expansion of Th1 and Th2 cells, while IL-1α activates Th17 cells [15].

Another widely studied biomarker in relation to periodontal disease is IL-6. It is a pro-inflammatory cytokine that can be secreted by various cell types, including immune cells, fibroblasts, keratinocytes, and adipocytes. This molecule plays a role in inflammation and in the host response to various infections and is linked to the pathogenesis of periodontal disease through its interaction with other molecular mediators of tissue destruction. It can regulate bone homeostasis through anti-osteogenic and pro-osteoclastic effects, ultimately affecting bone formation [20]. The IL-6 family comprises 10 identified molecules and their receptors and is associated with chronic inflammation, plasma cell development, and immunoglobulin production, as well as the induction of Th17 differentiation; therefore, this cytokine family is linked to the amplification of the immune response [15].

TNF was discovered in 1975 and isolated in 1980. It has the ability to induce cell death and plays a fundamental role in the pro-inflammatory response and cell communication. It has also been described as participating in bone metabolism by inducing the expression of RANK (receptor activator of nuclear factor kappa B) in pre-osteoclasts and RANKL in osteoblasts [15]. The presence of this ligand activates RANK on osteoclasts, leading to their maturation and enabling them to become functional and initiate the process of alveolar bone resorption [17].

Periodontal disease arises as a result of the complex interaction between microbiome dysbiosis and an unbalanced host immune response, which, while attempting to control the infection, ultimately leads to tissue destruction.

Effect of Radiotherapy on Periodontal Tissues

In addition to its antitumor role, radiotherapy can have direct effects on the host's systemic immune response, potentially affecting defense mechanisms and leading to periodontal compromise. The neutrophil-to-lymphocyte ratio has been described as an important subclinical marker for detecting inflammation. Furthermore, the production of matrix metalloproteinase-8 (MMP-8), generated by neutrophils and acting as a collagenase, has been highlighted. This molecule plays a fundamental role in the destruction of periodontal tissues following bacterial invasion, thereby promoting an inflammatory state, destructive mechanisms, the generation of reactive oxygen species, and the release of enzymes that contribute to periodontal breakdown. It has also been described that one of the systemic effects of radiotherapy is the direct impairment of lymphocytes and neutrophils [21]. MMP-8 is secreted as an inactive proenzyme, and its activation can be triggered by other MMPs, microbial proteases, or tumor-associated trypsins [20].

In 2023, Brandt, et al. conducted a pilot study to analyze the immediate effects of head and neck radiotherapy on

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blood neutrophil levels, the neutrophil-to-lymphocyte ratio, and salivary MMP-8 levels in patients with signs of periodontal damage. They found that three weeks after the start of radiotherapy, there were no statistically significant changes in neutrophil counts. However, statistically significant differences were observed in the neutrophil-to-lymphocyte ratio. The ratio before radiotherapy was reported to be 2.92 (SD = 1.16), and three weeks after the start of treatment, it increased to 5.46 (SD = 2.49), indicating systemic inflammation. A statistically significant increase in oral MMP-8 levels was also observed. At baseline, levels were 20.1 ng/mL, and three weeks after the start of treatment, they reached 59.4 ng/mL. These findings may indicate local damage in the oral cavity of patients undergoing active radiotherapy for head and neck cancer. The authors suggest that the increase in MMP-8 levels may be explained by the potential of radiotherapy to induce neutrophil degranulation, leading to the secretion of this enzyme and subsequent tissue destruction [21].

It is important to note that some undesirable effects of radiotherapy, such as xerostomia, physical changes, and emotional changes, may not have manifested during the three-week study period. However, the possibility that these adverse effects could also contribute to periodontal damage should not be ruled out [21].

This same group of researchers conducted a cohort study to evaluate the molecular levels of MMP-8, MMP-9, tissue inhibitors of metalloproteinases (TIMPs), and IL-6. They evaluated 21 patients diagnosed with head and neck cancer whose treatment plan included radiotherapy; patients with a history of immune disorders were excluded [22]. The levels of the molecules under study were measured using an ELISA test, and a complete periodontal examination was performed to assess different clinical parameters. Clinical attachment level showed the most significant changes, with patients reportedly losing an average of 1.4 mm of clinical attachment during the study observation period, indicating rapid disease progression. MMP-8 was identified as the biomarker that showed the greatest change in the study, with levels similar to those reported in the 2023 study. MMP-9 levels were also observed to increase during the course of treatment; however, these changes were not statistically significant [22].

Keskin et al. in 2021 conducted a pilot study to evaluate the feasibility of using MMP-8 and IL-6 as biomarkers of periodontal deterioration following radiotherapy in patients with head and neck cancer. Salivary levels of these biomarkers were analyzed alongside periodontal parameters, including clinical attachment level, probing depth, tooth mobility, and furcation involvement. Clinical attachment level again showed the most significant changes, with patients losing an average of 1.7 mm between the start and end of treatment. Both IL-6 and MMP-8 levels increased during the first six weeks of radiotherapy and did not return to baseline values, suggesting persistent inflammatory activity after treatment. MMP-8 levels rose from 17.99 ng/mL at baseline to 75.12 ng/mL at six weeks, decreasing to 38.00 ng/mL one-month post-treatment, while IL-6 levels increased from 19.94 pg/mL to 133.73 pg/mL and subsequently decreased to 32.27 pg/mL. However, only the changes in MMP-8 reached statistical significance. These findings suggest a positive association between radiotherapy and periodontal tissue destruction [20].

Keskin et al., again in 2021, presented an observational study that aimed to determine whether salivary calprotectin and lactoferrin levels could serve as indicators of periodontitis progression in irradiated patients. Lactoferrin is a glycoprotein that binds iron and is present in various body fluids, such as breast milk, tears, and saliva; it has been described as having antimicrobial, anti-inflammatory, and anticancer properties. Calprotectin, on the other hand, is a calcium-binding protein found in the cytoplasm of neutrophils, keratinocytes, and macrophages; it is activated by neutrophil degranulation or by monocyte adhesion to the vascular endothelium. Both proteins have been described as playing an important role in tissue modulation. Calprotectin promotes neutrophil chemotaxis and function and has the capacity to protect periodontal tissue from Porphyromonas gingivalis invasion. Lactoferrin also plays a role in the inflammatory response, and its absence has been associated with hyposalivation. Elevated levels of these proteins in crevicular fluid have been associated with worsening periodontal status and increased levels of inflammatory biomarkers of periodontitis [23].

Twenty patients with head and neck cancer scheduled to receive radiotherapy were included in the study. Periodontal parameters were analyzed, and samples were collected before radiotherapy, at the third and sixth weeks of treatment, and four weeks after its completion. Lactoferrin levels at baseline were approximately 8.00 ng/mL. By week 3 of treatment, they had increased to approximately 13.00 ng/mL, by week 6 to approximately 15.00 ng/mL, and one month after completion, they returned to approximately baseline values. Statistically significant differences were observed between the values at week 6 of treatment and one month after completion, showing an upward trend, although this trend did not reach statistical significance throughout the entire radiotherapy period. Regarding calprotectin, levels were approximately 1.5 ng/mL at baseline, 2.2 ng/mL at week 3, 2.5 ng/mL at week 6, and 1.2 ng/mL after treatment completion; all changes were statistically significant. These findings suggest that radiotherapy induces a transient pro-inflammatory environment in the oral cavity, with the potential to increase the onset or progression of periodontal

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disease [23].

In 2004, Marques, et al. [24] aimed to analyze the effects of radiotherapy on periodontal parameters in patients with head and neck cancer before treatment and at six- and eight-months post-treatment. All patients received external beam radiotherapy to the head and neck region where the tumor was located. Clinical probing depth, clinical attachment level, and gingival recession were recorded. They found that 70.3% of patients presented with attachment loss during the observation period, and 85.2% exhibited gingival recession with root exposure. These findings suggest that radiotherapy may contribute to progressive attachment loss, although this relationship appears to be influenced by the anatomical structures exposed to radiation.

That same year, the authors also reported that periodontitis may be considered a late complication of radiotherapy, due to changes in the oral microbiome, as well as hypoxia and hypovascularization of periodontal tissues following treatment. This suggests that patients with pre-existing periodontitis may experience a worsening of their condition during therapy. Irradiated periodontal tissues exhibit a reduced capacity for repair and are more prone to infection [25].

Discussion

As has been shown throughout this review, radiotherapy is a necessary therapeutic tool for the management of neoplastic and cancerous processes. Although it is one of the most widely used approaches for the treatment of these diseases, it has the potential to induce local and systemic side effects, as demonstrated in the case of the periodontium.

These effects derived from radiotherapy appear to be mediated by immunoinflammatory mechanisms that promote periodontal dysbiosis, thereby favoring the onset or progression of destructive processes in patients undergoing ionizing radiation therapy.

Several studies presented in this publication agree that radiotherapy has a direct effect on key components of the immune system, such as neutrophils, lymphocytes, and interleukins. This imbalance leads to an exacerbated immune response, reflected in an increased neutrophil-to-lymphocyte ratio, overexpression of enzymes such as MMP-8 and MMP-9, and increased secretion of IL-6, lactoferrin, and calprotectin.

Enzymes such as MMP-8 and MMP-9 have been identified as biomarkers associated with active periodontal damage. It has been suggested that radiation can induce neutrophil degranulation, and through this mechanism, these collagenolytic enzymes are released, contributing to the degradation of tooth-supporting tissues. In 2023 and 2024, Brandt et al. demonstrated elevated salivary concentrations of these biomarkers in patients with head and neck cancer treated with radiotherapy, suggesting a possible correlation between the treatment and the increased expression of these enzymes.

In addition, other publications have reported increases in the salivary concentration of molecules such as IL-6, calprotectin, and lactoferrin during radiotherapy, which may help to support the hypothesis that radiotherapy generates a transient inflammatory environment in the oral cavity.

Apart from the molecular changes observed in saliva during radiotherapy, Marques et al. reported that more than 70% of patients undergoing this treatment presented clinical attachment loss and more than 85% exhibited gingival recession, thus demonstrating a worsening of the oral clinical condition of cancer patients receiving radiation.

Despite the published evidence, it should be noted that it is not sufficient to establish radiotherapy as a risk factor for the onset or progression of periodontal disease; further longitudinal and cohort studies with larger sample sizes are needed to demonstrate a direct causal relationship between radiation therapy and the deterioration of the periodontal clinical condition in patients undergoing treatment.

Conclusions

In summary, the available evidence considered in this review supports the hypothesis that radiotherapy may contribute to the onset or progression of periodontal disease. Although it is a fundamental treatment due to its antitumor effects, it alters the body's immunoinflammatory homeostasis, which may result in various conditions exacerbated by this imbalance, such as periodontal disease. It is essential to explore preventive and multidisciplinary management strategies to minimize the impact of radiotherapy on periodontal tissues and thereby preserve the periodontal health of cancer patients.

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