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An Overview of How HNCs Radiotherapy Affects Oral Microbiota: Shifts, Complications, and Management Strategies

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Abstract

Introduction: Radiotherapy (RT) is a primary treatment for head and neck cancers (HNCs). However, it can lead to acute and chronic side effects that diminish patients' quality of life. RT-induced radiation can damage tissues and alter the oral microbiota. Multiple studies indicate that the oral microbiota significantly influences the development of these complications.

Methods: This research aims to examine how radiotherapy affects the oral microbiota thoroughly, explore the link between these changes and clinical issues, and evaluate strategies for prevention and management.

Results: RT damages salivary glands and the oral mucosa, leading to xerostomia (dry mouth) and oral mucositis. These physical and chemical changes alter the oral environment, resulting in dysbiosis. This dysbiosis is characterized by reduced microbial diversity and an increase in pathogenic species, including cariogenic bacteria like Streptococcus mutans and Lactobacillus, as well as inflammatory bacteria such as Prevotella, Fusobacterium, and Candida albicans. The review suggests that this dysbiotic profile may significantly contribute to the worsening of oral mucositis (through inflammatory and LPS-dependent pathways), promote radiation-induced caries (due to increased xerostomia and acidogenic bacteria), elevate the risk of oropharyngeal candidiasis, and play a role in osteoradionecrosis development.

Conclusion: The findings indicate that the oral microbiota is not just a secondary factor in RT-induced damage but plays an active role in worsening RT-related side effects. Gaining a precise understanding of the oral microbiota as a potential therapeutic target is crucial, and incorporating oral microbiology into oncology protocols can greatly enhance patients' quality of life and pave the way for new approaches in cancer supportive care.

Keywords: Radiotherapy, Oral microbiota, Management strategies, Complications

Introduction

Head and neck cancers (HNCs) rank as the sixth most common cancer worldwide, with approximately 490,000 new cases and 450,000 deaths each year.[1] The primary treatment approach includes surgery, chemotherapy, and, notably, radiotherapy (RT).[2] RT employs ionizing radiation to damage DNA and induce apoptosis in rapidly dividing cells, helping to control the local and regional tumor[1,2]. However, because these rays are non-selective, they can also harm healthy tissues such as the oral mucosa, saliva glands, and bone structures.[2] This damage can lead to acute and chronic complications, adversely affecting patients' quality of life [3] and potentially worsening disease prognosis.[4] Critical complications include oral mucositis, dry mouth, dysphagia, and osteoradionecrosis.[5] One of the direct effects of radiation therapy is induction of dysbiosis, an imbalance in the microbial community, in the microbiome, specifically oral microbiota.

Microbiota are composed of trillions of microorganisms that are vital for metabolism, the immune system, and physiology.[6] The oral cavity, the entry point to the digestive and respiratory systems, hosts one of the

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body's most intricate microbial communities, the oral microbiota.[2] This microbiota comprises about 700 bacterial species, fungi, and viruses.[2] These microbes are crucial for colonizing pathogens, regulating systemic and innate immune responses, and metabolizing external compounds.[3,4] Oral microbiome dysbiosis can stimulate dental caries, periodontal disease, and systemic illnesses such as cardiovascular disease, diabetes, and certain cancers (Figure 1).[5]

Integrating radiation oncology and oral microbiology insights is crucial to better understanding how RT affects the pathophysiology of the oral ecosystem.[6] RT can directly harm the salivary glands,[6,7] leading to reduced saliva production, altered salivary composition, lower salivary pH, and diminished levels of antimicrobial proteins like lactoferrin, lysozyme, and secretory immunoglobulin A (sIgA)[7]. Additionally, RT can damage the oral epithelium, causing mucositis, which destroys the physical barrier and fosters microbial colonization.[7] These effects disturb the oral microbiota balance, resulting in significant dysbiosis.[8] A study using next-generation sequencing (NGS) showed that RT can alter the oral microbial community and diversity, decreasing beneficial bacteria and promoting the growth of opportunistic species such as Streptococcus mutans, Lactobacillus, and fungi like Candida albicans (Table 1).[9-11]

These microbial shifts can worsen complications caused by radiotherapy.[11] It has also been noted that microbial biofilm colonization in oral mucositis can heighten inflammatory responses and increase systemic disease risks.[12] Additionally, some research suggests that oral microbiota may influence osteoradionecrosis development by triggering chronic inflammation.[13] Based on current studies, our understanding of how oral microbiota changes during or after radiotherapy relate to disease severity and side effects remains limited, as does the development of targeted strategies to address this dysbiosis.[14,15] Existing management mainly aims to control symptoms and does not fully resolve these issues. Hence, this review offers a detailed and practical analysis of how radiotherapy affects oral microbiota, the links between dysbiosis and clinical complications, and potential management strategies. By synthesizing molecular, clinical, and ecological data, we aim to identify research gaps and outline future directions to improve treatment outcomes and life quality for head and neck cancer patients.

Oral microbiota in health and disease

The most common gram-positive bacteria in the oral cavity are streptococcal species, with Group A beta-hemolytic streptococcus being the most prevalent.[16] These bacteria can cause local infections like tonsillitis and systemic diseases such as meningitis, skin infections, and pulmonary issues.[17] Additionally, Streptococcus mutans contributes to dental caries by producing polysaccharides and acids and influencing plaque formation.[3] S. salivarius, an opportunistic pathogen, is abundant in saliva and can colonize the oral mucosa, producing extracellular polysaccharides and raising oral pH.[18] During procedures like tooth extraction, Streptococcus mutans can cause bacteremia and endocarditis.[19] Other bacteria, such as Streptococcus vestibularis, generate peroxide and urease, which increase the mouth pH.[20] Conversely, S. anginosus, found in the dental sulcus and gums, may protect against caries, as it does not produce polysaccharides; however, it can also migrate to organs and cause disease under certain conditions (Figure 1).[21]

Effects of radiotherapy on the oral ecosystem

Since RT is an invasive treatment for HNCs, it can alter the oral ecosystem, leading to changes in the microbial community, severe dysbiosis, and disease. Additionally, RT can heavily damage the acinar cells in the salivary glands.[22] The resulting cell damage and apoptosis cause atrophy of the glands and a dry mouth, creating an environment conducive to opportunistic microorganisms.[23] RT may also harm the stem cells of the basal layer of the oral mucosa epithelium, impairing its regenerative capacity, which can result in atrophy and oral mucositis ulcers.[24] These ulcers compromise the protective barrier against microbes and fungi, promoting rapid pathogen growth. Furthermore, damage to small blood vessels causes tissue hypoxia, hindering treatment efficacy.[25] This altered environment can upset the microbial balance, leading to dysbiosis, where pathogenic and opportunistic organisms thrive and cause disease (Table 2).

Table 1. Leading groups of bacteria associated with radiotherapy-induced dysbiosis

Microbial Group	Key Species	Pathogenic Role in RT Patients
Acidogenic and Cariogenic Bacteria	*Streptococcus mutans*, *Lactobacillus spp.*	They thrive in low pH, rapidly ferment sugars, and accelerate post-RT dental caries development.
Inflammatory Gram-Negative Bacteria	*Prevotella spp.*, *Fusobacterium spp.*, *Veillonella spp.*, *Porphyromonas spp.*	They produce LPS, activate TLR4/NF-κB pathways, exacerbate inflammation, and prolong mucositis.
Health-Associated Bacteria (Reduced)	*Neisseria spp.*, *Haemophilus spp.*, *Streptococcus sanguinis*	They maintain ecological balance and nitrate metabolism; reduction is linked to increased pathogen overgrowth
Fungi	*Candida albicans*	Opportunistic growth under reduced salivary flow and local immunity causes oral candidiasis.
Other Opportunists	Coagulase-positive *Staphylococcus aureus*, *Actinomyces spp.*	They are involved in osteoradionecrosis and secondary opportunistic infections.

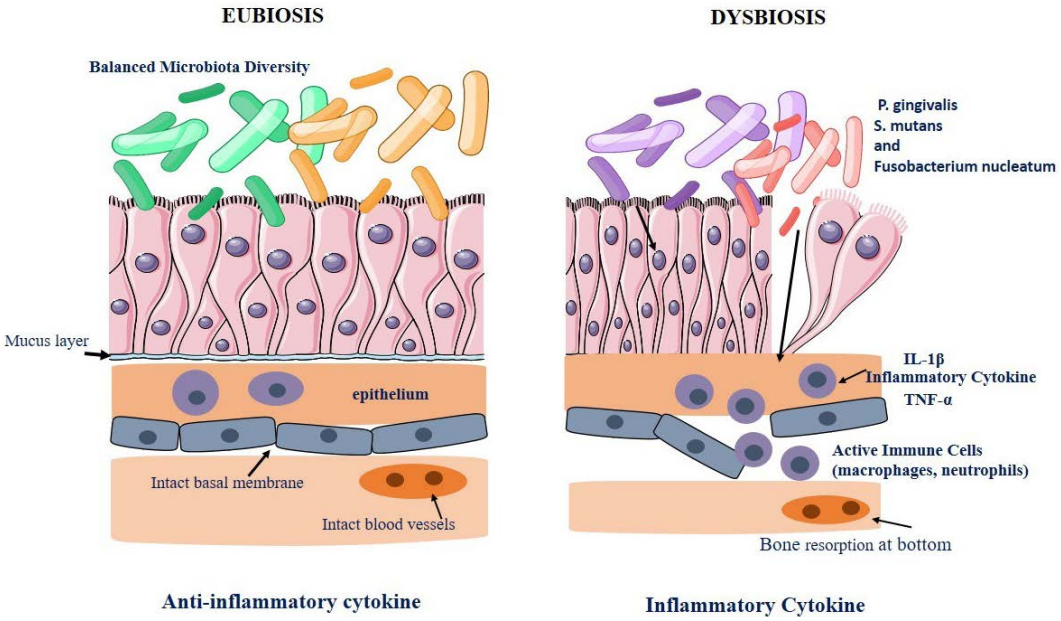

Figure 1. Comparison of oral microbiota in EUBIOSIS and DYSBIOSIS states; the image on the left schematically shows a healthy oral environment with high and beneficial microbial diversity, and the image on the right shows a decrease in the diversity of beneficial bacteria and the growth of pathogenic and inflammatory bacteria

Table 2. A review of the effects of RT on various functions of the oral ecosystem

Affected Component	Direct Effect of Radiotherapy	Clinical Outcome
Salivary glands	Acinar cell atrophy	Xerostomia (dry mouth)
Oral mucosa	Basal layer damage	Mucositis
Teeth	Demineralization	Dental caries
Jawbone	Reduced blood supply	Osteoradionecrosis
Saliva	Decreased secretion and composition change	Altered pH, increased infection risk

Changes in oral microbiota after radiotherapy

RT-induced changes in the oral ecosystem alter the structure and composition of oral microbiota. Studies using next-generation sequencing (NGS), particularly 16S rRNA gene sequencing, reveal a significant decrease in α-diversity within the oral microbial community, indicating ecosystem instability [26]. In this unstable state, the previously resilient simple microbial community becomes susceptible to disturbances, allowing pathogenic and opportunistic microorganisms to thrive (Table 3)[27].

These changes also shift the microbial community from facultative anaerobic Gram-positive bacteria to obligate anaerobic and pathogenic Gram-negative bacteria.[27] Notably, the abundance of health-associated bacteria like Neisseria, Haemophilus, and multiple Streptococcus species, including S. sanguinis, decreases.[27,33] Conversely, pathogenic bacteria such as acidogenic and cariogenic Streptococcus mutans and Lactobacillus species rise sharply, thriving in acidic environments caused by reduced saliva.[27] Additionally, bacteria linked to periodontal diseases, including Prevotella, Veillonella, Fusobacterium, and Porphyromonas, also increase and often grow after RT.[25] These bacteria further stimulate the host's inflammatory response by producing lipopolysaccharide (LPS) virulence factors, worsening oral mucositis. Some studies indicate that alterations in the oral microbiota promote the growth of Candida species like Candida albicans.[24] As an opportunistic fungus, C. albicans can cause oropharyngeal candidiasis in these patients by suppressing immunity. Ultimately, these changes create a dysbiotic microbial profile that can be a biomarker for RT-related damage.[34] Furthermore, such alterations may contribute to disease pathogenesis and elevate the risk of acute and chronic complications (Figure 2).

Clinical complications associated with radiotherapy-induced dysbiosis

RT-induced damage to oral tissues disrupts the oral ecological system. These disruptions promote the development and severity of both acute and chronic clinical complications.[35] Next, we will explore the key role of dysbiosis in four primary types of complications: mucositis, candidiasis, radiation-induced caries, and osteoradionecrosis.

1. Oral mucositis causes painful inflammation in the mouth and is one of the most debilitating acute side effects of radiotherapy.[36] Its underlying mechanism involves DNA damage and the creation

Table 3. Summary of key studies on changes in oral microbiota after radiotherapy (RT)

Main findings (which taxa ↑ / ↓)	Microbial analysis method	Study population & cancer type	Reference
Increased: Actinobacteria and Veillonellaceae are associated with delayed healing of mucositis; overall community composition differs in patients with severe delayed healing.	16S rRNA sequencing	64 patients with nasopharyngeal carcinoma (NPC) undergoing RT	28
Decreased: Porphyromonadaceae, Prevotellaceae; Increased: Lactobacillaceae (post-treatment). Microbial shifts correlated with treatment response and salivary DMBT1 changes.	16S rRNA sequencing	Patients with oral squamous cell carcinoma (SCC) treated with chemoradiotherapy (longitudinal saliva samples)	29
RT caused significant compositional changes: a reduction in some commensal Gram-negative taxa and a relative increase in Gram-positive commensals; overall, RT altered the oral community and was linked to changes in oral neutrophil markers.	16S rRNA sequencing+ mmune assays	68 head & neck tumour (HNT) patients receiving IMRT (pre-, mid-, post-RT samples)	30
Increase in ORN: Prevotellaceae, Fusobacteriaceae, Porphyromonadaceae, Actinomycetaceae, Staphylococcaceae; genera Prevotella and Staphylococcus enriched — suggests dysbiosis associated with ORN.	16S rRNA sequencing of tissue samples	30 high-dose RT head & neck cancer patients (ORN vs unaffected tissue)	31
RadInfection is associated with shifts in microbial composition and increases in cariogenic and opportunistic taxa in many patients (an association with post-RT caries development is noted).	16S rRNA sequencing / oral swabs	Head & neck cancer patients post-radiation (caries outcomes examined)	32

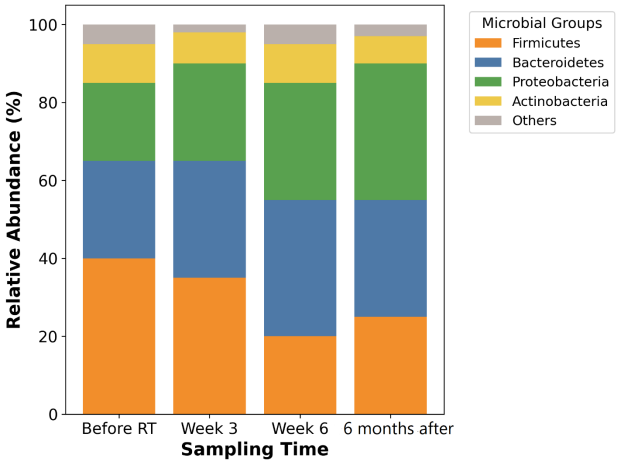

Figure 2. Schematic diagram of microbial changes before and after radiotherapy (RT)

of reactive oxygen species, leading to the death of basal epithelial cells and intense inflammation. Research indicates that oral mycobiota can worsen this inflammation.[37] During dysbiosis, the environment includes gram-negative bacteria like Prevotella and Fusobacterium, which can produce lipopolysaccharide (LPS). LPS interacts with Toll-like receptor 4 (TLR4) on macrophages and immune cells, triggering a strong inflammatory response via the NF-κB pathway.[30] This process releases proinflammatory cytokines, such as TNF-α and IL-1β, which further damage tissue, increase pain, and hinder wound healing. Multiple studies demonstrate that mucositis severity correlates with specific microbial loads, making the microbiota an active participant in the inflammatory cycle that influences how severe and prolonged mucositis becomes, rather than just a secondary factor.[38]

2. Oropharyngeal Candidiasis: Candida albicans normally exists as a harmless part of the body's microbiome, kept in check by the immune system and bacterial competition. Radiation therapy (RT) disrupts this balance, initially causing xerostomia and reducing antifungal proteins like histamines, creating a more favorable environment for C. albicans growth.[39] Subsequently, antibiotics used to treat secondary bacterial infections can also remove bacterial competitors, allowing the fungus to flourish.[40] Additionally, RT can suppress local immune responses, impairing the body's ability to combat Candida. The dysbiosis resulting from RT destroys beneficial bacteria that inhibit C. albicans, aggravating its proliferation. This leads to erythematous (red mucosa) or pseudomembranous (white cheesy patches) candidiasis, which causes pain and difficulty swallowing and generally worsens the disease burden.[41]

3. Radiation-Related Caries is characterized by its swift and aggressive progression. It results from alterations in the quantity and composition of oral microbiota. Xerostomia eliminates saliva's cleansing effect, leading to a prolonged acidic oral pH.[42] This environment favors acid-producing bacteria like Streptococcus mutans and Lactobacillus. These bacteria rapidly ferment dietary sugars, generating lactic acid that demineralizes tooth enamel and causes quick, extensive tooth decay.[43]

4. Osteoradionecrosis (ORN) is a severe, long-lasting condition involving avascular necrosis of the jawbone. Radiation harms small blood vessels, and microbial infections significantly worsen this damage.[43] Trauma, such as tooth extractions or mucosal wounds exposing the damaged bone to oral bacteria, can lead to bacterial growth. After radiotherapy (RT), bacteria often colonize this environment, which can invade the exposed bone and trigger chronic inflammation. This infection and ongoing inflammation speed up necrosis and hinder wound healing. While dysbiosis is not the leading cause of ORN, it plays a critical role in its development and progression.[44]

Treatment and management solutions

To address the complications of radiation therapy (RT), a comprehensive approach is necessary to alleviate symptoms and promote homeostasis within the oral ecosystem. These strategies are categorized into three groups: preventive, supportive-relief, and restorative.[45,46] The preventive approach, crucial before RT, involves a dental assessment to thoroughly remove plaque, decay, and periodontal issues.[41] Complete oral hygiene education is also vital, including brushing with a soft toothbrush, fluoride toothpaste, and alcohol-free mouthwashes to lower the microbial load.[47] During RT, supportive care aims to manage issues like oral mucositis and xerostomia; for mucositis, rinsing with gentle saline solutions and topical anesthetics for pain relief are used, and for dry mouth, saliva substitutes, stimulants like pilocarpine, saliva, and moisture therapies are used.[26,27] According to the 2020 MASCC/ISOO guidelines and ESMO recommendations, alcohol-containing mouthwashes should be avoided—favoring alcohol-free options, bicarbonates, and topical anesthetics for mucositis management.[33,47] While these do not directly alter oral microbiota, they improve the environment, preventing dysbiosis. Caution is advised with antimicrobial drugs to avoid resistance and disruption of the balance. Emerging approaches, such as probiotics with beneficial bacteria like Lactobacillus and Bifidobacterium, show promise for maintaining microbial harmony.[48] Early studies suggest that they control pathogens, modulate immune responses, and lessen mucositis and candidiasis severity by strengthening the mucosal barrier.[23] Oral microbiota transplantation (OMT), similar to fecal microbiota transplantation (FMT), may offer a practical method for restoring microbial balance.[5] Though still in early research, these strategies could become vital in biological therapy, reducing RT side effects (Table 4).

A critical review of conflicting research on how radiotherapy (RT) affects changes in oral microbiota

This study reviewed research on how radiotherapy affects oral microbiota in head and neck cancer patients and found many contradictions. Therefore, this section critically analyzes these inconsistencies concerning bacterial and fungal species.

Lactobacilli

Some studies, like Yang et al. (2021), found Lactobacilli in patients' saliva samples within a few weeks after RT.[49]

Conversely, Khalil et al. (2020) found a marked reduction in Lactobacilli in patients' mucosal swabs linked to a dry mouth.[50]

These inconsistencies in the results could stem from variations in sampling sites, examination techniques, sampling times, and dietary factors.

Streptococcus

In a 2024 study, de Freitas Neiva et al. observed an increase in Streptococcus mutans and Streptococcus sanguinis species following RT, which they linked to radiation-related caries.[51]

However, Peng et al. 2024 reported reduced Streptococcus salivarius species linked to salivary gland damage and pH fluctuations.[52]

This ambiguity in the results stems from variations in the sampling environment and the patients' underlying factors.

Candida

Suryawanshi et al. (2012) reported a significant rise in Candida albicans among patients suffering from severe mucositis and dry mouth.[53]

However, a study by Rupe et al. in 2022 observed a relative decrease in Candida in patients who took antifungal drugs.[54]

These discrepancies might also stem from concurrent

Table 4. Summary of a practical guide to managing oral complications after radiotherapy (RT) treatment

Treatment stage	Complication	Preventive / Management strategies
Before RT	Dental caries	Comprehensive dental exam; extraction of hopeless teeth; application of topical fluoride; patient education on oral hygiene
	Oral mucositis	Oral health optimization; prophylactic mouth rinses (e.g., saline, sodium bicarbonate)
	Xerostomia	Counseling on hydration; initiation of fluoride gel; salivary substitutes discussed
	Candidiasis	Oral hygiene reinforcement; antifungal prophylaxis in high-risk patients
During RT	Dental caries	Daily fluoride gel or varnish; strict oral hygiene; diet counseling (low sugar)
	Oral mucositis	Bland rinses (saline/bicarbonate); cryotherapy (ice chips); topical anesthetics; pain control; avoidance of irritants (alcohol, tobacco)
	Xerostomia	Frequent sips of water; saliva substitutes; sugar-free chewing gum/lozenges; sialogogues (e.g., pilocarpine if appropriate)
	Candidiasis	Regular antifungal mouth rinses (nystatin, clotrimazole); maintaining oral hygiene
After RT	Dental caries	Long-term use of fluoride gel, regular dental check-ups, and minimally invasive restorative care
	Oral mucositis	Usually resolves; manage residual pain or ulceration; monitor for secondary infections.
	Xerostomia	Long-term salivary substitutes; sialogogues; preventive care for dental health; lifestyle modifications
	Candidiasis	Prompt antifungal therapy for relapses; continuous oral hygiene monitoring

treatments and the patients' immune responses.

Ultimately, the contradictions found in the studies suggest that the study design for examining changes in oral microbiota after RT needs standardized criteria. These should include a consistent sampling site and control of clinical variables. Only through such rigorous methods can valid, reliable comparisons be made and existing evidence correctly interpreted.

Conclusion

This review explores various studies showing that radiotherapy (RT) for head and neck cancer can disrupt the oral ecosystem, leading to complications like mucositis and xerostomia. It also indicates that oral microbiota can worsen pathophysiological issues.[54] Initially, radiation damages salivary glands and mucosal epithelium, reducing saliva production, causing dry mouth, lowering oral pH, and compromising the oral defense barrier, which decreases beneficial microbes and allows opportunistic pathogens to flourish.[54] One study analyzed oral microbiota changes via next-generation sequencing (NGS), revealing that RT reduces alpha diversity and promotes opportunistic pathogen growth.[18,49] The decline in nitrate-metabolizing bacteria like Neisseria and Haemophilus can lead to significant oral ecosystem changes. Meanwhile, increased pathogens such as Streptococcus mutans and Lactobacillus may worsen dental caries and tissue invasion.[55] An increase in bacteria like Prevotella, Fusobacterium, and Veillonella, which are involved in inflammation and periodontal disease, further reflects microbial community shifts.[2,7] These bacteria produce LPS, aggravating mucositis. Additionally, opportunistic fungi like Candida albicans exploit immune suppression, raising the risk of diseases like oropharyngeal candidiasis.[21]

This article also identified a direct link between the severity of oral mucositis and bacteria that produce LPS. Although hypoxia is a key factor in osteoradionecrosis (ORN), bacterial infections can significantly worsen the condition.[30] "Bacterial invasion of damaged bone can trigger a chronic inflammatory response, hindering healing and leading to necrosis. Our findings suggest that managing the oral microbiota could be as important as controlling tissue damage.

Our understanding of RT-induced changes in the oral microbiota remains limited, and existing studies have notable gaps. Future research should focus on functional analyses, utilizing advanced techniques like metatranscriptomics, metaproteomics, and metabolomics to better elucidate the biochemical pathways within microbial communities, particularly in the oral microbiota. Identifying key metabolites involved in inflammation, tissue destruction, and caries could reveal new therapeutic targets. Large-scale, comprehensive studies are essential to track temporal microbial shifts and to identify profiles that serve as biomarkers for severe complications. Next-generation probiotics, including engineered strains, may offer anti-inflammatory effects and inhibit specific pathogens. Prebiotics can help promote beneficial microbes, restoring balance. Oral microbiota transplantation is another promising method for re-establishing microbial equilibrium, but all these approaches require rigorous clinical trials to ensure safety and effectiveness.

As a final point, the oral microbiota should no longer be considered a secondary factor in head and neck cancer but rather an active component in ecosystem therapy that can help improve patients' quality of life. Also, integrating oral microbiology methods and oncology protocols could be essential for effectively treating these patients.

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Competing interests

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