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Narrative Review

Beyond Dry Mouth: Clinical Consequences and Management of Chemoradiotherapy-Induced Xerostomia in Head and Neck Cancer Survivors: A Narrative Review

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Abstract

Xerostomia is a prevalent and frequently persistent complication among cancer survivors treated with chemoradiotherapy, particularly those with head and neck malignancies. Although commonly described as "dry mouth," xerostomia reflects salivary gland hypofunction accompanied by qualitative alterations in salivary composition. Xerostomia refers to the subjective perception of oral dryness, whereas salivary gland hypofunction denotes objectively measurable reduction in salivary flow; these entities, although related, are not interchangeable. These changes disrupt oral homeostasis and contribute to oral morbidity, functional impairment, and reduced quality of life. ultimately impairing salivary secretion and protective functions. While concurrent chemotherapy does not directly injure salivary glands, it may exacerbate symptom severity through mucosal toxicity, systemic inflammation, dehydration, and reduced treatment tolerance. The clinical impact extends beyond subjective dryness: compromised lubrication, buffering capacity, antimicrobial defense, and remineralization contribute to difficulties with mastication, swallowing, speech, and sleep. Xerostomia is also associated with radiation-related dental caries, periodontal disease progression, and tooth loss, particularly in long-term survivors. This narrative review synthesizes current evidence on the mechanisms, clinical consequences, and evidence-based management of chemoradiotherapy-induced xerostomia across the cancer continuum. Emphasis is placed on survivorship-oriented care, including standardized assessment of salivary dysfunction, preventive dental strategies, and multidisciplinary supportive approaches. Despite advances in radiotherapy planning and symptomatic therapies, durable restoration of salivary gland function remains an unmet clinical need, underscoring the importance of risk-adapted prevention, long-term oral surveillance, and integration of oral health outcomes into comprehensive survivorship care models. This narrative review aims to synthesize the current evidence on the mechanisms, clinical consequences, assessment, and management of chemoradiotherapy-induced xerostomia in head and neck cancer survivors. A structured literature search was performed using major databases (PubMed, Scopus, and Web of Science), focusing on studies published in the modern radiotherapy era.

Keywords: Xerostomia; Salivary Gland Hypofunction; Chemoradiotherapy; Head and Neck Cancer; Survivorship; Radiation-Related Caries; Periodontal Disease; Supportive Care

Introduction

Head and neck cancers (HNCs) account for approximately 3-5% of all malignancies worldwide and frequently require multimodality treatment, including surgery, radiotherapy (RT), and concurrent chemoradiotherapy (CRT), creating a growing population of long-term survivors in whom treatment-related toxicities increasingly shape oral health outcomes [1,2]. Improvements in oncologic outcomes have shifted clinical attention toward long-term toxicities that increasingly shape survivorship quality. Among these, CRT-induced xerostomia remains one of the most prevalent and functionally debilitating complications [3,4]. Radiation-induced xerostomia has consistently been reported as a predominant late toxicity in HNC cohorts, with a substantial impact on long-term oral health and quality of life [4]. Although often described simply as "dry mouth," xerostomia represents a complex clinical syndrome characterized by persistent salivary gland hypofunction and qualitative alterations in saliva that disrupt oral homeostasis [5,6]. These changes predispose patients to progressive oral morbidity, including dental caries, periodontal disease, mucosal injury, dysphagia, nutritional compromise, and reduced quality of life [3,6,7]. Despite the implementation of salivary gland-sparing techniques such as intensity-modulated radiotherapy (IMRT), xerostomia continues to affect a substantial proportion of survivors. Dose-volume analyses demonstrate that clinically meaningful salivary dysfunction persists even with contemporary RT planning when parotid dose constraints are exceeded [8], underscoring the need for comprehensive, oral oncology-oriented management strategies that extend beyond dosimetric optimization alone [7].

Despite growing recognition of its clinical burden, the management of CRT-induced xerostomia remains fragmented across disciplines and is often limited to symptomatic palliation. Prior reviews have largely focused either on radiotherapy dose-response relationships or on individual therapeutic modalities, without integrating mechanistic understanding, oral health consequences, and survivorship care frameworks. A comprehensive, oral oncology-oriented perspective is therefore needed to contextualize xerostomia within the broader continuum of cancer treatment and long-term follow-up. Unlike prior reviews that primarily address radiation dose-response relationships or symptomatic treatment approaches, the present review provides an integrated synthesis of radiobiological mechanisms, disruption of the oral ecosystem, and downstream clinical consequences in head and neck cancer survivorship. By linking salivary gland injury to dental, periodontal, microbiome-related, and functional complications within a unified oral oncology framework, this review aims to highlight xerostomia as a central driver of long-term oral morbidity rather than merely a symptomatic adverse effect.

This narrative review synthesizes current evidence regarding the pathophysiology of treatment-induced salivary gland injury, its downstream oral and functional consequences, and contemporary management strategies, with particular emphasis on preventive dentistry, risk-adapted care, and multidisciplinary survivorship models. In this framework, xerostomia is conceptualized not merely as a symptomatic toxicity but as a complex disruption of the oral ecological and functional network following cancer therapy, with downstream implications for oral health, functional recovery, and long-term survivorship outcomes in patients with HNC. Beyond summarizing existing knowledge, the present review critically integrates radiobiological, oral health, and survivorship evidence to highlight conceptual links between salivary gland injury, oral ecosystem disruption, and long-term clinical outcomes, while identifying key gaps that may inform future preventive and regenerative strategies in oral oncology.

Literature search strategy

This article was developed as a structured narrative review to synthesize current knowledge on chemoradiotherapy-induced xerostomia and its clinical implications for HNC survivors. To identify relevant literature, a targeted search was conducted in PubMed/MEDLINE, Scopus, and Web of Science for articles published in English between January 1990 and December 2024. The review integrates evidence from approximately 190 studies, including clinical trials, observational studies, and systematic reviews, with emphasis on clinically relevant and translational findings. Search queries included combinations of keywords such as xerostomia, salivary gland hypofunction, head and neck cancer, radiotherapy, chemoradiotherapy, salivary gland injury, radiation caries, periodontal disease, and survivorship care. Titles and abstracts were screened for relevance to the pathophysiology, clinical consequences, and management of treatment-related salivary gland dysfunction in oncologic populations. Priority was given to systematic reviews, clinical studies, consensus statements, and influential translational or mechanistic investigations relevant to oral oncology practice. Additional pertinent publications were identified through manual screening of reference lists from key reviews and guideline documents. The selected literature was

critically evaluated and synthesized to provide an integrated overview of the biological mechanisms, oral health consequences, and contemporary management strategies associated with CRT-induced xerostomia.

Radiobiology of salivary gland injury

Radiosensitivity of salivary glands

Salivary glands exhibit a notable paradox in their radiosensitivity: they are highly sensitive to ionizing radiation despite a relatively low proliferative index [9]. Upon exposure to radiotherapy (RT), acinar cells experience rapid functional impairment that precedes observable cell death and subsequent glandular atrophy [10,11]. Among the cellular constituents, serous acinar cells—predominant within the parotid gland—are especially susceptible, resulting in a swift and pronounced decline in stimulated salivary secretion [12]. The relationship between radiation dose and salivary gland dysfunction has been robustly characterized in both clinical and preclinical models [8]. Specifically, mean radiation doses to the parotid gland exceeding 24-26 Gy have been correlated with persistent, and frequently irreversible, reductions in salivary output [12,13]. Conversely, the submandibular glands manifest distinct dose-response dynamics, with evidence suggesting that partial functional recovery is achievable when mean radiation doses are maintained below approximately 39 Gy [14] (Table 1).

Salivary Structure	Dosimetric Parameter	Recommended Threshold	Clinical Implication	Reference
Parotid gland (contralateral or least-irradiated)	Mean dose	< 20 Gy	Substantially reduced risk of moderate-severe xerostomia	[8,25]
Parotid glands (bilateral mean)	Mean dose	< 25-26 Gy	Severe xerostomia generally avoided; meaningful preservation of stimulated salivary flow	[8,25]
Parotid gland	D80 (dose to 80% volume)	Lower values associated with improved outcomes	Predictor of higher-grade xerostomia in selected analyses; not a universal planning constraint	[25]
Submandibular gland	Mean dose	≤ 39 Gy	Partial functional recovery possible; doses above this associated with marked hypofunction	[12]
Oral cavity (minor salivary gland surrogate)	Mean dose	Lower is better (no universal threshold)	Correlates with patient-reported xerostomia severity; reflects minor gland contribution	[25]

Table 1: Dosimetric Predictors of Radiation-Induced Xerostomia.

Note: Thresholds synthesized from QUANTEC salivary gland dose-volume analyses and subsequent IMRT-era validation studies, highlighting clinically relevant planning parameters associated with long-term salivary gland dysfunction and patient-reported xerostomia severity. Mean dose parameters correlate with long-term stimulated salivary flow and patient-reported xerostomia severity.

Cellular and vascular mechanisms of radiation-induced salivary gland injury

Ionizing radiation exerts multifaceted cytotoxic effects on salivary gland cells, primarily through the induction of DNA double-strand breaks, generation of reactive oxygen species (ROS), and disruption of cellular membranes [15]. These insults impair receptor-mediated intracellular signaling cascades critical for regulating fluid secretion [16]. Notably, the pathogenesis of early glandular dysfunction extends beyond apoptosis, as selective plasma membrane injury and derangement of intracellular signaling networks have emerged as predominant contributors to acute secretory failure [17].

Radiation-induced endothelial cell injury and subsequent microvascular rarefaction significantly diminish salivary gland perfusion, undermining the tissue's capacity for homeostasis and

repair [18]. Persistent microvascular dysfunction precipitates tissue hypoxia, chronic inflammatory activation, and progressive fibroatrophic remodeling, ultimately culminating in irreversible glandular atrophy [19]. Collectively, these interrelated cellular and vascular mechanisms provide a mechanistic framework for understanding the chronic, and frequently progressive, manifestation of xerostomia observed in cancer survivors.

Pathophysiology of chemoradiotherapy-induced xerostomia

Salivary flow rates have been documented to decline rapidly—by approximately 50-60%—within the first week of radiotherapy (RT), with a continued and cumulative reduction observed over the course of treatment [20]. Although partial functional recovery may occur within 12-18 months in a subset of patients, most individuals who receive substantial salivary gland radiation doses develop persistent, often irreversible xerostomia [21,22]. The underlying pathophysiology is multifactorial: radiation impairs the regenerative capacity of salivary tissue through depletion of progenitor cell populations, disruption of the glandular stromal microenvironment, and progressive fibroatrophic remodeling, collectively limiting tissue repair and long-term functional recovery [8,23]. In addition, concurrent chemotherapy may further exacerbate salivary dysfunction by promoting systemic inflammatory activation, inducing mucosal toxicity, precipitating dehydration, and reducing overall treatment tolerance [3,24]. Accordingly, CRT-induced xerostomia should be regarded as a chronic and clinically significant sequela of cancer therapy rather than a transient adverse effect [25].

Alterations in salivary composition and oral homeostasis

Beyond quantitative reductions in salivary flow, CRT induces profound qualitative alterations in salivary composition that further disrupt oral homeostasis [26]. Radiation-related injury to acinar and ductal cells modifies electrolyte balance, reduces bicarbonate secretion, and impairs the production of salivary proteins essential for antimicrobial defense and mucosal lubrication [26]. Decreased concentrations of immunoglobulin A, lysozyme, lactoferrin, and other innate defense mediators compromise host-microbial equilibrium, while diminished buffering capacity promotes sustained oral acidification [26]. These compositional shifts, coupled with reduced mechanical clearance, create a permissive environment for microbial dysbiosis [27] and enhanced dental demineralization [28]. Thus, xerostomia represents not merely a reduction in fluid volume but a complex biochemical alteration of the oral milieu that predisposes survivors to progressive dental and periodontal pathology.

Dental, periodontal, and functional consequences of xerostomia

Dental caries and tooth loss

Saliva plays a pivotal role in maintaining oral health by neutralizing acid, promoting enamel remineralization, and regulating the oral microbiome. Following radiotherapy (RT), a marked decline in salivary flow and buffering capacity is consistently observed, resulting in a substantially increased susceptibility to radiation-induced dental caries and subsequent tooth loss [30,31]. Accumulating clinical and experimental evidence indicates that radiation caries represents a distinct pathobiologic entity rather than merely an accelerated form of conventional caries. Irradiated dental tissues exhibit heightened structural vulnerability, particularly at the enamel-dentin junction, where rapid demineralization and structural breakdown are frequently observed [31,32]. These changes reflect the combined effects of salivary hypofunction, altered oral microbiota, and radiation-mediated alterations in dental hard-tissue integrity, contributing to the aggressive, multifactorial nature of radiation-associated dental deterioration [31,32].

Periodontal disease and oral microbiome dysbiosis

Xerostomia, a common sequela of head and neck radiotherapy, profoundly alters the oral microbial ecosystem by creating an environment characterized by reduced salivary clearance, diminished buffering capacity, and impaired antimicrobial defense. This ecological shift favors the proliferation of cariogenic and aciduric microorganisms, including Streptococcus mutans, Lactobacillus species, Candida albicans, and Staphylococcus species [33-35]. The resulting dysbiotic state is further compounded by radiation-induced vascular compromise and local immune dysfunction, thereby weakening periodontal host defenses. These alterations promote chronic gingival inflammation, accelerate the progression of periodontitis, and contribute to alveolar bone resorption [36,37]. From an oral oncology perspective, preservation of periodontal integrity in xerostomic patients is clinically critical—not only for long-term tooth retention, but also for maintaining mucosal resilience, optimizing post-extraction wound healing, and reducing the risk of osteoradionecrosis

following dental interventions [3,38]. Preservation of periodontal integrity through preventive dental care and controlled timing of invasive procedures may reduce the risk of osteoradionecrosis by minimizing local trauma and infection

Functional impairment and quality of life

The interplay between salivary gland hypofunction, microbial dysbiosis, increased vulnerability of dental hard tissues, and compromised mucosal defenses establishes a self-reinforcing cycle of progressive oral pathology. These complications are not isolated but represent interrelated pathophysiological processes with cumulative effects that progressively amplify morbidity. This convergence of adverse outcomes has important implications for nutritional status, tolerance of oncologic therapies, and long-term survivorship, ultimately diminishing overall quality of life. Recognition of these interconnected mechanisms underscores the need for comprehensive, multidisciplinary oral oncology strategies that prioritize prevention, early intervention, and sustained follow-up (Table 2).

Domain	Clinical Complications	Key Pathophysiological Drivers
Dental	Radiation-related caries, accelerated enamel-dentin breakdown, tooth loss	Reduced salivary flow, impaired buffering capacity, decreased remineralization, sustained oral acidification, and radiation-mediated vulnerability of dental hard tissues
Periodontal	Gingivitis, progressive periodontitis, alveolar bone loss	Microbial dysbiosis with expansion of acidogenic and opportunistic taxa, reduced antimicrobial proteins (e.g., IgA, lactoferrin), impaired host immune defense, chronic inflammatory activation
Mucosal	Ulceration, mucosal fragility, secondary infections (including candidiasis)	Impaired lubrication, decreased mucin production, reduced epithelial resilience, altered innate immune mediators
Functional	Dysphagia, impaired bolus formation, taste alteration, speech difficulty	Reduced mucosal lubrication and impaired solubilization of tastants, altered salivary protein composition
Skeletal/Maxillofacial	Increased risk of osteoradionecrosis	Radiation-induced vascular injury and fibroatrophic remodeling, compromised mucosal barrier, impaired wound healing, and increased susceptibility following dental trauma or extraction
Nutritional/ Systemic	Protein-calorie malnutrition, feeding tube dependence, weight loss	Dysphagia, taste disturbance, oral pain, reduced intake secondary to mucosal and dental pathology

Table 2: Integrated Clinical and Pathophysiological Consequences of Chemoradiotherapy-Induced Xerostomia in Head and Neck Cancer Survivors.

Note: Complications are interdependent and frequently coexist, reflecting the interconnected effects of salivary hypofunction, microbial dysbiosis, vascular injury, and fibroatrophic remodeling following chemoradiotherapy. Mechanisms and clinical associations are synthesized from studies of radiation-induced salivary gland dysfunction, dental hard-tissue vulnerability, microbiome dysregulation, and survivorship outcomes in head and neck cancer [3,4,6,8,20-25,26-30,32-34].

Assessment of xerostomia

Comprehensive evaluation of xerostomia requires a multidimensional approach integrating subjective patient-reported experiences with objective quantification of salivary gland function. A clinically important discordance often exists between the perceived sensation of oral dryness and measured salivary output, underscoring the distinction between xerostomia as a symptomatic complaint and salivary gland hypofunction as a physiological deficit [42,43]. Validated patient-reported outcome (PRO) instruments, including the Xerostomia Inventory and head-and-neck-specific quality-of-life modules such as the EORTC QLQ-H&N35, provide structured frameworks for assessing symptom severity, frequency, and functional impact [44,45]. To enhance conceptual clarity, assessment tools can be broadly categorized as follows: (i) Screening tools (e.g., Xerostomia Inventory), (ii) Clinical diagnostic tools (e.g., sialometry), (iii) Research-oriented instruments (e.g., imaging and biomarker-based analyses) (Table 3).

Category	Tool/Method	Purpose	Clinical Utility	Limitations
Screening Tools	Xerostomia Inventory (XI)	Rapid symptom screening	Easy to use, patient-reported, useful in outpatient settings	Subjective; not correlated with flow rates
	EORTC QLQ-H&N35	QoL-based symptom evaluation	Captures functional impact and survivorship burden	Not specific for salivary function
Clinical Assessment Tools	Unstimulated salivary flow (sialometry)	Objective measurement of baseline secretion	Standard diagnostic tool for hypofunction	Technique-sensitive, time-consuming
	Stimulated salivary flow	Functional gland reserve assessment	Useful for treatment planning and follow-up	Influenced by patient factors
Imaging-Based Methods	Scintigraphy	Functional gland imaging	Quantitative glandular function	Limited availability
	Ultrasonography	Structural assessment	Non-invasive, accessible	Operator-dependent
	MRI	Detailed structural-functional analysis	High-resolution evaluation	Expensive
Research-Oriented Tools	Salivary proteomics	Molecular profiling	Identifies biomarkers and subtypes	Not yet a clinical standard
	Microbiome analysis	Dysbiosis assessment	Supports precision medicine approaches	Limited routine applicability
Toxicity Grading Systems	CTCAE, RTOG/EORTC, LENT-SOMA	Standardized reporting	Essential for trials and comparisons	Limited sensitivity to patient perception

Table 3: Classification of Xerostomia Assessment Tools in Head and Neck Cancer Survivors.

Objective assessment is typically performed using unstimulated and stimulated whole salivary flow measurements (sialometry), with internationally recognized diagnostic thresholds defining clinically significant glandular hypofunction [37]. For more detailed evaluation, gland-specific imaging modalities—including salivary gland scintigraphy, high-resolution ultrasonography, and magnetic resonance imaging—enable structural and functional characterization of irradiated tissues, supporting diagnostic clarification and prognostic stratification in both clinical and research settings [46,47]. In clinical trials and survivorship studies, standardized toxicity grading systems—such as the Radiation Therapy Oncology Group (RTOG)/European Organisation for Research and Treatment of Cancer (EORTC) criteria, the Late Effects in Normal Tissues-Subjective, Objective, Management, and Analytic (LENT-SOMA) scales, and the Common Terminology Criteria for Adverse Events (CTCAE)—are essential for consistent reporting, risk stratification, and cross-study comparability [48]. Collectively, comprehensive assessment frameworks not only document treatment-related morbidity but also enable risk-adapted prevention, targeted symptomatic intervention, and structured survivorship management in HNC populations.

Management strategies in oral oncology

Preventive approaches

A comprehensive pre-treatment dental and periodontal assessment is a cornerstone of preventive oral oncology care, enabling systematic identification and management of latent infection foci, periodontal disease, and other oral pathologies that may exacerbate post-radiotherapy complications. Targeted elimination of infectious and inflammatory sites prior to oncologic therapy, coupled with individualized fluoride protocols, substantially reduces the risk of radiation-related dental caries,

periodontal breakdown, and osteoradionecrosis [49]. From a radiotherapeutic perspective, contemporary advances in treatment planning—particularly intensity-modulated radiotherapy (IMRT) and adaptive planning strategies—allow precise reduction of mean radiation dose to major salivary glands, which remains the most effective evidence-based strategy for attenuating the incidence and severity of chronic xerostomia in HNC survivors [7,50]. Recent systematic reviews, consensus statements, and protocol-oriented studies have further emphasized the importance of structured oral hygiene programs, preventive dental surveillance, and coordinated supportive oral care pathways for patients undergoing HNC therapy [51-53].

In addition to these principles, clinically actionable preventive strategies include structured oral hygiene protocols, regular use of high-concentration fluoride agents, individualized recall intervals based on patient risk profiles, and implementation of preventive surveillance programs. Particular emphasis should be placed on pre-treatment dental stabilization, risk-based management of compromised teeth, and careful timing of invasive procedures, including extractions, to minimize local trauma and reduce the risk of osteoradionecrosis. Integration of these measures within a multidisciplinary treatment framework is essential to optimize long-term oral health outcomes in HNC survivors. Patients should be enrolled in structured recall programs at 3-6 month intervals, incorporating individualized fluoride regimens, reinforcement of oral hygiene measures, and continuous preventive surveillance.

Symptomatic and supportive management

State-of-the-art management of xerostomia in HNC survivors remains largely palliative, with the primary objective of alleviating subjective dryness and preserving essential oral functions, including mastication, deglutition, and phonation. The therapeutic armamentarium encompasses both non-pharmacological and pharmacological modalities. Artificial saliva substitutes and topical lubricants, commonly formulated with carboxymethylcellulose or mucin analogs, provide transient mucosal hydration and mechanical lubrication but do not replicate the biochemical complexity of native saliva [28]. Pharmacologic sialogogues, particularly muscarinic receptor agonists such as pilocarpine and cevimeline, can stimulate residual salivary output in patients with partially preserved glandular function; however, their efficacy is variable and may be limited by adverse effects and contraindications in select populations [54,55]. Although these interventions provide symptomatic relief, they neither restore the protective, digestive, and antimicrobial functions of endogenous saliva nor achieve true glandular regeneration [28]. These limitations underscore the need for continued translational research into regenerative strategies—including stem cell-based therapies, tissue engineering, gene transfer approaches, and targeted disease-modifying agents—aimed at restoring or preserving salivary gland structure and function following radiation-induced injury [28].

Multidisciplinary survivorship care

Long-term oral surveillance in HNC survivorship requires a structured, multidisciplinary framework that integrates the expertise of radiation oncologists, oral and maxillofacial surgeons, periodontists, restorative dentists, dental hygienists, speech and swallowing therapists, dietitians, and supportive care specialists. This collaborative model is based on standardized, longitudinal protocols for comprehensive oral assessment, incorporating diagnostic tools such as digital radiography, salivary flow analysis, and cross-sectional imaging to facilitate early identification and risk stratification of radiation-related complications.

Late sequelae include radiation-associated dental caries, progressive periodontal attachment loss, osteoradionecrosis, trismus, salivary gland dysfunction, and chronic mucosal injury, all of which contribute cumulatively to functional impairment and diminished quality of life [3]. Structured survivorship pathways aligned with evidence-based guidelines and supported by coordinated interprofessional communication are associated with improved detection, prevention, and management of dental and maxillofacial complications, while enhancing rehabilitation, nutritional status, communicative function, and psychosocial well-being in affected patients [56,57]. Integration of patient-centered education, anticipatory preventive strategies, and timely therapeutic interventions remains central to sustaining oral health and mitigating the long-term burden of radiation-induced oral disease.

Future Directions

Building on the mechanistic and clinical synthesis presented in this review, several priority directions emerge for advancing the prevention and management of treatment-related xerostomia in head and neck cancer survivorship. Despite substantial advances in gland-sparing radiotherapy and supportive care, durable restoration of salivary gland function remains a critical unmet need

in oral oncology. Future progress will likely depend on integrating precision preventive strategies—tailored to individual risk profiles and informed by mechanistic biomarkers—with biologically targeted regenerative interventions to restore salivary gland structure and function. Emerging approaches under investigation include transplantation or in situ activation of salivary gland stem/progenitor cells, tissue-engineered constructs designed to recapitulate the glandular microenvironment, and gene-transfer technologies such as aquaporin-1-based vectors, several of which have demonstrated promising preclinical or early clinical results in restoring salivary gland function following radiation injury [23,58-61]. In parallel, disease-modifying strategies—including radioprotective and antifibrotic agents—seek to mitigate endothelial injury, chronic inflammatory signaling, and fibroatrophic remodeling, thereby expanding the therapeutic window for functional preservation within risk-stratified treatment paradigms [18,62].

Equally important, future research must move beyond toxicity grading alone and adopt multidimensional outcome frameworks that incorporate objective salivary testing, validated patient-reported instruments, and longitudinal oral health endpoints, including caries incidence, periodontal progression, tooth retention, and osteoradionecrosis-related events [37,38,44,45]. Integration of oral microbiome profiling together with salivary proteomic and metabolomic analyses may enable biologically informed subphenotyping—such as distinguishing inflammatory from dysbiotic low-flow states—thereby supporting precision supportive care models in patients with treatment-related xerostomia [46,60,62,63]. Finally, implementation science approaches are needed to scale multidisciplinary survivorship pathways that integrate oncology, dental, rehabilitative, and nutritional care, ensuring consistent delivery of evidence-based preventive and early-intervention strategies across health systems [57].

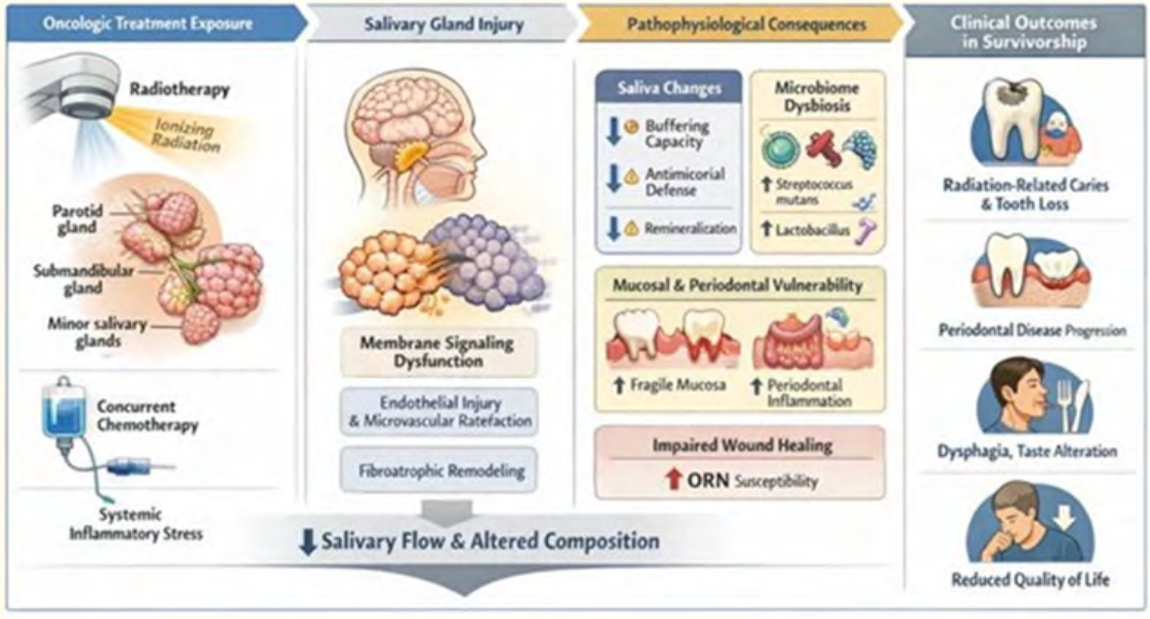

Figure 1: Mechanistic cascade and clinical consequences of chemoradiotherapy-induced xerostomia in survivors of head and neck cancer.

The schematic illustrates an integrated mechanistic cascade linking oncologic treatment exposures to downstream salivary gland dysfunction and long-term oral survivorship outcomes. Radiotherapy, concurrent chemotherapy, and systemic inflammatory stress induce salivary gland injury characterized by membrane signaling dysfunction, endothelial injury with microvascular rarefaction, acinar cell loss, and fibroatrophic remodeling. These alterations collectively result in reduced salivary flow and qualitative compositional changes. Subsequent pathophysiological effects include diminished buffering capacity, impaired antimicrobial defense, reduced remineralization, microbiome dysbiosis, increased mucosal and periodontal vulnerability, impaired wound healing, and heightened susceptibility to osteoradionecrosis. Collectively, these disturbances contribute to radiation-related caries, progression of periodontal disease, dysphagia, taste alteration, and reduced quality of life in long-term survivors.

Figure 2: Continuum of management strategies for chemoradiotherapy-induced xerostomia in head and neck cancer survivors.

This schematic presents a progressive framework that integrates current management strategies, emerging therapeutic approaches, and anticipated future directions in care. Current management focuses on foundational interventions, including comprehensive dental care, oral hygiene, salivary stimulation, and patient education, with the primary aim of reducing symptom burden and preventing complications. Emerging therapies increasingly prioritize regenerative and biologically informed treatments, such as stem cell-based and gene therapy approaches, as well as novel pharmacologic agents, such as targeted radioprotectors and advanced saliva substitutes. Many of these interventions are currently being investigated in various clinical research projects. Future directions include salivary gland regeneration through tissue engineering, precision radiotherapy with optimized dosing and proton-based techniques, and the systematic integration of xerostomia management into structured survivorship care pathways. Across all phases, the framework is anchored in a holistic survivorship model that incorporates comprehensive oral assessment, preventive dental strategies, and coordinated multidisciplinary support.

Conclusion

CRT-induced xerostomia in HNC survivors represents a chronic, multifactorial disorder reflecting sustained disruption of salivary gland physiology secondary to ionizing radiation and cytotoxic therapy. It is characterized by both quantitative reductions in salivary output and qualitative alterations in salivary composition—including diminished antimicrobial proteins, electrolytes, and mucins—resulting in destabilization of the oral ecosystem. The combined effects of hypofunction and compositional change promote microbial dysbiosis, dental hard-tissue demineralization, periodontal breakdown, and compromised mucosal integrity, establishing a self-reinforcing cycle of progressive oral morbidity. The heightened incidence of dental caries, periodontal deterioration, osteoradionecrosis, dysphagia, nutritional compromise, and diminished quality of life underscores the need to conceptualize xerostomia as a treatment-defining chronic condition requiring longitudinal, multidisciplinary management.

Despite advances in gland-sparing radiotherapy and preventive dental protocols, current therapeutic strategies remain predominantly palliative and do not restore native glandular architecture or secretory capacity. Comprehensive multidimensional assessment—including objective sialometry, imaging, and validated patient-reported measures—combined with risk-adapted preventive care and coordinated survivorship models, is therefore central to contemporary oral oncology practice. Future progress will depend on integrating mechanistically informed biomarkers, regenerative therapeutics—including stem cell-based and gene-transfer approaches—and precision supportive care within structured survivorship pathways. Embedding robust oral health endpoints into the broader oncologic continuum may enable a shift from symptom mitigation toward biologically targeted preservation and restoration of salivary gland function, ultimately improving survivorship and quality-of-life outcomes for patients with HNC.

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Conflict of Interest

The authors declared that they have no commercial or financial relationships that could be construed as potential conflicts of interest.

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