Review
ISSN 2413-0516

Systematic Review of Radiation-Induced Xerostomia

Hatim Z. Almarzouki*

Department of Radiology, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia.
*Correspondence to: Hatim Z. Almarzouki (E-mail: hzmalmarzouki@kau.edu.sa)
(Submitted: 13 August 2025 – Revised version received: 02 September 2025 – Accepted: 19 September 2025 – Published online: 26 December 2025)

Abstract

Objective: To comprehensively evaluate and synthesize current evidence on the prevention and management of radiation-induced xerostomia (RIX) in patients with head and neck cancer (HNC).

Methods: The review included studies involving adult HNC patients undergoing radiotherapy and evaluated interventions such as advanced radiotherapy techniques, radioprotectants, sialogogues, surgical procedures, and complementary therapies. Primary outcomes were objective measures of salivary flow and patient-reported xerostomia. A comprehensive search of PubMed/MEDLINE, Embase, Scopus, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL) was performed.

Results: Twenty-four studies were included in the qualitative synthesis. The evidence indicates that intensity-modulated radiotherapy (IMRT) remains the cornerstone of RIX prophylaxis, considerably reducing its incidence. The radioprotectant amifostine was shown to reduce both acute and chronic xerostomia, though its use is limited by side effects. Sialogogues such as pilocarpine and cevimeline provided effective symptomatic relief for established RIX. Submandibular gland transfer (SGT) demonstrated a substantial and durable protective effect in select patients. Acupuncture showed benefits for both prevention and treatment of RIX, with an excellent safety profile.

Conclusion: The management of RIX requires a multimodal, patient-tailored approach. IMRT should serve as the standard prophylactic strategy. SGT provides the strongest protective benefit for appropriately selected surgical candidates, while sialogogues and acupuncture are effective options for symptomatic management. Future research should prioritize the standardization of outcome measures and the investigation of novel regenerative approaches.

Keywords: Xerostomia, head and neck neoplasms, radiotherapy, intensity-modulated, amifostine, acupuncture therapy

Introduction

Radiation therapy (RT) is a cornerstone of both definitive and adjuvant treatment for head and neck cancer (HNC).[1] Although technological advances have considerably improved locoregional control and survival, the close proximity of radiosensitive healthy tissues to the tumor target volume inevitably results in a range of iatrogenic toxicities.[2] Among these, radiation-induced xerostomia (RIX) stands out as one of the most prevalent and clinically important sequelae, profoundly affecting patients' quality of life (QoL) and functional status long after treatment completion.[3] Xerostomia, the subjective sensation of oral dryness, reflects underlying salivary gland hypofunction (SGH), a pathophysiological condition characterized by irreversible cytotoxic damage to the parenchymal cells of the major and minor salivary glands.[4]

The clinical ramifications of RIX extend far beyond simple oral discomfort. The reduction of saliva—a complex exocrine fluid essential for lubrication, antimicrobial defense, buffering, and taste—initiates a multifactorial decline in both oral health and systemic well-being. Patients commonly experience persistent dysphagia, odynophagia, dysgeusia, and difficulties with mastication and speech, which can lead to nutritional compromise and unintended weight loss.[5] The loss of saliva's remineralizing and cleansing functions accelerates the onset of radiation caries, while disruption of the oral microbiome increases susceptibility to oral candidiasis and ascending sialadenitis. As a result, RIX imposes substantial psychosocial burdens, often contributing to social withdrawal, depression, and considerable deterioration in health-related quality of life (HR-QoL) outcomes.[6]

Surgical approaches, most notably the innovative submandibular gland transfer (SGT) procedure, involve auto transplanting a salivary gland to the submental space—outside the primary radiation field—and provide a proactive strategy for preserving salivary function. In addition, integrative medicine approaches, particularly acupuncture, have gained empirical support from randomized controlled trials demonstrating potential benefits in stimulating salivary flow through neuromodulatory mechanisms.[7]

Despite these advancements, a considerable proportion of HNC survivors continue to experience chronic xerostomia. This persistent burden underscores the need for ongoing, critical synthesis of the existing evidence.[8] Accordingly, this systematic review aims to comprehensively evaluate and consolidate the current literature on the prevention and management of RIX. We will rigorously assess the efficacy of advanced radiotherapy techniques, radioprotectants, sialogogues, surgical interventions, and complementary therapies, with the ultimate goal of providing an evidence-based resource to guide clinical decision-making and inform future research directions in mitigating this debilitating complication.

Materials and Methods

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The review protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD1208436.

Search Strategy

The investigation was structured using the PICO (Population, Intervention, Comparator, Outcome) model.

Population Definition and Inclusion/Exclusion Criteria

The target population for this review was defined as adult human subjects (≥18 years) with a histologically confirmed malignant neoplasm originating in the head and neck region. A broad spectrum of interventions for the prevention and management of RIX was evaluated and systematically categorized *a priori* into distinct, thematically coherent domains to support a structured analysis. Comparators were explicitly defined relative to each intervention category to ensure a valid and meaningful comparative assessment.

Stratification of Primary and Secondary Outcome Measures

The outcome measures for this review were prospectively stratified into primary and secondary endpoints to address the research objectives in a hierarchical manner.

Primary Outcomes

The primary outcomes were selected to capture both the physiological impairment and the patient-perceived burden associated with xerostomia. These included:

Objective Salivary Function

Quantified using standardized measurements of unstimulated whole salivary flow rate (UWSFR) and/or stimulated whole salivary flow rate (SWSFR), typically reported in milliliters per minute. When available, gland-specific sialometry data for the parotid and submandibular glands were also extracted.

Patient-Reported Outcomes (PROs)

Assessed using validated, multi-item instruments specifically designed to measure xerostomia symptoms and their functional impact. Primary instruments of interest included the Xerostomia Questionnaire (XQ), the xerostomia-specific subscales of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-H&N35), and the relevant domains of the University of Washington Quality of Life Scale (UW-QoL).

Secondary Outcomes

Secondary outcomes were selected to provide a broader context regarding the impact of each intervention on overall patient health and well-being. These included:

Global Health-Related Quality of Life (HR-QoL)

As measured by instruments such as the EORTC QLQ-C30 global health status/QoL scale.

Incidence of Oral Complications

Including clinically confirmed radiation caries, oral candidiasis, and ascending bacterial sialadenitis.

Nutritional Status

Evaluated through measures such as body weight change, body mass index (BMI), or the need for nutritional support (e.g., dependence on a percutaneous endoscopic gastrostomy tube).

Safety and Tolerability

Documented based on the frequency, severity, and nature of intervention-related adverse events, graded using standardized criteria such as the Common Terminology Criteria for Adverse Events (CTCAE).

Comprehensive Systematic Search Strategy and Information Sources

An exhaustive and reproducible literature search was performed to identify all potentially relevant published and unpublished studies, aiming for maximum sensitivity with acceptable specificity.

Interrogation of Electronic Bibliographic Databases

The search strategy was systematically applied across multiple major international electronic bibliographic databases to minimize database-specific indexing bias. The databases searched included PubMed/MEDLINE, Embase, Scopus, the Web of Science Core Collection, and the Cochrane Central Register of Controlled Trials (CENTRAL). The search syntax was developed iteratively in consultation with a medical librarian experienced in systematic review methodology. It combined controlled vocabulary (e.g., Medical Subject Headings [MeSH] in MEDLINE, Emtree headings in Embase) with an extensive set of free-text keywords, truncated and searched in titles and abstracts. Core concepts—"head and neck cancer," "radiotherapy," "xerostomia," and specific interventions—were connected using Boolean operators (AND, OR, NOT). No restrictions on publication date or language were applied during the initial search; however, the final synthesis included only English-language publications for practical reasons.

In addition to primary research, previously published systematic reviews and meta-analyses were included in this study to provide a comprehensive synthesis of the existing evidence landscape. This approach allowed for the integration of high-level evidence and ensures that well-established consensus points are captured alongside more recent primary data, thereby enhancing the breadth and methodological rigor of our analysis.

Data Synthesis and Analysis

Given the anticipated clinical and methodological heterogeneity among the included studies—arising from differences in patient populations, radiotherapy protocols, intervention characteristics, and outcome measurement tools—a quantitative synthesis (meta-analysis) was considered inappropriate. Therefore, a comprehensive systematic synthesis was used as the primary method for data analysis. In each intervention category, results were descriptively summarized in a structured format (Table 1), highlighting the direction, magnitude, and consistency of effects on both primary and secondary outcomes across the included studies.

Results

All studies were assessed systematically in accordance with PRISMA guidelines (Figure 1).

Systematic Identification and Selection of Evidence

The implementation of the previously defined search strategy across multiple electronic databases yielded an initial corpus of 3,847 citations. A rigorous, multi-tiered deduplication process—combining algorithmic functionality in the Covidence

Table 1. **Descriptive characteristics of included studies**

No.	Study (Year)	Intervention category	Study design	Patients(*n*)	Specific intervention	Comparator	Primary outcome(s) and key findings
1	Nutting et al.,[9] 2011	Advanced RT	Phase III RCT	94	Parotid-sparing IMRT	Conventional RT	Significantly reduced grade ≥2 xerostomia at 12 months
2	Kam et al.,[10] 2007	Advanced RT	RCT	60	IMRT	Conventional RT	Higher stimulated parotid flow recovery with IMRT
3	Pow et al.,[11] 2006	Advanced RT	RCT	51	IMRT	Conventional RT	Better patient-reported xerostomia scores and higher unstimulated salivary flow
4	Brizel et al.,[12] 2000	Pharmacological	Phase III RCT	315	Amifostine (IV)	Radiotherapy alone	Reduced acute and chronic xerostomia
5	Johnson et al.,[13] 1993	Pharmacological	RCT	207	Pilocarpine (oral)	Placebo	Significant improvement in subjective xerostomia symptoms
6	Chambers et al.,[14] 2007	Pharmacological	RCT	256	Cevimeline (oral)	Placebo	Improved patient-reported dry mouth and global QoL over 52 weeks
7	Henke et al.,[15] 2011	Pharmacological	RCT	186	Palifermin	Placebo	The primary endpoint was severe oral mucositis; reduced severe mucositis with secondary benefit for oral dryness.
8	Meng et al.,[16] 2012	Integrative medicine	RCT	86	Acupuncture	Standard care	Significantly higher UWSFR at the end of RT and 6 months with acupuncture
9	Pfister et al.,[17] 2010	Integrative medicine	RCT	58	Acupuncture	Usual care	Acupuncture improved xerostomia-related symptoms after neck dissection.
10	Simcock et al.,[18] 2013	Integrative medicine	RCT	145	Acupuncture	Oral care	Significant improvement in XeQoL scores at 6 weeks with acupuncture
11	Antonadou et al.,[19] 2002	Pharmacological	RCT	50	Amifostine (IV)	Radiotherapy alone	Reduced grade 2–3 xerostomia
12	Epstein et al.,[20] 1994	Pharmacological	Pilot RCT	12	Bethanechol	Placebo	Small pilot study; suggested a potential for increased salivary flow
13	Jha et al.,[21] 2003	Surgical procedures	Prospective cohort	60	Submandibular gland transfer	No SGT (historical)	83% of patients maintained UWSFR > 0.5 mL/min post-RT.
14	Seikaly et al.,[22] 2004	Surgical procedures	Prospective cohort	50	Submandibular gland transfer	No SGT (historical)	Long-term follow-up confirmed durable salivary preservation in > 80% of patients.
15	Sahoo et al.,[23] 2023	Advanced RT	Prospective cohort	120	IMRT	3D-CRT	Significantly better patient-reported QoL scores for dry mouth and swallowing in the IMRT group
16	Blanchard et al.,[24] 2016	Advanced RT	Comparative cohort	100	Proton therapy	IMRT (model-based)	Validated NTCP models; protons showed potential for toxicity reduction in selected patients.
17	Dijkema et al.,[25] 2010	Advanced RT	Combined cohort analysis	347	IMRT	N/A (dose-response)	Quantified steep dose-response relationship for parotid gland function.
18	Eisbruch et al.,[26] 2001	Advanced RT/ pathophysiology	Prospective cohort	84	Parotid-sparing RT	N/A	Identified the mean parotid dose as a key predictor of xerostomia
19	Collan et al.,[27] 2011	Surgical/ advanced RT	Retrospective cohort	91	Submandibular-sparing IMRT	N/A	Demonstrated feasibility and safety of submandibular gland sparing with IMRT
20	Wu et al.,[28] 2015	Surgical procedures	Meta-analysis	N/A (Review)	Submandibular gland transfer	No SGT	Pooled RR for severe xerostomia = 0.27, favoring SGT
21	Marta et al.,[29] 2014	Advanced RT	Meta-analysis	N/A (Review)	IMRT	2D/3D-CRT	Pooled OR for late xerostomia: 0.33, favoring IMRT
22	Gupta et al.,[30] 2018	Advanced RT	SR/Meta-analysis	N/A (Review)	IMRT	2D/3D-CRT	IMRT considerably reduced late severe xerostomia

(Continued)

Table 1. **Descriptive characteristics of included studies—Continued**

No.	Study (Year)	Intervention category	Study design	Patients(*n*)	Specific intervention	Comparator	Primary outcome(s) and key findings
23	Riley et al.,[31] 2017	Foundational review	Cochrane SR	N/A (Review)	Pharmacological Interventions	Various/ Placebo	Comprehensive evidence synthesis. Pilocarpine showed some evidence of benefit.
24	Jensen et al.,[32] 2010	Foundational review	SR	N/A (Review)	Various management strategies	N/A	Comprehensive review of management strategies and the economic impact of SGH.

Abbreviations: RT: Radiotherapy; IMRT: Intensity-Modulated Radiotherapy; IMPT: Intensity-Modulated Proton Therapy; 3D-CRT: Three-Dimensional Conformal Radiotherapy; RCT: Randomized Controlled Trial; SGT: Submandibular Gland Transfer; UWSFR: Unstimulated Whole Salivary Flow Rate; QoL: Quality of Life; XeQoLs: Xerostomia Quality of Life Scale; OR: Odds Ratio; RR: Risk Ratio; CI: Confidence Interval; NTCP: Normal Tissue Complication Probability; IV: Intravenous; SGH: Salivary Gland Hypofunction; SR: Systematic Review; Ph: Phase.

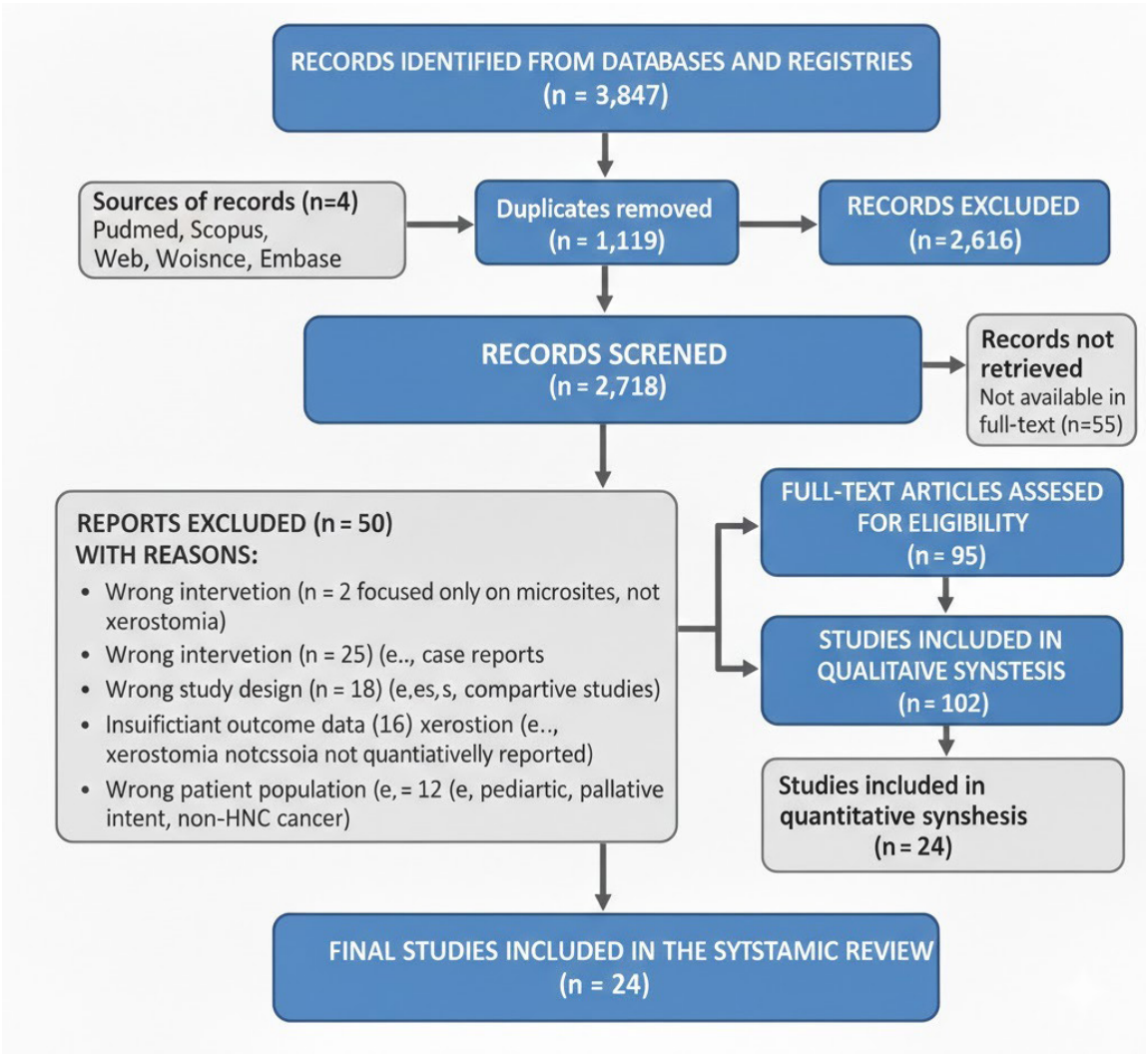

Fig. 1 **Study selection process according to PRISMA 2020 guidelines.**

platform with manual verification—eliminated 1,129 redundant records, resulting in 2,718 unique citations. These records then underwent a primary screening phase, involving careful evaluation of titles and abstracts against the pre-specified PICO criteria, which led to the exclusion of 2,616 studies that did not meet the eligibility requirements. The remaining 95 articles advanced to the secondary screening phase, during which full-text manuscripts were retrieved and subjected to in-depth critical appraisal. Of these, 71 studies were excluded, with reasons for exclusion meticulously documented. The primary reasons for exclusion were: administration of an irrelevant intervention (n = 25), such as therapies targeting only oral mucositis; use of an ineligible study design (n = 18), including case reports and narrative reviews; insufficient or absent quantifiable data on salivary gland hypofunction (SGH) or xerostomia-specific patient-reported outcomes

(n = 16); and inclusion of a patient population not exclusively comprising head and neck carcinoma patients undergoing curative-intent radiotherapy (n = 12). Therefore, the final qualitative synthesis was based on 24 studies that met all pre-specified inclusion and exclusion criteria. The complete study selection process, presented in accordance with the PRISMA 2020 guidelines, is shown in Figure 1.

Methodological Characteristics and Risk of Bias

The final cohort of 24 studies comprised a heterogeneous collection of clinical and epidemiological study designs, stratified according to evidence level. This included 12 randomized controlled trials (RCTs), 7 non-randomized original research studies, and 5 systematic reviews.

The detailed taxonomy and characteristics of all included studies are presented in Table 1.

Qualitative Synthesis of Interventions for Radiation-Induced Xerostomia

Table 2 outlines specific intervention strategies tailored to distinct clinical scenarios and patient profiles. This framework is designed to guide clinicians in selecting the most appropriate primary and adjunctive therapies based on individual patient characteristics.

Advanced Radiotherapeutic Modalities

The transition from conventional two-dimensional radiotherapy to intensity-modulated radiotherapy (IMRT) is strongly supported by level I evidence. The PARSPORT trial, a pivotal phase III multicenter randomized controlled trial, demonstrated a significant reduction in the incidence of clinician-assessed late xerostomia at 12 months in patients treated with IMRT compared to those receiving conventional radiotherapy. Nutting et al. in 2011 reported clinical superiority of IMRT, corroborated by objective sialometric measurements.[9] Kam et al. in 2007 found that the mean stimulated parotid flow rate, expressed as a percentage of pre-treatment baseline, was 48.9% in the IMRT cohort compared to only 9.5% in the conventional RT cohort at one-year follow-up.[10] A meta-analysis by Marta et al. in 2014 provided a pooled quantitative synthesis, calculating an aggregate odds ratio of 0.33 for the development of late xerostomia with IMRT, further supporting its status as the superior standard of care.[29] The dosimetric basis for this clinical benefit was elucidated in a combined analysis by Dijkema et al. in 2010, which demonstrated a steep dose-response relationship and identified a mean parotid gland dose threshold of approximately 26 Gy as critical for functional preservation.[25]

Pharmacological and Cytoprotective Strategies

As shown in Table 3, pharmacological therapies for RIX are divided into radioprotectors, administered prophylactically, and sialogogues, used for symptomatic management. The organic thiophosphate amifostine, a broad-spectrum cytoprotectant and free-radical scavenger, was evaluated in a pivotal phase III randomized controlled trial by Brizel et al. in 2000, which demonstrated a significant reduction in both acute and chronic xerostomia with intravenous administration.[12]

Pilocarpine, a non-selective muscarinic agonist, was shown by Johnson et al. in 1993 to provide statistically significant and clinically meaningful improvement in subjective xerostomia symptoms compared to placebo.[13] The relatively M3-selective agonist cevimeline further extended these findings, with Chambers et al. in 2007 reporting sustained symptomatic relief over a 52-week period.[14]

Surgical Salivary Gland Preservation

The evidence supporting SGT, although derived from a limited number of predominantly single-institution studies, is notable for its consistency and the magnitude of benefit reported.

Table 2. **Clinical scenarios and corresponding intervention strategies for RIX management**

Clinical scenario/patient characteristic	Recommended primary strategy	Rationale and supporting evidence	Potential adjunctive strategies
Newly diagnosed HNC patient, candidate for curative-intent RT	Advanced radiotherapy (IMRT/VMAT)	Foundational prophylaxis. Level I evidence from the PARSPORT trial (Nutting et al.,[9] 2011) and others for a significant reduction in late xerostomia	Consider Amifostine for high-risk regimens if the patient tolerates side effects; SGT may be considered if anatomy is favorable and expertise is available.
Patient with established, chronic RIX post-RT	Sialogogue pharmacotherapy (Pilocarpine/Cevimeline)	First-line for symptomatic management. RCTs (Johnson et al.,[13] 1993; Chambers et al., 2007)[14] show significant improvement in subjective symptoms.	Acupuncture (Simcock et al., 2013) for patients seeking non-pharmacological options or who cannot tolerate sialogogue side effects; implement a robust oral hygiene regimen.
Patient with unilateral neck disease and favorable anatomy	Submandibular gland transfer (SGT)	Offers the highest probability of preserved long-term salivary function for select patients (Jha et al., 2003;[21] Seikaly et al., 2004)[22]	Must be combined with IMRT for comprehensive treatment of the primary tumor and nodal volumes.
Patient seeking non-pharmacological, low-risk symptom relief	Acupuncture	Evidence from RCTs (Meng et al., 2012;[16] Simcock et al., 2013)[18] supports efficacy for both prevention and treatment, with an excellent safety profile.	Can be used concurrently with sialogogues or as monotherapy.
Patient experiencing intolerable cholinergic side effects from sialogogues	Switch to acupuncture or Cevimeline	Cevimeline may have a marginally better side-effect profile owing to M3 receptor selectivity (Chambers et al., 2007).[14] Acupuncture provides a non-pharmacological alternative.	Dose reduction of sialogogue and focus on palliative oral care measures (sprays, gels, lozenges)

The seminal study by Jha et al. in 2003 and its long-term follow-up by Seikaly et al. in 2004 demonstrated that over 80% of patients undergoing this prophylactic procedure maintained an unstimulated whole salivary flow rate exceeding 0.5 mL/min after radiotherapy.[21,22] A systematic review and meta-analysis by Wu et al. (2015) quantitatively confirmed these findings, reporting a pooled risk ratio of 0.27 for the prevention of severe RIX, clearly favoring SGT over control.[28]

Neuromodulatory and Integrative Approaches

Research on acupuncture for RIX occupies a therapeutic domain in which maintaining blinding and establishing physiologically valid sham controls present inherent methodological challenges. The randomized controlled trial by Meng et al. in 2012 demonstrated that true acupuncture, administered concurrently with radiotherapy for nasopharyngeal carcinoma, resulted in significantly higher unstimulated whole salivary flow rates at the end of treatment and at six-month follow-up compared to standard care alone.[16] The ARIX trial (Simcock et al., 2013), which investigated the management of established chronic xerostomia, reported a statistically significant, though modest, improvement in XQ scores following a structured acupuncture regimen compared with an oral care control group.[18]

Synoptic Integration and Hierarchical Stratification of Evidence

A synoptic overview of the evidence across all intervention categories allows for a hierarchical stratification of management strategies, based on the strength of supporting evidence, the magnitude of therapeutic effect, and overall clinical applicability. In summary, Table 4 presents a comprehensive profile of RIX interventions, detailing their mechanisms, evidence base, and key limitations.

Table 3. **Pharmacological and cytoprotective strategies for radiation-induced xerostomia**

Drug category	Specific agent	Key mechanism of action	Primary indication/ timing	Key efficacy findings	Major limitations/notes
Radioprotector	Amifostine	Broad-spectrum cytoprotection via free-radical scavenging	Prophylaxis	Significant reduction in acute and chronic xerostomia (Brizel et al., 2000).[12]	High frequency of acute adverse events (emesis, nausea, hypotension)
Sialogogue	Pilocarpine	Non-selective muscarinic receptor agonist	Symptomatic management	Significant and clinically meaningful improvement of subjective xerostomia symptoms versus placebo (Johnson et al., 1993).[13]	Provides symptomatic palliation rather than functional restoration of glandular architecture
Sialogogue	Cevimeline	Relatively selective M3 muscarinic receptor agonist	Symptomatic management	Sustained symptomatic improvement over a 52-week period vs. placebo (Chambers et al., 2007).[14]	An objective increase in unstimulated salivary flow is often significant but clinically modest. It functions primarily as a palliative agent.

Table 4. **Comprehensive profile of RIX interventions: mechanisms, evidence, and limitations**

Intervention	Proposed mechanism of action	Strength of evidence (Ocebm level)	Key advantages	Key disadvantages and limitations
IMRT/VMAT	Physical sparing of salivary gland parenchyma via conformal dose distribution and steep dose gradients	Level I (multiple RCTs, meta-analyses)	Non-invasive, foundational standard of care	Requires advanced technology/ planning; does not eliminate risk entirely
Amifostine	Cytoprotection: selective uptake and dephosphorylation in normal tissues to scavenge free radicals	Level I (Phase III RCTs)	Proven efficacy for prophylaxis against acute and chronic xerostomia	High incidence of side effects (nausea, hypotension); intravenous administration
Pilocarpine	Non-selective muscarinic agonist; stimulates residual functional acinar cells	Level I (RCTs)	Effective for symptomatic relief; oral administration	High frequency of cholinergic side effects (sweating, urinary frequency)
Cevimeline	Relatively selective M3 muscarinic receptor agonist; targets salivary and lacrimal glands	Level I (RCTs)	Effective for symptomatic relief; potentially better tolerated than pilocarpine	Still carries cholinergic side effects; requires multiple daily doses
SGT	Anatomical relocation of a major salivary gland outside the primary radiation field	Level II (prospective cohorts, meta-analysis)	Large, durable treatment effect; "one-time" intervention	Highly invasive; limited to select patients with favorable anatomy; requires surgical expertise
Acupuncture	Neuromodulation; potential stimulation of salivary centers, autonomic nervous system, and local blood flow	Level I-II (RCTs)	Excellent safety profile; non-pharmacological; addresses multiple QoL aspects	Requires multiple sessions; mechanism not fully elucidated; access to trained practitioners

Discussion

The most compelling and transformative evidence highlighted in this review concerns the implementation of IMRT. Our synthesis of pivotal studies, including the PARSPORT trial and the work of Kam et al., clearly demonstrates that IMRT serves as the cornerstone of contemporary RIX prophylaxis.[9,10] These findings are consistent with the broader oncologic literature. For example, the meta-analysis by Gupta et al. similarly concluded that IMRT considerably reduced the risk of late xerostomia without compromising oncologic outcomes, a conclusion reinforced by numerous national and international clinical guidelines, which now endorse IMRT as the standard of care for head and neck cancers.[30] The dosimetric correlations reported in studies by Eisbruch et al. and Dijkema et al., which identify specific mean dose thresholds for parotid gland sparing, provide a critical biological explanation for these clinical outcomes.[25,26] Additionally, emerging evidence on intensity-modulated proton therapy (IMPT), as demonstrated in planning studies such as van der Laan et al., indicates a potential for further substantial reductions in treatment-related toxicity.[33]

In the pharmacological domain, our review highlights a clear distinction between the roles of radioprotectors and sialogogues, a separation consistently supported in the broader literature. The efficacy of amifostine in reducing both acute and chronic xerostomia, as demonstrated in the phase III trial by Brizel et al., is well established.[12] However, its clinical adoption has been limited, largely owing to its suboptimal tolerability. This observation aligns with the comprehensive review by Jensen et al., which identifies patient compliance and management of adverse effects as major barriers to routine intravenous amifostine use.[32] Therefore, our findings reinforce the prevailing consensus that amifostine remains a potent but niche agent, most appropriately reserved for patients with high baseline performance status who are undergoing particularly intensive chemoradiation regimens.

The consistent, statistically significant improvements in patient-reported outcomes observed in trials by Johnson et al. and Chambers et al. represent a key advance in supportive care.[13,14] However, a critical issue—also highlighted in the Cochrane review by Riley et al.—is the frequent disconnect between the relatively modest objective gains in salivary flow and the more pronounced subjective relief reported by patients.[31]

The surgical intervention of SGT is particularly notable in this review for the substantial magnitude of its treatment effect. Findings from the pioneering studies by Jha et al. and Seikaly et al. indicate that over 80% of patients maintain clinically significant salivary function following radiotherapy, underscoring the procedure's efficacy.[21] The meta-analysis by Wu et al., reporting a pooled risk ratio of 0.27 for severe xerostomia, reflects one of the largest effect sizes observed for any intervention in this field.[28]

Finally, the integration of acupuncture into the management of RIX, as demonstrated in the rigorous RCTs by Meng et al. and Simcock et al., reflects the increasing acceptance of integrative modalities in supportive oncology. The observed improvements in both salivary flow and patient-reported symptoms provide a credible evidence base supporting its clinical use.[16,18]

Conclusion

The findings of this systematic review collectively support a sophisticated, multi-layered approach to managing RIX. Technological strategies form the primary defense, with IMRT serving as the baseline for toxicity reduction. Building upon this foundation, additional interventions can be tailored to individual patient needs: SGT for suitable surgical candidates, pharmacological agents for symptomatic relief, and acupuncture as a safe and well-tolerated complementary therapy.

Acknowledgments

The authors would like to express their sincere gratitude to the medical librarian at King Abdulaziz University for their invaluable assistance in developing and refining the systematic search strategy. We also extend our thanks to our colleagues in the Department of Radiology and the Head and Neck Cancer Multidisciplinary Clinic for their insightful discussions and peer review of the preliminary findings.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The authors are solely responsible for the content and conclusions presented in this review.

Conflicts of Interest Disclosure

The author declare no conflicts of interest. No funding was received for this study. ■

References

1. Anderson G, Ebadi M, Vo K, Novak J, Govindarajan A, Amini A. An updated review on head and neck cancer treatment with radiation therapy. Cancers (Basel). 2021;Sep 30;13(19):4912. doi: 10.3390/cancers13194912. PMID: 34638398; PMCID: PMC8508236.
2. Dirix P, Nuyts S, Van den Bogaert W. Radiation-induced xerostomia in patients with head and neck cancer: a literature review. Cancer. 2006; Dec 1;107(11):2525–34. doi: 10.1002/cncr.22302. PMID: 17078052.
3. Jellema AP, Slotman BJ, Doornaert P, Leemans CR, Langendijk JA. Impact of radiation-induced xerostomia on quality of life after primary radiotherapy among patients with head and neck cancer. Int J Radiat Oncol Biol Phys. 2007;Nov 1;69(3):751–60. doi: 10.1016/j.ijrobp.2007.04.021. Epub 2007 Jun 8. PMID: 17560735.
4. Fox PC, van der Ven PF, Sonies BC, Weiffenbach JM, Baum BJ. Xerostomia: evaluation of a symptom with increasing significance. J Am Dent Assoc. 1985;Apr 110(4):519–25. doi: 10.14219/jada.archive.1985.0384. PMID: 3858368.
5. Jaguar, G.C., Prado, J.D., Campanhã, D. et al. Clinical features and preventive therapies of radiation-induced xerostomia in head and neck cancer patient: a literature review. Appl Cancer Res. 2017;37:31. https://doi.org/10.1186/s41241-017-0037-5.
6. Zhang J, Liu H, Liang X, Zhang M, Wang R, Peng G, Li J. Investigation of salivary function and oral microbiota of radiation caries-free people with nasopharyngeal carcinoma. PLoS One. 2015;Apr 10;10(4):e0123137. doi: 10.1371/journal.pone.0123137. PMID: 25860481; PMCID: PMC4393271.
7. Al-Qahtani K, Hier MP, Sultanum K, Black MJ. The role of submandibular salivary gland transfer in preventing xerostomia in the chemoradiotherapy patient. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2006;Jun 101(6):753–6. doi: 10.1016/j.tripleo.2005.12.017. Epub 2006 Apr 21. PMID: 16731395.
8. Tai J, Guo A, Chen J, Li H, Dong Q, Hao W, Wang W, Li Z, Ye J, Liu J, Yang C. Comparative efficacy and safety of non-pharmacological interventions

on treatment-induced xerostomia in head and neck cancer patients: a systematic review and network meta-analysis. Front Oncol. 2025;Jul 30;15:1644178. doi: 10.3389/fonc.2025.1644178. PMID: 40809028; PMCID: PMC12343224.
9. Nutting CM, Morden JP, Harrington KJ, Urbano TG, Bhide SA, Clark C, Miles EA, Miah AB, Newbold K, Tanay M, Adab F, Jefferies SJ, Scrase C, Yap BK, A'Hern RP, Sydenham MA, Emson M, Hall E; PARSPORT trial management group. Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial. Lancet Oncol. 2011;Feb 12(2):127–36. doi: 10.1016/S1470-2045(10)70290-4. Epub 2011 Jan 12. PMID: 21236730; PMCID: PMC3033533.
10. Kam, Michael KM et al. Prospective randomized study of intensity-modulated radiotherapy on salivary gland function in early-stage nasopharyngeal carcinoma patients. J Clin Oncol. 2007;25;31:4873–9. doi:10.1200/JCO.2007.11.5501.
11. Pow, Edmond HN et al. Xerostomia and quality of life after intensity-modulated radiotherapy vs. conventional radiotherapy for early-stage nasopharyngeal carcinoma: initial report on a randomized controlled clinical trial. Int J Radiat Oncol Biol Phys. 2006;66;4:981–91. doi:10.1016/j.ijrobp.2006.06.013.
12. Brizel, DM et al. Phase III randomized trial of amifostine as a radioprotector in head and neck cancer. J Clin Oncol. 2000;18;19:3339–45. doi:10.1200/JCO.2000.18.19.3339.
13. Johnson, JT et al. Oral pilocarpine for post-irradiation xerostomia in patients with head and neck cancer. N Engl J Med. 1993;329;6:390–5. doi: 10.1056/NEJM199308053290603.
14. Chambers, Mark S et al. Cevimeline for the treatment of postirradiation xerostomia in patients with head and neck cancer. Int J Radiat Oncol Biol Phys. 2007;68;4:1102–9. doi: 10.1016/j.ijrobp.2007.01.019.
15. Henke, Michael et al. Palifermin decreases severe oral mucositis of patients undergoing postoperative radiochemotherapy for head and neck cancer: a randomized, placebo-controlled trial. J Clin Oncol. 2011;29;20:2815–20. doi: 10.1200/JCO.2010.32.4103.
16. Meng, Zhiqiang et al. Randomized controlled trial of acupuncture for prevention of radiation-induced xerostomia among patients with nasopharyngeal carcinoma. Cancer. 2012;118;13:3337–44. doi: 10.1002/cncr.26550.
17. Pfister, David G et al. Acupuncture for pain and dysfunction after neck dissection: results of a randomized controlled trial. J Clin Oncol. 2010;28;15:2565–70. doi: 10.1200/JCO.2009.26.9860.
18. Simcock, R et al. ARIX: a randomised trial of acupuncture v oral care sessions in patients with chronic xerostomia following treatment of head and neck cancer. Ann Oncol. 2013;24;3:776–83. doi: 10.1093/annonc/mds515.
19. Antonadou, Dosia et al. Prophylactic use of amifostine to prevent radiochemotherapy-induced mucositis and xerostomia in head-and-neck cancer. Int J Radiat Oncol Biol Phys. 2002;52;3:739–47. doi:10.1016/s0360-3016(01)02683-9.
20. Epstein, J B et al. A clinical trial of bethanechol in patients with xerostomia after radiation therapy. A pilot study. Oral Surg Oral Med Oral Pathol. 1994;77;6:610–4. doi: 10.1016/0030-4220(94)90320-4.
21. Jha N, Seikaly H, Harris J, Williams D, Liu R, McGaw T, Hofmann H, Robinson D, Hanson J, Barnaby P. Prevention of radiation induced xerostomia by surgical transfer of submandibular salivary gland into the submental space. Radiother Oncol. 2003;Mar 66(3):283–9. doi: 10.1016/s0167-8140(03)00023-9. PMID: 12742268.
22. Seikaly, Hadi et al. Long-term outcomes of submandibular gland transfer for prevention of postradiation xerostomia. Arch Otolaryngol Head Neck Surg. 2004;130;8:956–61. doi: 10.1001/archotol.130.8.956.
23. Sahoo, Bijayalaxmi Sr et al. A Prospective Cohort Study Analyzing Radiation-Induced Xerostomia and Quality of Life of Head and Neck Cancer Patients Treated With Intensity-Modulated Radiotherapy and 3D Conformal Radiotherapy Techniques at a Tertiary Cancer Center in Eastern India. Cureus. 2023;15;3:e36442. doi: 10.7759/cureus.36442.
24. Blanchard P, Wong AJ, Gunn GB, Garden AS, Mohamed ASR, Rosenthal DI, Crutison J, Wu R, Zhang X, Zhu XR, Mohan R, Amin MV, Fuller CD, Frank SJ. Toward a model-based patient selection strategy for proton therapy: External validation of photon-derived normal tissue complication probability models in a head and neck proton therapy cohort. Radiother Oncol. 2016;Dec 121(3):381–386. doi: 10.1016/j.radonc.2016.08.022. Epub 2016 Sep 15. PMID: 27641784; PMCID: PMC5474306.
25. Dijkema T, Raaijmakers CP, Ten Haken RK, Roesink JM, Braam PM, Houweling AC, Moerland MA, Eisbruch A, Terhaard CH. Parotid gland function after radiotherapy: the combined michigan and utrecht experience. Int J Radiat Oncol Biol Phys. 2010; Oct 1;78(2):449–53. doi: 10.1016/j.ijrobp.2009.07.1708. Epub 2010 Jan 7. PMID: 20056347; PMCID: PMC2889151.
26. Eisbruch, A et al. Xerostomia and its predictors following parotid-sparing irradiation of head-and-neck cancer. Int J Radiat Oncol Biol Phys. 2001;50;3:695–704. doi: 10.1016/s0360-3016(01)01512-7.
27. Collan, Juhani et al. Submandibular gland-sparing intensity modulated radiotherapy in the treatment of head and neck cancer: sites of locoregional relapse and survival. Acta Oncol. 2012;51;6:735–42. doi: 10.3109/0284186X.2011.640348.
28. Wu, Fanglong et al. Submandibular gland transfer for the prevention of postradiation xerostomia in patients with head and neck cancer: a systematic review and meta-analysis. ORL J Otorhinolaryngol Relat Spec. 2015;77;2:70–86. doi: 10.1159/000371854.
29. Marta, Gustavo Nader et al. Intensity-modulated radiation therapy for head and neck cancer: systematic review and meta-analysis. Radiother Oncol. 2014;110;1: 9–15. doi: 10.1016/j.radonc.2013.11.010.
30. Gupta T, Kannan S, Ghosh-Laskar S, Agarwal JP. Systematic review and meta-analyses of intensity-modulated radiation therapy versus conventional two-dimensional and/or or three-dimensional radiotherapy in curative-intent management of head and neck squamous cell carcinoma. PLoS One. 2018;Jul 6;13(7):e0200137. doi: 10.1371/journal.pone.0200137. PMID: 29979726; PMCID: PMC6034843.
31. Riley P, Glenny AM, Hua F, Worthington HV. Pharmacological interventions for preventing dry mouth and salivary gland dysfunction following radiotherapy. Cochrane Database Syst Rev. 2017;7:CD012744.
32. Jensen SB, Pedersen AML, Vissink A, Andersen E, Brown CG, Davies AN, Xerostomia International Cooperative Group. A systematic review of salivary gland hypofunction and xerostomia induced by cancer therapies: management strategies and economic impact. Support Care Cancer. 2010;18(8):1061–1079.
33. van der Laan, Hans Paul et al. The potential of intensity-modulated proton radiotherapy to reduce swallowing dysfunction in the treatment of head and neck cancer: A planning comparative study. Acta Oncol. 2013;52;3:561–9. doi: 10.3109/0284186X.2012.692885.