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Cancer treatment-related xerostomia: basics, therapeutics, and future perspectives

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Abstract

Xerostomia, generally addressed as dry mouth, poses significant challenges to patients' quality of life, particularly in the context of cancer treatment. Although various medications and interventions, including salivary substitutes and stimulants, muscarinic agonists, antineoplastic detoxifying agents, anti-inflammatory agents, superoxide dismutase mimetics, mesenchymal stem cells, submandibular gland transfer, intensity-modulated radiation therapy, dose fractionation, transcutaneous electrical nerve stimulation, hyperbaric oxygen therapy, photobiomodulation, acupuncture, and nutritional interventions, have been proposed for this condition, no approved or definite treatments are currently available. Moreover, the evidence supporting the efficacy of proposed interventions remains limited and subject to controversy in terms of safety, efficacy, and optimal protocol. This review provides a comprehensive insight into cancer treatment-related xerostomia, underlying its pathophysiology, etiology, clinical manifestation, and therapeutic options, providing a clinical guide for clinicians to adopt a patient-tailored approach to cancer treatment-related xerostomia and offering vision on current ongoing and future studies in the field.

Keywords Cancer-related salivary dysfunction, Cancer treatment-associated xerostomia, Head and neck cancer, Muscarinic agonists, Palliative care, Radiotherapy, Xerostomia

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Background

Xerostomia, commonly known as dry mouth, is a distressing condition characterized by a patient's subjective sense of a reduced or absent saliva flow [1]. Xerostomia could be clinically accompanied by hyposalivation, also called salivary gland hypofunction [2]. It can result from various etiologies, including medications, radiation therapy, autoimmune disorders, and systemic conditions [3, 4]. This condition poses significant challenges to patients' quality of life due to increased risk of mucositis, difficulties in speaking, painful swallowing, and predisposition to oral infections. In this review, we will explore the clinical insights of cancer treatment-related xerostomia, discuss its pathophysiology, evaluate the available treatment options and ongoing candidates, and provide future perspectives.

Etiology and pathophysiology

Saliva is pivotal in maintaining oral health by lubricating the oral mucosa, facilitating speech, bolus formation, digestion, and protection against dental caries and oral infections [5, 6]. Xerostomia disrupts this delicate balance, leading to a cascade of adverse effects. Three main salivary glands, parotid, submandibular, and sublingual, along with numerous minor salivary glands distributed throughout the oral cavity, carry the duty of saliva production. Under normal physiological conditions, saliva production is regulated by a complex interplay of neural, hormonal, and local factors, including autonomic nervous system innervation and stimulation by cholinergic and adrenergic neurotransmitters [7]. Various etiologies, such as medications, radiation therapy, autoimmune diseases, and systemic conditions, can disrupt salivary gland function, resulting in xerostomia [8].

The pathophysiology of xerostomia involves dysfunction in salivary gland secretion, either due to reduced saliva production or altered saliva composition [9–13]:

- Reduced saliva production: Several factors could contribute to reduced saliva production, including:
  - Radiation therapy: As the leading cause of hyposalivation in cancer patients, radiation therapy to head, neck, and upper thoracic regions could irreversibly damage salivary gland tissues and impair their ability to produce saliva, leading to acute and chronic xerostomia.
  - Medications: Certain medications, including anticholinergics, antidepressants, antihypertensives, and antihistamines, can inhibit salivary gland secretion by blocking muscarinic receptors or interfering with neurotransmitter release.
  - Systemic diseases: Autoimmune disorders, such as Sjögren's syndrome, and systemic conditions, such as diabetes mellitus, could cause immune-mediated destruction of salivary gland tissues, resulting in xerostomia.
- Altered saliva composition: In addition to reduced saliva production, xerostomia can also result from altered saliva composition, including changes in electrolyte concentrations, pH levels, and protein content. Reduced saliva flow rates can lead to increased salivary viscosity and decreased buffering capacity, predisposing individuals to dental caries and oral infections. Altered saliva composition also affects oral mucosal integrity.

Several factors could affect the salivary glands and saliva composition, resulting in xerostomia. Table 1 summarizes the most important general causes of xerostomia. However, cancer treatment-related xerostomia could be classified to five main categories:

Radiation therapy-induced

Xerostomia is one of the most common adverse effects of radiation therapy [14, 15]. The salivary glands, including the major parotid, submandibular, and sublingual glands, are often exposed to radiation during treatment, leading to long-term and irreversible damage to the glandular tissues and impairment of saliva production.

Table 1 Causes of xerostomia

Etiology	Description
Radiation therapy and radioisotopes	Radionuclides and external radiation therapy involving the head and neck region could reversibly or irreversibly damage the salivary glands
Systemic cytotoxic chemotherapy/immunotherapy	Chemotherapeutic agents such as 5-Fluorouracil result in altered salivary gland functions
Medications	Anticholinergics, antidepressants, antihypertensives, and antihistamines are common reasons for drug-induced xerostomia
Underlying systemic disease	Sjögren's syndrome, diabetes mellitus, and autoimmune diseases can manifest with xerostomia
Dehydration	Inadequate fluid intake or conditions causing dehydration can result in transient xerostomia

Previous studies have suggested that around two-third of the patients undergoing conventional two-dimensional radiotherapy techniques experience moderate-to-severe degrees of xerostomia due to irreversible damage to salivary glands [16, 17]. Newer approaches, such as intensity-modulated radiation therapy (IMRT), come with a reduced post-radiation xerostomia incidence and enhanced salivary recovery [18, 19]. A recent meta-analysis has reported an over 70% reduction in the long-term prevalence of post-radiation xerostomia, in favor of IMRT over three-dimensional conformal radiotherapy [20]. The extent and severity of xerostomia depend on various factors, including the radiation dose, treated volume, fractionation schedule, and individual patient factors, such as age and pre-existing salivary gland dysfunction [21]. Acinar cells are highly sensitive to radiation, and direct DNA damage rapidly escalates to cell death and reduced salivary flow. The repeated cell loss from radiation-induced apoptosis and necrosis can lead to glandular atrophy [22]. Radiation results in high-volume production of reactive oxygen species (ROS), damaging cellular components through oxidative stress. Preclinical studies have demonstrated a significant overexpression of genes associated with ROS, such as NOX4, following the exposure to radiation [23]. Apart from the acute impacts of radiation on salivary glands, chronic inflammation from radiation exposure can lead to excessive deposition of extracellular matrix (ECM) proteins, such as collagen, which replaces functional glandular tissue with non-functional fibrotic tissue [24, 25]. Less common, radiation-induced ductal changes may contribute to reduced salivary output [26].

Chemotherapy-induced

Chemotherapy agents can also contribute to the development of xerostomia, either directly or indirectly [27, 28]. The mechanisms of chemotherapy-induced xerostomia are also not exactly understood. Apart from the direct cytotoxic impacts of chemotherapy agents on salivary glands, the subsequent increase in ROS production and trigger of pro-inflammatory pathways potentially affects the salivary function through structural alterations, oxidative damage, and changes in vascular permeability [17, 29, 30]. Studies have shown the impact of systemic cytotoxic chemotherapy on oral microbiome composition, which in turn could lead to oral complications, such as xerostomia [31, 32]. Moreover, some agents, such as taxanes, are linked to reduced salivary function, possibly due to their neurotoxic properties [33]. The prevalence of chemotherapy-induced xerostomia is not known well, but previous studies have reported a range of 32–93% prevalence for hyposalivation [34, 35]. Certain chemotherapeutic drugs, such as cisplatin, 5-fluorouracil (5-FU), and methotrexate, may exert toxic effects on the salivary glands, leading to reduced saliva production [36–39]. In addition, chemotherapy-induced mucositis can result in pain, discomfort, and dryness in the mouth, further exacerbating xerostomia symptoms [40, 41].

Immunotherapy-induced

Immunotherapy has emerged as a promising treatment modality for various malignancies, including head and neck cancers [42]. However, immunotherapy agents, such as immune checkpoint inhibitors (ICIs), can cause immune-related adverse events, including xerostomia [43]. Xerostomia is the most common oral immune-related adverse event (irAE). Although most studies are still ongoing, an estimated xerostomia prevalence of as high as 53–58% has been linked with ICIs in some studies [44, 45]. ICIs increase the levels of inflammatory cytokines, such as interferon-gamma (IFN-γ) and interleukin-6 (IL-6) [46]. Glandular inflammation, vascular permeability changes, and edema are well-anticipated as a result of these changes. Reports are suggesting lymphocytic infiltration as a potential cause of damage to the salivary acini and ICI-related xerostomia [47, 48]. Xerostomia associated with immunotherapy may also result from autoimmune-mediated damage to the salivary glands or secondary effects of immune activation on oral mucosal tissues [49]. However, the exact mechanisms of these effects are still under investigation [50].

Surgery-associated

Although rare, salivary gland malignancies such as mucoepidermoid carcinomas are normally removed through surgery [51]. As a result of parotidectomy, saliva production decreases, and xerostomia symptoms appear in the patient.

Graft-versus-host disease

Graft-versus-host disease (GVHD) is a common complication of allogeneic hematopoietic stem cell transplantation (HSCT), occurring when donor-derived immune cells attack the recipient tissues [52]. Oral GVHD can manifest with a range of symptoms, including xerostomia, oral mucositis, and oral ulcerations [53, 54]. Xerostomia in GVHD may result from immune-mediated damage to the salivary glands, leading to decreased saliva production and oral dryness.

Other etiologies

Some other cancer treatment-related causes could indirectly lead to xerostomia [55, 56]:

- Dehydration: Inadequate fluid intake could result in transient xerostomia, particularly in cancer patients undergoing aggressive treatments or experiencing

gastrointestinal side effects, such as nausea/vomiting or diarrhea.
- Polypharmacy: Cancer patients often receive multiple medications, including chemotherapy agents, supportive medications, and medications for comorbid conditions, many of which can contribute to xerostomia as a side effect.
- Psychological factors: Psychological stress, anxiety, and depression commonly experienced by cancer patients can also exacerbate xerostomia symptoms through effects on autonomic nervous system regulation and saliva production.

Figure 1 demonstrates the underlying etiologies and causes of treatment-related xerostomia in people with cancer.

Clinical manifestations

Patients with xerostomia may present with various accompanying symptoms, ranging from mild discomfort to severe impairment of oral functions. Common clinical manifestations include [29, 57–60]:

- Dryness: Patients complain of persistent dryness in the mouth and throat, which can be exacerbated by environmental factors, such as dry air or mouth breathing.
- Difficulty in chewing and swallowing: Reduced saliva impairs the lubrication and bolus formation, leading to difficulties in chewing and swallowing food.
- Dysphagia: Severe cases of xerostomia may result in dysphagia, making it challenging for patients even to swallow liquids (Grade IV dysphagia).
- Oral infections: Diminished saliva flow compromises the oral mucosal defense mechanism, increasing the risk of oral infections, such as candidiasis and bacterial overgrowth.
- Dental caries: Saliva is crucial in remineralizing enamel and buffering oral pH. Xerostomia predisposes individuals to dental caries and tooth decay. Radiation caries can develop shortly after radiation. Radiation can weaken the enamel, making teeth more susceptible to decay. Without sufficient saliva due to radiation-induced xerostomia, enamel demineralization accelerates and caries appear. Radiation caries typically appear with enamel craze lines, black/brownish tooth discoloration, delamination, and rapid tooth destruction or crown amputation.
- Tooth loss: Dryness, changes in the oral mucosa, and the development of dental caries may lead to permanent periodontal tissue damage and increase the risk of tooth loss.

The severity of xerostomia symptoms can vary depending on the underlying etiology, duration of the problem, and patient-centered factors, such as age, overall health status, and concomitant use of medications. Table 2 presents the standard clinical grading for xerostomia based on the Common Terminology Criteria for Adverse Events (CTCAE) [61].

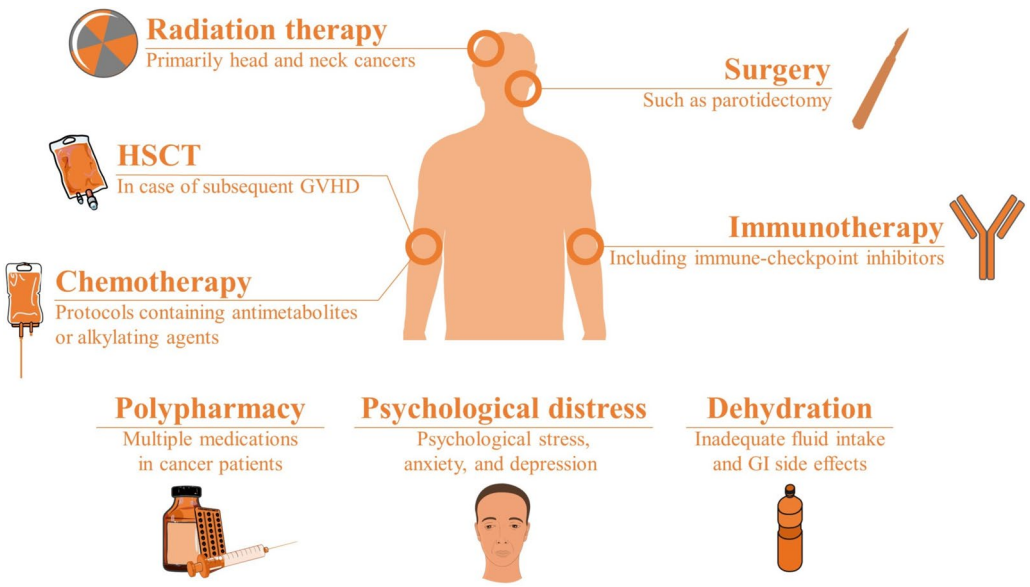

Fig. 1 Underlying causes of treatment-related xerostomia in cancer patients (*GI* gastrointestinal, *GVHD* graft vs host disease, *HSCT* hematopoietic stem cell therapy)

Table 2 Clinical grading of xerostomia, based on the common terminology criteria for adverse events (CTCAE)

Grading	Clinical implication	Unstimulated saliva flow
Grade 1 (mild)	Symptomatic, without significant dietary changes	≥ 0.2 mL/min
Grade 2 (moderate)	Symptomatic, with significant dietary changes (Large intake of water or use of other lubricants, or diet limited to soft food)	0.1–0.2 mL/min
Grade 3 (severe)	Symptomatic, with oral feeding inability—requiring enteral or parenteral nutrition	< 0.1 mL/min
Grade 4 (life-threatening)	–	–
Grade 5 (fatal)	–	–

Management

Currently, there are no approved treatments for cancer treatment-related xerostomia. However, several modalities have shown promise in preclinical and clinical studies [62]. Figure 2 presents an inclusive outline of currently suggested interventions for the management of cancer treatment-related xerostomia, their mechanisms of action, molecular/cellular targets, safety, and adverse effects, along with examples and clinical recommendations.

Pharmacological treatments

Muscarinic agonists

Muscarinic agonists, including pilocarpine and cevimeline, are currently the primary pharmacological candidates for cancer treatment-related xerostomia [63]. These agents activate the muscarinic acetylcholine receptors (mAChRs) located on the surface of salivary gland cells [64]. As a subdomain of the G protein-coupled receptors family, these receptors are predominantly of the M1 and M3 subtypes, primarily responsible for stimulating salivary gland secretion [64].

Pilocarpine is a non-selective muscarinic agonist. Upon binding to muscarinic receptors, pilocarpine activates intracellular signaling pathways that result in increased intracellular calcium levels and subsequent exocytosis of secretory vesicles [65]. This mechanism leads to enhanced saliva production and improved oral moisture, relieving symptoms of dry mouth. On the other hand, cevimeline is a selective muscarinic M1 and M3 receptor agonist that is expected to show a greater specificity for salivary gland tissue compared to pilocarpine [66]. By targeting the M3 subtype of muscarinic receptors, cevimeline specifically stimulates salivary gland secretion without significantly affecting other muscarinic receptor subtypes present in non-salivary tissues. This selective action reduces the likelihood of off-target adverse effects commonly associated with non-selective muscarinic agonists.

Both pilocarpine and cevimeline have demonstrated efficacy in increasing salivary flow rates and improving symptoms of xerostomia in patients undergoing cancer treatment [67, 68]. In general, some studies have suggested higher salivary flow in post-treatment cancer patients under cevimeline, but the differences have not been statistically significant [69]. On the other hand, apart from the etiology and considering other patients, including the ones with Sjögren's syndrome, diabetes mellitus, and other contributing diseases, studies have suggested pilocarpine with slightly higher salivary flow, which is also statistically non-significant [70]. Moreover, muscarinic agonists have also been effective in palliating other post-cancer treatment xerostomia-associated complications, such as oral mucosal inflammation and dental caries [62].

Considering the high heterogeneity of the available data, the optimum dosage of pilocarpine and cevimeline has not been determined so far; however, 5 mg and 30 mg tablets are typically recommended, respectively, both three times per day [71]. Some studies have also suggested pilocarpine administration as a mouthwash solution [72]; however, the results seem inferior to systemic administration, though inconclusive [73]. However, considering the lower adverse effects frequency and better patient compliance, topical pilocarpine is still considered an equivalent to its systemic routes of administration [67]. Several common adverse effects, including sweating, gastrointestinal discomfort, flushing, and urinary symptoms, are associated with the use of these muscarinic agonists [65]. Both medications are well-tolerated and safe, though pilocarpine has been associated with slightly higher rates of sweating, flushing, and gastrointestinal discomfort adverse effects [69].

Overall, current studies cannot determine the superiority of either medication, and the choice between pilocarpine and cevimeline should be made according to each patients' baseline characteristics, the clinical response to each medication, their subjective satisfaction with the treatment, and most importantly, the frequency and severity of adverse effects.

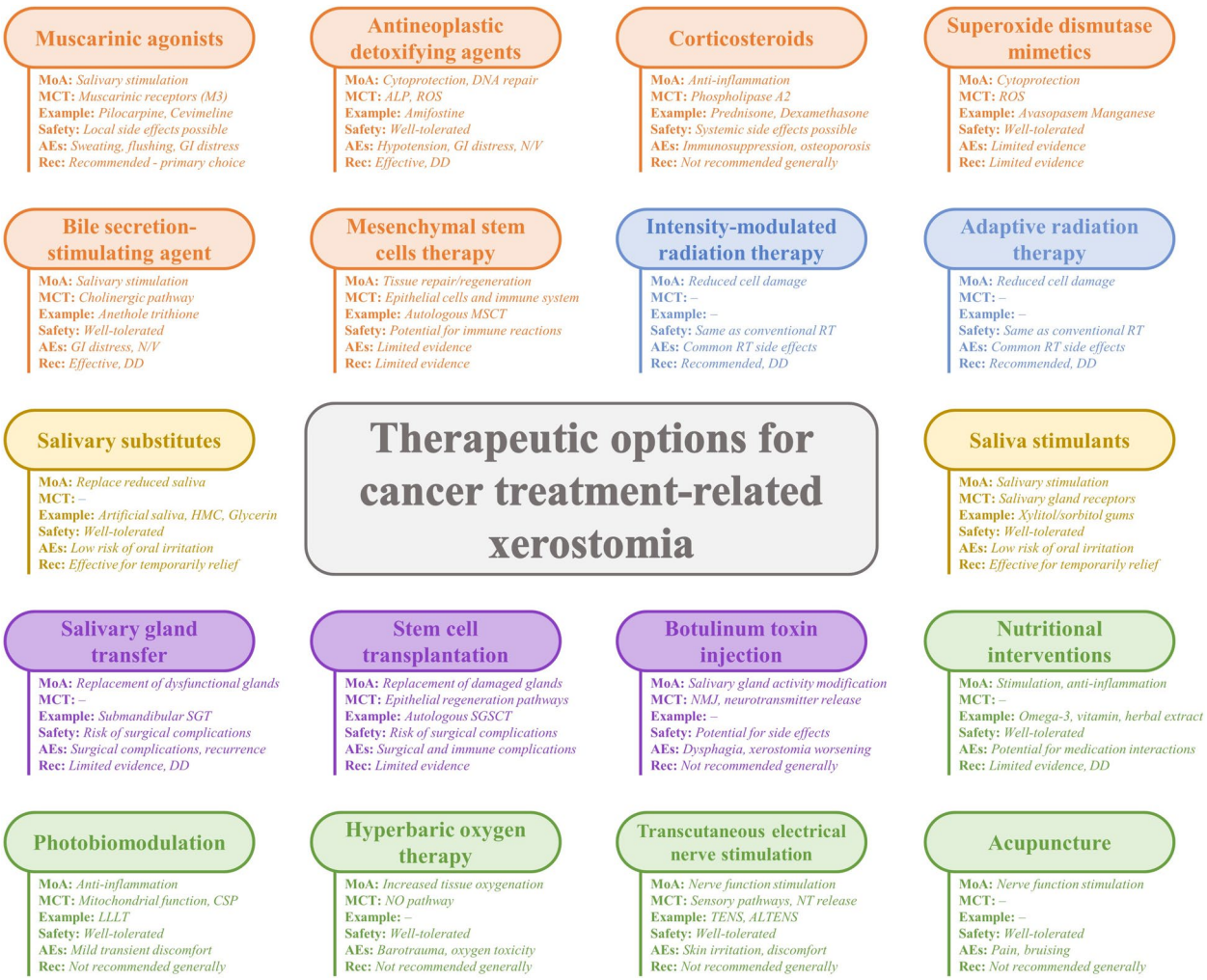

Fig. 2 Comprehensive overview of proposed interventions for cancer treatment-related xerostomia, their mechanisms of action, molecular and cellular targets, available examples, safety, adverse effects, and general recommendation (*AEs* Adverse effects, *ALP* Alkaline phosphatase, *ALTENS* Acupuncture-like Transcutaneous electrical nerve stimulation, *CSP* Cellular signaling pathways, *DD* Discretionary decision (per physician's judgement), *GI* Gastrointestinal, *HMC* Hydroxyethylcellulose, *IMRT* Intensity-modulated radiation therapy, *LLLT* Low-level laser therapy, *MCT* Molecular/cellular target, *MoA* Mechanism of action, *MSCT* Mesenchymal stem cells transplantation, *N/V* Nausea/Vomiting, *NMJ* Neuromuscular junction, *NO* Nitric Oxide, *NT* Neurotransmitter, *Rec* Recommendation, *ROS* Reactive oxygen species, *RT* Radiotherapy, *SGSCT* Salivary gland stem cells transplantation, *SGT* Salivary gland transfer, *TENS* Transcutaneous electrical nerve stimulation)

Antineoplastic detoxifying agents

Antineoplastic detoxifying agents are used to reduce the toxic effects of chemotherapy and radiation therapy on normal tissues while preserving the therapeutic efficacy against cancer cells. These agents function by various mechanisms, including scavenging free radicals, enhancing DNA repair mechanisms, and reducing inflammation and oxidative stress [74, 75]. As a promising antineoplastic detoxifying agent, amifostine transforms to free thiol metabolite by the mediating effect of alkaline phosphatase—which is observed to be significantly more active in the normal tissues than the tumor tissue—reducing radiation toxicity in non-tumor tissue [76]. In addition, amifostine is known to enhance the activity of DNA repair enzymes, reduce inflammation by suppressing the release of pro-inflammatory cytokines and chemokines, such as tumor necrosis factor-alpha (TNF-α) and IL-6, and improve tissue oxygenation by vasodilation, thereby reducing the radiation-induced hypoxic state [77]. Amifostine is generally well-tolerated among the patients [78].

Anti-inflammatory agents

Corticosteroids are one of the widely used interventions for Sjögren's syndrome-associated xerostomia, suggesting the potential applicability of these anti-inflammatory

agents to cancer treatment-related xerostomia [79]. Corticosteroids suppress the release of pro-inflammatory cytokines, such as IL-1, IL-6, and TNF-α, and increase the expression of lipocortin, therefore inhibiting the phospholipase A2 and the subsequent synthesis of inflammatory mediators, such as prostaglandins and leukotrienes [80].

Corticosteroids have been recently utilized for cancer treatment-related, mainly immunotherapy-related xerostomia [81]. However, corticosteroids are associated with a variety of potential adverse effects, ranging from hyperglycemia to osteoporosis [82]. Moreover, corticosteroids might not be administrable in some phases of cancer treatment; therefore, are less favored for this condition [83].

Superoxide dismutase mimetics

Superoxide dismutase enzymes catalyze the conversion of superoxide radicals (O_2^-) into oxygen (O_2) and hydrogen peroxide (H_2O_2), thereby neutralizing ROS and preventing oxidative damage to cellular components [84]. Superoxide dismutase mimetics, such as MnTE-2-PyP manganese porphyrin and avasopasem manganese, have been previously studied for cancer treatment-related xerostomia, showing effectiveness in reducing post-radiation xerostomia and mucositis [85–87]. However, further studies are needed to establish the efficacy and safety of these agents.

Anethole trithione

As a bile secretion-stimulating drug and dithiole–thione derivative, anethole trithione could be used to treat xerostomia due to its parasympathomimetic effects and consequent impact on salivary secretion [88]. Anethole trithione is generally well-tolerated, with some cases of gastrointestinal discomfort [88].

Autologous mesenchymal stem cells

Autologous mesenchymal stem cells have attracted attention in regenerative medicine due to their unique ability in modulating immune responses and promote tissue repair. Several preliminary studies have demonstrated the safety and clinically significant efficacy of the autologous mesenchymal stem cells for cancer treatment-related xerostomia [89, 90]. Although is not currently an optimal approach, mesenchymal stem cells could be an interesting option for future research and practice.

Symptom-based care

Oral moisturizing products

Moisturizing oral products such as oral rinses, gels, mouthwashes, lip balms, and artificial saliva can temporarily relieve xerostomia symptoms. These products often contain humectants, such as glycerin or sorbitol, which attract and retain moisture in the oral cavity [91]. Honey, aloe vera, and seaweed could act as natural humectants, briefly relieving the symptoms of xerostomia (also see 'complementary and alternative treatments') [92, 93].

Salivary substitutes

Salivary substitutes mimic the composition and function of natural saliva, providing lubrication and moisture to the oral mucosa. These substitutes generally contain carboxymethylcellulose, hydroxyethylcellulose, mucin, or glycerin as active ingredients, and are available in different forms, including gels, sprays, and lozenges [94, 95]. Salivary substitutes are available in various formulations, including sprays, gels, and lozenges. Some herbal and natural extracts, such as thyme, honey, and rice bran oil, have shown positive potential in managing xerostomia by substituting saliva and increasing the salivary flow, which are further discussed in Table 3 and the 'complementary and alternative treatments' section.

Saliva stimulants

The general concept behind using saliva-stimulating interventions is the same as the commonly prescribed muscarinic receptor agonists: relieving xerostomia symptoms by increasing saliva production. Gums, particularly the ones containing xylitol or sorbitol, natural products with citric acid, and some ginger-based supplementations have been proposed for this purpose (also see 'complementary and alternative treatments') [96].

Complementary and alternative treatments

Previous studies have suggested the potential role of several complementary and alternative treatments in ameliorating the symptoms of xerostomia and improving patients' quality of life [97]. Table 3 broadly reviews the key trials from complementary and integrative approaches to cancer treatment-related xerostomia.

Acupuncture

Acupuncture, rooted in traditional Chinese medicine, involves precise insertion of needles into specific acupoints to stimulate physiological responses [98]. Several studies have investigated the efficacy of acupuncture in managing xerostomia, particularly in patients undergoing radiation therapy for head and neck cancer [99, 100]. Acupuncture is believed to modulate salivary gland function by activating neural pathways and promoting vasodilation, leading to increased saliva production and improved oral moisture [101]. While some clinical trials have reported positive outcomes regarding subjective symptom relief and objective measures of saliva flow, the evidence remains inconclusive due to methodological

Table 3 Trials with complementary and integrative approaches to cancer treatment-related xerostomia

Author (Reference)	Year	Country	Design	Intervention	Patients and participants	Study groups	Outcomes
Garcia et al. [134]	2019	USA and China	RCT	Acupuncture	Head and neck cancer patients (339 patients)	- Standard care control (SCC): 112 patients - Intervention group (True acupuncture): 112 patients - Control group (Sham acupuncture): 115 patients	Xerostomia in the intervention group was significantly lower than in the SCC group, but the difference with the control group was not statistically significant. Symptoms were fewer and less severe 1 year after treatment compared to SCC
Simcock et al. [135]	2012	UK	Crossover RCT	Acupuncture	Patients with chronic radiation-induced xerostomia (145 patients)	- Educational oral care program - Weekly group acupuncture (8 sessions)	Acupuncture provided significantly better symptom management for patients suffering from chronic radiation-induced xerostomia. However, no significant changes were observed in objective saliva measurements
Meng et al. [136]	2011	China	RCT	Acupuncture	Nasopharyngeal carcinoma patients undergoing radiotherapy (86 Patients)	- Intervention group: 40 patients - Control group: 46 patients	The acupuncture group had a significantly lower prevalence of xerostomia and showed a preventing potential, leading to improved quality of life
Forner et al. [137]	2011	Denmark	Uncontrolled pilot study	Hyperbaric oxygen	Irradiated head and neck cancer patients (80 patients)	- Intervention group: 80 patients	Subjective improvement was reported among the patients with hyposalivation and xerostomia
Palma et al. [138]	2017	Brazil	Clinical trial	Photobiomodulation	Head and neck cancer patients with radiation-induced xerostomia (29 patients)	- Intervention group (Low-level laser therapy for 24 sessions in 3 months): 29 patients	Salivary flow rates and quality of life were improved
Louzeiro et al. [139]	2020	Brazil	RCT	Photobiomodulation	Head and neck patients undergoing radiotherapy (21 patients)	- Intervention group: 10 patients - Control group (sham group): 11 patients	The salivary flow deteriorated in both groups. No difference was observed between groups regarding salivary flow and composition, xerostomia, or quality of life

Table 3 (continued)

Author (Reference)	Year	Country	Design	Intervention	Patients and participants	Study groups	Outcomes
de Carvalho e Silva et al. [140]	2023	Brazil	RCT	Photobiomodulation and artificial saliva	Patients with head and neck squamous cell carcinoma (53 patients)	- Intervention group (artificial saliva and photobiomodulation) - Control group (artificial saliva and sham laser simulation)	The intervention group experienced a significantly improved state of xerostomia and quality of life. The groups had no significant difference in the DMFT index or periodontal charts
Nuchit et al. [141]	2020	Thailand	RCT	Saliva substitutes (Oral moisturizing jelly versus a topical saliva gel)	Post-radiation head and neck cancer patients (62 patients)	- Intervention group 1 (OMJ): 31 patients - Intervention group 2: 31 patients	Continuous use of saliva substitutes (OMJ or SG) for over 1 month improves xerostomia, enhancing the swallowing ability. Edible OMJ is superior to topical SG
Apperley et al. [142]	2017	New Zealand	Crossover RCT	Emulsion of rice bran oil, soy lecithin, and propylene glycol	Patients treated with head and neck radiotherapy (40 patients)	- Intervention group (emulsion) - Control group 1 (methylcellulose) - Control group 2 (water)	None of the products showed a significant difference in patient outcomes
Rupe et al. [143]	2023	Italy	Crossover RCT	Sodium-hyaluronate mouthwash	Patients with head and neck cancer (39 patients)	- Intervention group (GUM Hydral®) - Control group (Placebo)	The intervention significantly reduced the symptoms of xerostomia. The intervention group had higher reported satisfaction levels among the patients
Beuth et al. [144]	2013	Germany	Clinical trial	A combination of sodium selenite, proteolytic plant enzymes (bromelain and papain), and Lens culinaris lectin	Breast cancer patients undergoing adjuvant hormone therapy (310 patients)	- Intervention group: 310 patients	Almost two-thirds of patients with severe mucosal dryness significantly benefited from complementary medicine. Side-effects of hormone therapy were significantly reduced after 4 weeks
Heydarirad et al. [145]	2017	Iran	RCT	*Alcea digitata* and *Malva sylvestris*	Head and neck cancer patients (60 patients)	- Intervention group: 30 patients - Control group: 30 patients	In the intervention group, a significant improvement in quality of life, pain, and ease of swallowing, speaking, and eating was observed
Quimbt et al. [146]	2020	Canada	Uncontrolled pilot study	Coconut oil	Post-radiation head and neck cancer patients (30 patients)	- Intervention group: 30 patients	No significant difference was observed before and after the intervention

Table 3 (continued)

Author (Reference)	Year	Country	Design	Intervention	Patients and participants	Study groups	Outcomes
Charalambou et al. [147]	2018	Cyprus	RCT	Thyme honey rinses	Head and neck cancer patients (72 patients)	- Intervention group: 36 - Control group (saline rinses): 36	The intervention group had significantly lower grades of xerostomia. Patients' quality of life was also significantly higher in the intervention group
Chamani et al. [148]	2017	Iran	RCT	Ginger capsule	Patients with post-radiotherapy xerostomia (61 patients)	- Intervention group: 30 patients - Control group (Placebo): 31 patients	Although the intervention group had a marginally improved status, no significant difference was observed between groups
Chung et al. [149]	2016	South Korea	RCT	Antioxidant supplements (vitamin E + vitamin C)	Head and neck cancer patients with radiotherapy-induced xerostomia (45 patients)	- Intervention group: 25 patients - Control group (Placebo): 20 patients	The intervention group showed significant long-term improvement compared to the control group
Heiser et al. [150]	2016	Germany	Clinical trial	Liposomal nose and mouth spray (LipoNasal, LipoSaliva)	Head and neck cancer patients (98 patients)	- Intervention groups (three subgroups per cancer treatment): 98 patients	A positive subjective outcome was observed, which could suggest liposomal sprays as a first-line treatment due to their safety
Steinmann et al. [151]	2012	Germany	Non-randomized trial	Homeopathy (Mouth rinses with either Traumeel S solution or *Salvia officinalis*)	Patients under radiation therapy for head and neck cancer (20 patients)	- Intervention group (Traumeel S): 10 patients - Control group (sage tea or *Salvia officinalis*): 10 patients	No significant difference was observed among the study groups
Dalbem Paim et al. [152]	2019	Brazil	RCT	Transcutaneous electrical nerve stimulation (TENS)	Post-radiation head and neck cancer patients (68 patients)	- Intervention group (TENS): 37 patients - Control group: 31 patients	The intervention group showed a progressive increase in salivary flow in long-term follow-up
Wong et al. [153]	2015	USA	Clinical trial	Acupuncture-like transcutaneous electrical nerve stimulation (ALTENS)	Patients with post-radiation xerostomia (146 patients)	- Intervention group 1 (ALTENS): 75 patients - Intervention group 2 (Oral Pilocarpine): 73 patients	No significant difference was observed between the groups. However, less toxicity was seen in patients receiving ALTENS. Radiation-induced xerostomia improved over time for all patients

ALTENS Acupuncture-like transcutaneous electrical nerve stimulation, *DMFT index* decayed, missing, and filled teeth index, *OMJ* Oral moisturizing jelly, *RCT* randomized controlled trial, *SG* Saliva gel, *TENS* Transcutaneous electrical nerve stimulation

limitations and heterogeneity among study designs (Table 3) [102]. Moreover, recent evidence-based studies have revealed no clinically significant efficacy of acupuncture in the treatment of radiation-induced xerostomia [103]. Further well-designed randomized controlled trials (RCTs) are required to clarify the efficacy and optimal treatment protocols of acupuncture for xerostomia.

Nutritional interventions

Many nutraceuticals have garnered interest in managing xerostomia due to their antioxidative, anti-inflammatory, and mucoprotective properties. Examples of nutraceuticals studied for xerostomia include omega-3 fatty acids, vitamin C, vitamin E, and herbal extracts, such as green tea polyphenols and aloe vera [104–106]. These compounds are hypothesized to alleviate xerostomia symptoms by reducing oxidative stress, inflammation, and mucosal damage. While some preclinical and clinical studies have shown promising results in improving saliva flow rates and subjective symptom relief, the evidence remains limited, and further research is needed to establish their efficacy, optimal dosing regimens, and long-term safety profiles. Avoidance of caffeine, alcohol, and tobacco can also help mitigate xerostomia symptoms, as these substances can exacerbate dry mouth [107, 108].

Photobiomodulation

Photobiomodulation has been investigated for its potential to stimulate salivary gland function and increase saliva production in patients with xerostomia. Low-level laser therapy applied to the salivary glands may enhance cellular metabolism, promote tissue repair, and modulate inflammatory responses, leading to improved salivary flow rates and alleviation of xerostomia symptoms [109, 110].

Xerostomia often involves inflammatory changes in the salivary glands and oral mucosa and photobiomodulation has anti-inflammatory effects [111]. By modulating inflammatory mediators and cytokines, photobiomodulation may palliate tissue damage, enhance tissue repair processes, and alleviate symptoms associated with oral dryness and discomfort. In addition, photobiomodulation could promote minimum analgesic effects by modulating pain perception, reducing nerve sensitivity, and promoting the release of endogenous opioids, providing brief symptomatic relief of xerostomia-related pain and enhancing the patient's quality of life [112, 113]. There are significant variations in procedures among studies regarding the number of points, energy, and density, but generally, parotid and submandibular glands were treated through extraoral protocols at 808 nm, while sublingual glands followed the extraoral protocols at 660 nm. Nevertheless, most clinical evidence only shows subjective improvement in patients' symptoms (Table 3).

Transcutaneous electrical nerve stimulation

Transcutaneous electrical nerve stimulation (TENS) is a non-invasive modality involving the application of low-voltage electrical currents through electrodes placed on the skin. While TENS is primarily used for pain management, it has also been explored for its potential therapeutic effects in various medical conditions, including xerostomia [114]. The electrical stimulation delivered by TENS could directly stimulate nerve fibers innervating the salivary glands, potentially enhancing neural signaling and promoting salivary flow [115]. TENS could stimulate the release of endogenous opioids, relieving xerostomia-related symptoms and pain. It may also improve blood flow to the salivary glands and surrounding tissues [114]. TENS protocols also vary significantly among the studies, with frequency starting from 4 Hz, pulse width of 250 μs–250 ms, and sessions ranging from 5 to 20 min [116]. The current studies on TENS present lower levels of evidence with limited confidence in results for clinical use. Similar to photobiomodulation, TENS requires extensive future studies to ensure efficacy and become integrated into the conventional approach to this condition.

Hyperbaric oxygen therapy

Hyperbaric oxygen therapy delivers high concentrations of oxygen to tissues, reducing inflammation and improving the oxygenation of hypoxic tissues. While hyperbaric oxygen therapy is primarily used to treat conditions, such as decompression sickness and gas embolism, it has also been explored for its potential therapeutic effects in various medical conditions, including xerostomia. The primary idea behind the initial use of hyperbaric oxygen for this condition is the promotion of neovascularization and nitric oxide pathway in hypoxic tissues, suppressing pro-inflammatory cytokines, and modulating immune cell function in salivary glands [117].

Meanwhile, hyperbaric oxygen could also result in barotrauma, oxygen toxicity, and claustrophobia in occasional cases. Overall, this intervention could lead to long-term subjective satisfaction of patients, but the available evidence does not demonstrate objective clinical significance [118, 119].

Homeopathic treatments

Homeopathic treatments involve using highly diluted natural substances, typically derived from plants or minerals, to stimulate self-healing mechanisms and restore balance. In the context of xerostomia, homeopathic treatments aim to address the underlying causes of dry mouth symptoms and promote salivary gland function and oral

moisture. Homeopathic remedies for oral complications of cancer may include substances, such as *Hypericum*, *Arsenicum album*, *Matricaria chamomilla*, or *Salvia officinalis* [120, 121]. Nevertheless, the impact of homeopathic treatments on xerostomia is a subject of serious debate, since the scientific basis and efficacy of these interventions are questionable, and the available studies are limited, doubtful, and inconclusive [122].

Surgical approach

Submandibular salivary gland transfer

One of the widely known suggested approaches to cancer treatment-related xerostomia is the submandibular salivary gland transfer [123]. The relocation of the healthy submandibular salivary gland from its original anatomical location to a site outside the radiation field, typically in the submental region, could improve the salivary flow rates [124]. However, studies have reported variable outcomes following surgery, with some patients experiencing significant improvements in oral moisture and quality of life, while others may have more modest or transient benefits. Several factors, including patients' characteristics, timing of surgery relative to radiation therapy, surgical technique, and postoperative management, could impact the outcomes. Besides, this approach makes the patients prone to surgical complications, such as surgical site infection or hematoma, salivary fistula, vascular compromise of the transferred gland, or transient/permanent facial nerve injury.

Autotransplantation and stem cell transplantation

There are some reports of successful intervention for post-radiation xerostomia using autotransplantation of cryopreserved minor salivary glands [125]. Autologous salivary gland stem cell transplantation has also been around for over a decade, showing impressive outcomes [126]. However, lack of long-term follow-up data, financial burdens, and non-applicability for all patients have limited the clinical pertinence of these approaches.

Botulinum toxin injection

Although botulinum toxin injection has been suggested to prevent radiation-induced sialadenitis, studies have shown a generally reduced salivary flow, which would lead to worsening symptoms in patients with xerostomia [127]. In general, patients with cancer treatment-related xerostomia might not benefit from botulinum toxin injection.

Gland-preserving radiation therapy techniques

As an effective preventive measure, techniques such as IMRT or proton therapy may be employed to minimize radiation exposure to the salivary glands.

Intensity-modulated radiation therapy

IMRT is a radiation technique that delivers highly conformal doses of radiation to the tumor target while minimizing radiation exposure to surrounding normal tissues, such as salivary glands [128]. IMRT uses multiple radiation beams that can be modulated in intensity and directed from different angles to precisely shape the radiation dose distribution and spare critical structures, such as the salivary glands. By optimizing the radiation dose distribution, IMRT reduces the risk of radiation-induced damage to the salivary glands and preserves salivary function.

Proton therapy

Proton therapy is an advanced form of radiation therapy that uses protons, rather than conventional photons, to deliver radiation to the tumor target. Proton therapy offers the advantage of delivering radiation with greater precision and sparing healthy salivary glands from unnecessary radiation exposure [129].

Adaptive radiation therapy

Adaptive radiation therapy (ART) involves the real-time monitoring and adjustment of radiation therapy based on changes in tumor size, shape, and position during the course of treatment. This technique facilitates monitoring anatomical changes and could help minimize radiation exposure to salivary glands. However, recent studies have shown non-superiority of ART compared to IMRT [130].

Dose fractionation

Dose fractionation refers to delivering radiation therapy in smaller, divided doses over multiple treatment sessions, rather than in a single high-dose fraction. Fractionating the radiation dose allows for the repair of sublethal damage to normal tissues between treatment sessions, reducing the risk of acute and late radiation-induced xerostomia [131].

Salivary gland shields and positioning stents

During radiation therapy planning, customized shielding blocks or devices could be positioned to physically shield the salivary glands from direct radiation exposure. Positioning stents are simple and available options that have shown effectiveness in preventing mid-term complications, such as xerostomia, as higher salivary flow rates have been reported within 6 months after radiation [132, 133]. However, the level of evidence is still weak, and more studies are required [133].

Ongoing studies and future directions

Several studies are being conducted worldwide to find the optimum treatment of choice for cancer treatment-related xerostomia. Table 4 summarizes the ongoing trials of potential candidates for this condition.

Future studies, specifically, randomized controlled trials, with larger sample sizes and longer follow-up durations, are required to evaluate the efficacy, safety, and optimal treatment protocols of the discussed modalities. Considering the high prevalence of post-treatment xerostomia in cancer patients and the lack of approved treatments, this subject requires more attention and collaborative efforts, using multidisciplinary teams of medical, surgical, and radiation oncologists, palliative care physicians and nurses, dentists, and otolaryngologists. Standardized outcome measures are needed to consistently assess subjective symptom relief, objective salivary flow rates, and patient-reported outcomes across studies. Moreover, most of the current evidence with complementary and non-conventional interventions exclude patients with a history of cancer or prior head and neck radiation therapies, which results in limited insight into the management of cancer treatment-related xerostomia. While complementary therapies offer potential benefits, the limitations of the existing evidence should be considered, including the heterogeneity among study designs, lack of reproducibility due to subjective assessment,

Table 4 Active and ongoing trials for management of cancer treatment-related xerostomia

Country	Study design	Study population	Intervention(s)	Source ID (clinicaltrials.gov)
USA	Randomized, multicenter, double-blinded, controlled trial	Adults with radiation-induced late xerostomia	AAV2-hAQP1 Gene therapy	NCT05926765
USA	Dose-escalation phase I trial	Post-radiation adults with head and neck cancer	AAV2-hAQP1 Gene therapy	NCT02446249
Denmark	Randomized, single-center, double-blinded, controlled trial (phase II)	Post-radiation adults with head and neck cancer	Mesenchymal stem cells	NCT04776538
Denmark	Non-randomized phase I	Post-radiation adults with oropharynx cancer	Mesenchymal stem cells	NCT03874572
USA	Dose-escalation phase I trial	Adult head and neck cancer patients	Bone marrow cell transplantation into the salivary glands	NCT05820711
Brazil	Randomized, multicenter, single-blinded controlled clinical trial	Post-radiation adults with head and neck cancer	Photobiomodulation (Intraoral and extraoral)	NCT05242991
Brazil	Randomized, multicenter, single-blinded clinical trial	Adult patients undergoing hematopoietic cell transplantation	Photobiomodulation (Intraoral and extraoral)	NCT05759975
Spain	Randomized, single-center, double-blinded controlled trial	Adult head and neck cancer patients	Photobiomodulation (Intraoral and extraoral—along with M-health tool)	NCT05106608
USA	Single-arm prospective study	Post-radiation adults with head and neck cancer	Non-invasive acupuncture-like transcutaneous electrical nerve stimulation (ALTENS)	NCT04805528
USA and China	Randomized, multicenter, controlled trial	Adults with head and neck cancer, scheduled to undergo IMRT	Acupuncture	NCT01266044
France	Randomized, multicenter, single-blinded clinical trial	Adult head and neck cancer patients	Auriculotherapy	NCT04222478
Denmark	Single-arm pilot trial	Post-radiation adults with head and neck cancer	Craniosacral therapy	NCT05882890
France	Randomized, single-center, controlled trial	Post-radiation adults with head and neck cancer	Corticosteroids	NCT04584164
Cyprus	Randomized, multicenter, double-blinded controlled trial	Adult head and neck cancer patients undergoing radiotherapy	Thyme and honey spray	NCT04880148
China	Randomized, multicenter, non-inferiority, controlled trial	Adult patients with nasopharyngeal carcinoma	Intensity-modulated radiation therapy (IMRT)	NCT06282497
Switzerland	Single-arm trial	Adults with head and neck cancer	Adaptive radiation therapy	NCT03972072
USA	Randomized, single-center, controlled trial	Adults with squamous cell carcinoma of the head and neck	IMRT (margin-based vs. robust photon radiation therapy planning)	NCT03552965

AAV2-hAQP1 Adeno-associated viral vector encoding human Aquaporin-1, *ALTENS* Acupuncture-like transcutaneous electrical nerve stimulation, *IMRT* Intensity-modulated radiation therapy

variability in treatment protocols, and potential placebo effects.

Conclusions

Cancer treatment-related xerostomia is a complex and multifactorial condition that significantly impacts patients' quality of life. Clinicians should be skilled at recognizing serious cases of xerostomia and implementing appropriate management strategies tailored to individual patient needs. Muscarinic agonists, novel radiation therapy approaches, salivary substitutes, saliva stimulants, oral moisturizing products, and nutritional supplementations have shown the potential for improving xerostomia symptoms and patients' oral health and well-being; however, the current evidence is limited and, in some cases, probably biased, due to protocol variabilities and potential placebo effects. Further research is required to ensure the efficacy and safety of the proposed treatments and to develop well-tolerated protocols for xerostomia management in patients with cancer.

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