UNIVERSIDADE FERNANDO PESSOA

TREATMENT OF RADIO-INDUCED XEROSTOMIA IN HEAD AND NECK CANCER PATIENTS. A SYSTEMATIC REVIEW

[Tratamento da xerostomia radioinduzida em pacientes com cancro de cabeça e pescoço. Uma revisão sistemática]

Dissertação de Mestrado

[Mestrado Integrado de Medicina Dentária]

Francesco Guarino

Orientadora:

Mestre Filipa Pinto de Oliveira

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Dedicated to my family, who have always believed in me.

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Thanks to my teacher for her unwavering support throughout the project.

Thanks to my parents for their constant encouragement and backing.

Thanks to my wife, Roberta, for standing by me during this challenging journey.

And thanks to my little Beatrice for making this moment even more special.

ABSTRACT

Introduction: Xerostomia is a debilitating condition characterized by reduced or absent saliva production. This issue is particularly common in patients undergoing radiotherapy for head and neck cancers, as the salivary glands are often affected by radiotherapy treatments. Patients suffering from xerostomia may experience difficulties in swallowing, speaking, and sleeping. Furthermore, the lack of saliva increases the risk of oral infections, dental caries, and taste disorders, negatively impacting their quality of life.

Objective: This systematic literature review aims to examine the therapies currently available for managing radiotherapy-induced xerostomia, analyzing their effectiveness and impact on patients' quality of life. The question this thesis aims to answer is: “What are the treatment options available for patients treated with radiotherapy for head and neck cancer?”.

Methodology: To structure this investigation, the PICO model was used. Several electronic databases will be utilized, including PubMed, B-On, and the Cochrane Library. Articles will be searched using the following keywords: "Radiotherapy," "Oral cancer," "xerostomia”, “Treatment”, while excluding "Chemotherapy." These terms will be combined in various ways using the Boolean operators "OR," "AND," and "NOT." Our inclusion criteria were human clinical trials. The exclusion criteria were: systematic reviews, meta-analyses, studies in animals, and articles in languages other than English. The systematic review was carried out in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).

Results: Pilocarpine, which stimulates saliva production, remains one of the most well-established treatments. Acupuncture is a valid alternative when available, especially for patients who prefer non-pharmacological therapies. Sodium-hyaluronate mouthwash is useful as a short-term supportive measure. Low-level laser therapy, stem-cell injections, the vitamin C/E complex, and experimental topical sprays show promising results but require larger randomized trials before their comparative effectiveness can be defined. No study has reported serious treatment-related adverse events. The side effects noted (sweating with pilocarpine, mild swelling after stem-cell injections, and small bruises or hematomas from acupuncture) were rare.

Conclusions: RIX (Radiotherapy-Induced Xerostomia) remains a significant clinical issue that compromises the quality of life of head and neck cancer (HNC) survivors. Future research should focus on rigorous, large-scale trials with prolonged follow-up and standardized outcomes to establish the definitive effectiveness of these interventions and guide clinical practice in managing RIX.

Keywords: Radiotherapy; Oral Cancer; Xerostomia; Treatment

RESUMO

Introdução: A xerostomia é uma condição debilitante caracterizada pela produção reduzida ou ausente de saliva. Este problema é particularmente comum em doentes submetidos a radioterapia para cancros da cabeça e pescoço, visto que as glândulas salivares são frequentemente afetadas pelos tratamentos. Os pacientes com xerostomia podem apresentar dificuldades em engolir, falar e dormir. Além disso, a falta de saliva aumenta o risco de infeções orais, cáries dentárias e distúrbios do paladar, afetando negativamente a qualidade de vida.

Objetivo: Esta revisão sistemática da literatura tem como objetivo analisar as terapias atualmente disponíveis para o controlo da xerostomia induzida pela radioterapia, avaliando a sua eficácia e o impacto na qualidade de vida dos pacientes. A pergunta que a presente tese procura responder é: "Quais são as opções de tratamento disponíveis para doentes submetidos a radioterapia por cancro da cabeça e pescoço?".

Metodologia: Para estruturar esta investigação, foi utilizado o modelo PICO. Foram consultadas várias bases de dados eletrónicas, incluindo PubMed, B-On e Cochrane Library. Os artigos foram pesquisados com as seguintes palavras-chave: "Radiotherapy", "Oral cancer", "xerostomia", "Treatment", excluindo "Chemotherapy". Estes termos foram combinados de várias formas através dos operadores booleanos "OR", "AND" e "NOT". Os critérios de inclusão foram ensaios clínicos em humanos. Os critérios de exclusão foram: revisões sistemáticas, meta-análises, estudos em animais e artigos em idiomas diferentes do inglês. A revisão sistemática foi conduzida de acordo com as diretrizes da Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Resultados: A pilocarpina, que estimula a produção de saliva, continua a ser um dos tratamentos mais consolidados. A acupuntura é uma alternativa válida quando disponível, sobretudo para doentes que preferem terapias não farmacológicas. O colutório à base de hialuronato de sódio é útil como medida de suporte a curto prazo. A terapia laser de baixa potência, as injeções de células-estaminais, o complexo vitamínico C/E e os sprays tópicos experimentais apresentam resultados promissores, mas exigem ensaios randomizados de maior dimensão antes de se poder definir a sua eficácia comparativa. Nenhum estudo relatou eventos adversos graves relacionados com o tratamento. Os efeitos secundários observados (sudorese com a pilocarpina, ligeiro edema após as injeções de células-estaminais e pequenas equimoses ou hematomas provenientes da acupuntura) foram raros.

Conclusões: A xerostomia induzida pela radioterapia (RIX) permanece um importante problema clínico que compromete a qualidade de vida dos sobreviventes de cancro da cabeça e pescoço. Investigações futuras devem focar-se em ensaios rigorosos, de grande escala, com seguimento prolongado e desfechos padronizados, de modo a estabelecer a eficácia definitiva destas intervenções e orientar a prática clínica no manejo da RIX.

Palavras-chave: Radioterapia; Cancro Oral; Xerostomia; Tratamento.

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LIST OF ABBREVIATIONS AND ACRONYMS

3D-CRT	Three-Dimensional Conformal Radiation Therapy
ASCs	Mesenchymal Stem Cells
DMSO	Dimethyl sulfoxide
FACT-G	Functional Assessment of Cancer Therapy-General
GRIX	Groningen Radiotherapy-Induced Xerostomia
IMRT	Intensity-Modulated Radiotherapy
LLLT	Low-Level Laser Therapy
N/A	Not/Applicable
OHIP-14	Oral Health Impact Profile - 14
OSCC	Oral Squamous Cell Carcinoma
POCRT	Post-operative chemoradiotherapy
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
QoL	Quality of Life
RIX	Xerostomia Radio-Induction
SA	Sharm Acupuncture
SD	Standard Deviation
SFR	Salivar flow rate
SG	Salivar Glands
SOH	Standard Oral Hygiene
SWS	Stimulated Whole Saliva Flow Rate
SWSF	Stimulated Whole Saliva Flow
TA	True Acupuncture
UFS	Unstimulated Whole Salivary Flow Rate

UW-QoL	Quality of Life Score
UWS	Unstimulated Salivary Flow Rate
XI	Xerostomia Inventory
ZXQ	Zimmerman Xerostomia Questionnaire

1. INTRODUCTION

Head and neck cancer (HNC) represents a heterogeneous group of neoplasms with a significant global incidence (Jakobsen et al., 2024; Rupe et al., 2023). Radiotherapy (RT), often used in combination with surgery and/or chemotherapy, constitutes one of the main therapeutic modalities for many of these tumours (Palma et al., 2017; Porangaba et al., 2024). Although RT is effective in tumour control, it can cause damage to surrounding healthy tissues, particularly the salivary glands, which are highly radiosensitive (Jakobsen et al., 2024; Palma et al., 2017).

One of the most common and debilitating consequences of RT in the head and neck region is radiation-induced xerostomia (RIX) (Palma et al., 2017; Porangaba et al., 2024). This condition is characterized by the subjective sensation of dry mouth (Kaae et al., 2020; Porangaba et al., 2024) and/or an objective reduction in salivary flow (hyposalivation) (Jakobsen et al., 2024; Kaae et al., 2020). RIX is a frequent, often chronic, and sometimes irreversible side effect (Agrawal et al., 2022), affecting a high percentage of patients, up to 80% (Chung et al., 2016; Jakobsen et al., 2024), significantly compromising their quality of life (QoL) (Cohen et al., 2024; Paterson et al., 2019).

The quantitative reduction and qualitative alterations in saliva – such as increased viscosity (Kaae et al., 2020; Porangaba et al., 2024) and pH changes (Palma et al., 2017) – cause a series of problems: oral discomfort (Rupe et al., 2023), pain (Cohen et al., 2024), difficulties with speech (Cohen et al., 2024; Palma et al., 2017; Rupe et al., 2023), chewing (Cohen et al., 2024; Kaae et al., 2020), and swallowing (Palma et al., 2017; Rupe et al., 2023), altered taste (Paterson et al., 2019; Rupe et al., 2023), sleep disturbances (Agrawal et al., 2022; Cohen et al., 2024), and an increased risk of dental caries and oral infections (Kaae et al., 2020; Palma et al., 2017; Porangaba et al., 2024; Rupe et al., 2023). With increasing survival rates for HNC patients, particularly in younger patients with HPV-related tumours (Paterson et al., 2019), the effective management of long-term toxicities like RIX becomes crucial (Kaae et al., 2020).

Despite the development of radiotherapy techniques aimed at sparing salivary glands, such as intensity-modulated radiotherapy (IMRT) (Chung et al., 2016; Porangaba et al., 2024), and the use of pharmacological agents like sialogogues (e.g., pilocarpine; Chung et al., 2016; Pereira et al., 2020) or cytoprotectants (e.g., amifostine; Cohen et al., 2024),

RIX remains a significant clinical challenge (Jakobsen et al., 2024). To date, there is no universally effective definitive treatment to prevent or reverse radiation-induced damage to the salivary glands (Cohen et al., 2024; Jakobsen et al., 2024; Palma et al., 2017; Paterson et al., 2019). Management is often limited to symptomatic relief (Jakobsen et al., 2024; Kaae et al., 2020), highlighting the need for new therapeutic strategies (Jakobsen et al., 2024).

In this context, various types of interventions have been investigated. This systematic review aims to critically analyze the scientific evidence from recent randomized clinical trials (RCTs) focused on the management of RIX in patients treated for HNC. The studies included in this review, conducted by Cohen et al. (2024), Jakobsen et al. (2024), Palma et al. (2017), Pereira et al. (2020), Agrawal et al. (2022), Chung et al. (2016), Paterson et al. (2019), Porangaba et al. (2024), Rupe et al. (2023), and Kaae et al. (2020), evaluate the efficacy and safety of diverse therapeutic approaches, including acupuncture, stem cell therapy, low-level laser therapy (LLLT), pharmacological agents (pilocarpine, vitamins), salivary substitutes/stimulants, and mechanical stimulation (chewing gum).

The objective of this thesis is therefore to systematically synthesize and analyze the results of the selected randomized clinical trials, in order to evaluate the effectiveness and safety of these interventions in reducing xerostomia, improving salivary function, and enhancing the quality of life in patients previously treated with radiotherapy for head and neck cancer.

1.1. Materials and methods

The protocol on the methodology of this systematic review is registered under number CRD420251020798 on the PROSPERO platform.

This systematic review as conduced according to PRISMA (Preferred Reporting Items for Systematic review and Meta-Analyses) statement.

To develop the research question, PICO parameters (Population; Interventions; Comparison e Outcome) were employed (cf. Table 1). Two questions were developed:

- What treatment options are available for head and neck cancer patients who have received radiotherapy to address xerostomia?
- Does the amount of saliva imply a change in quality of life?

Table 1

PICO Strategy

Criteria	Determinants
P (Population)	Patients with head and neck cancer treated with radiotherapy who suffer from xerostomia
I (Intervention)	Pharmacological and non-pharmacological interventions aimed at reducing oral dryness or stimulating salivation
C (Comparison)	No treatment ou placebo
O (Outcome)	Improvement of quality of life and reduction of xerostomia symptoms

To conduct this study, an electronic literature search was performed in the PubMed, B-ON, and Cochrane Library databases.

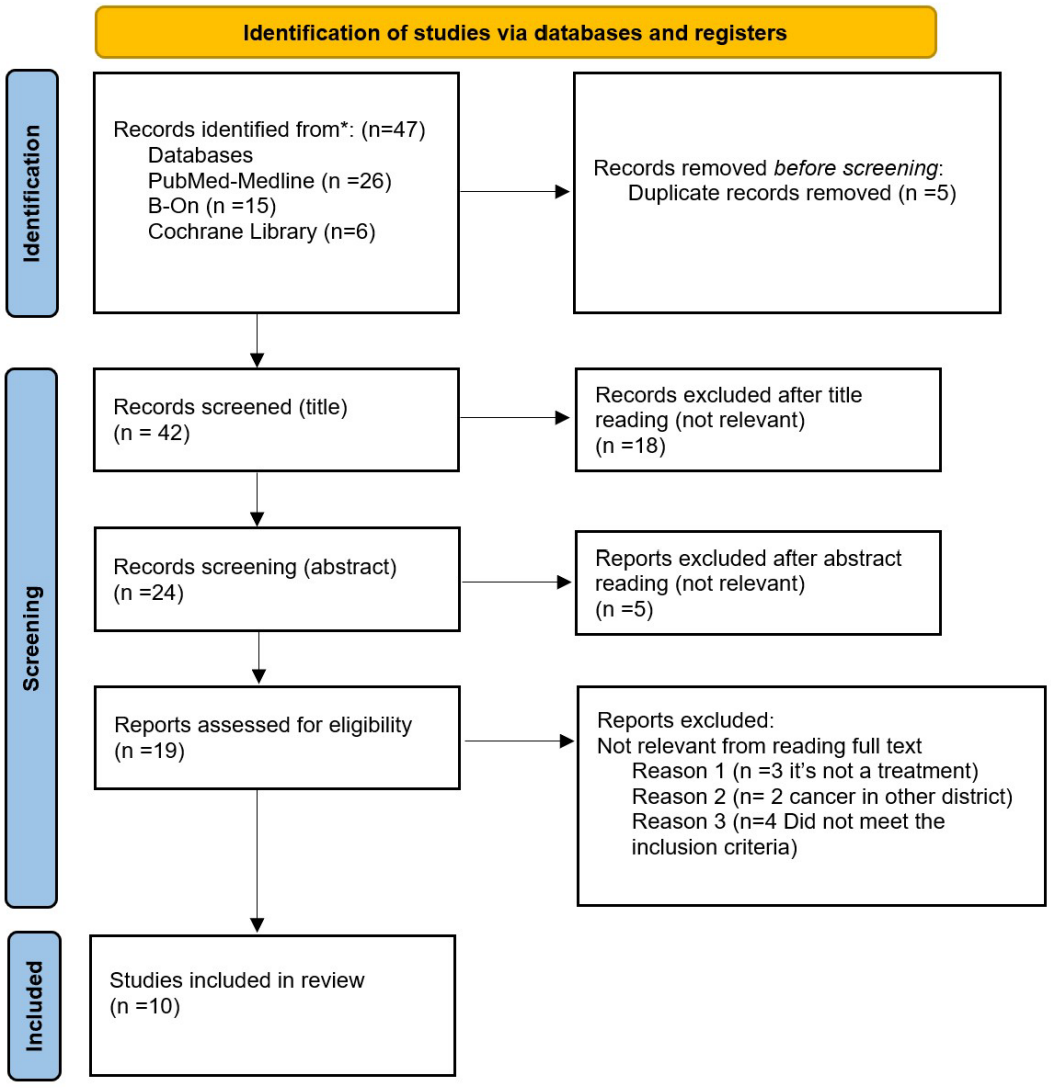
The search was carried out between October 2024 and December 2024, using the keywords “radiotherapy,” “oral cancer,” “xerostomia,” “treatment,” combined with the boolean connector “AND,” and “chemotherapy” combined with the boolean connector “NOT.”

Our inclusion criteria were human Clinical Trial and Randomized Controlled Trial in the last 10 years. The exclusion criteria were: systematic review, meta-analyses, studies in animals and articles in languages other than English.

Initially, a total of 47 articles were identified, distributed as follows: PubMed (26), B-On (15), and Cochrane Library (6). After reading the titles and abstracts, those that were not sufficiently aligned with the topic under study or whose availability proved impractical were discarded. Subsequently, the final screening phase was carried out after a complete analysis of each article's content, resulting in a final selection of 10 articles (cf. Figure 1).

Figure 1

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only



In the present analysis, the Cochrane Risk of Bias 2 (RoB 2) tool was used to evaluated each article for the risk of bias. This is a validated and widely recognized instrument for assessing the risk of bias in randomized clinical trials. RoB 2 comprises five main domains, each accompanied by specific questions whose responses allow classification of the risk of bias as low, moderate, or high. These domains cover the full spectrum of potential methodological distortions: from the generation and concealment of the randomization sequence, to the blinding of participants and outcome assessors, and finally to the handling of missing data and the selection of reported results.

For this purpose, software provided on the Cochrane website was used, which

systematically guides the completion of the questions for each domain and automatically generates the risk of bias judgments (Low Risk, Some Concerns, High Risk). The overall risk of bias judgment is based on the synthesis of the individual domains: if at least one domain is rated "High Risk," the overall risk of bias is considered high; if no domain is rated "High Risk" but at least one is rated "Some Concerns," the overall is defined as "Some Concerns." Finally, when all domains are rated "Low Risk," the overall judgment is "Low Risk." (cf. Table 2).

Table 2

Cochrane Risk of Bias 2 (RoB 2)

2. DEVELOPMENT

2.1. Oral Cancer

According to GLOBOCAN 2022 data (IARC), head and neck cancers (including lip and oral cavity, nasopharynx, oropharynx, hypopharynx, larynx, and salivary glands) exhibit a variable distribution in terms of overall incidence worldwide. Globally, lip and oral cavity carcinoma accounts for approximately 389,846 new cases (2.0% of all neoplasms), ranking as the 16th most frequent cancer site. Laryngeal cancer records 189,191 cases (0.95%), while oropharyngeal and hypopharyngeal cancers reach 106,400 (0.53%) and 86,257 (0.43%), respectively. Less frequent are tumours of the salivary glands (55,083; 0.28%) and nasopharynx (120,434; 0.60%).

Regarding mortality, data indicate that lip and oral cavity cancers result in 188,438 deaths (approximately 1.9% of total global cancer deaths), while laryngeal cancer accounts for 103,359 deaths (1.1%). Oropharyngeal (52,305) and hypopharyngeal (40,902) cancers present lower but still significant mortality rates. As for 5-year prevalence, 1,094,448 individuals live with a diagnosis of lip and oral cavity cancer, followed by larynx (583,868), nasopharynx (359,560), oropharynx (306,242), hypopharynx (159,986), and salivary glands (170,570). These numbers highlight that, although relatively less common than other malignancies (such as lung or colorectal cancer), head and neck neoplasms constitute a significant long-term epidemiological burden.

Focusing on Europe (GLOBOCAN 2022 data covering 44 countries), the incidence of head and neck cancers is proportionally similar but with different absolute volumes. Lip and oral cavity cancer accounts for 62,073 new cases (1.4% of all cancers in Europe), surpassing laryngeal cancer (40,387 cases, 0.90%), oropharyngeal cancer (29,800, 0.67%), and hypopharyngeal cancer (16,002, 0.36%). Tumours of the salivary glands (9,135; 0.20%) and nasopharynx (4,513; 0.10%) exhibit lower incidence rates.

In terms of mortality across the continent, lip and oral cavity cancers account for 24,253 deaths (approximately 1.2% of the total), while laryngeal cancer records 19,090 deaths (0.96%). Hypopharyngeal and oropharyngeal sites report 9,315 (0.47%) and 13,027 (0.66%) deaths, respectively, while nasopharyngeal cancer reaches 2,563 deaths (0.13%). Regarding 5-year prevalence, 202,275 individuals are living with lip and oral cavity cancer, followed by 141,669 with laryngeal cancer. Though less numerous, the prevalent

cases for oropharyngeal (96,199), hypopharyngeal (35,602), salivary gland (30,860), and nasopharyngeal (15,655) cancers remain significant.

2.2. Oral Squamouse Cell Carcinoma

Oral Squamous Cell Carcinoma (OSCC) accounts for over 90% of all malignant neoplasms arising in the oral cavity (Chamoli et al., 2021). Globally, the number of new cases diagnosed each year is substantial, with particularly high mortality rates in certain regions of South Asia, such as India and Sri Lanka (Tan et al., 2023). However, OSCC remains a significant public health issue even in industrialized countries due to frequent late diagnoses and high biological aggressiveness (Rivera, 2015).

Clinically, OSCC is often diagnosed at advanced stages, partly due to low awareness of early symptoms and the lack of effective screening programs (Bagan et al., 2010). This diagnostic delay underscores the crucial importance of a multidisciplinary approach that ensures both early detection and integrated treatments, involving specialists in maxillofacial surgery, medical oncology, and radiotherapy (Montero & Patel, 2015).

Among established risk factors, tobacco use is recognized as the primary carcinogenic agent, significantly increasing the risk of OSCC, particularly when combined with alcohol consumption (Chamoli et al., 2021). The synergy between tobacco and alcohol promotes the accumulation of genetic alterations in the oral epithelium, predisposing to neoplastic transformation (Bugshan & Farooq, 2020). In some Asian regions, the habit of chewing betel quid and areca nut is responsible for high rates of oral cancer, as areca nut is classified as a Group 1 carcinogen (Rivera, 2015).

From a molecular perspective, various studies highlight a set of mutations and epigenetic events, including the inactivation of tumour suppressors (e.g., TP53) and the aberrant activation of oncogenes (such as PIK3CA). These alterations, often driven by chemical carcinogens, contribute to increased cell proliferation rates and tumour angiogenesis (Tan et al., 2023). Additionally, the role of HPV, particularly relevant in oropharyngeal carcinomas, has also been investigated in the context of oral cancer, although its incidence appears lower than that of tobacco- and alcohol-related cases (Montero & Patel, 2015).

A key element in the natural history of oral carcinoma is the presence of potential malignant lesions, such as leukoplakia, erythroplakia, oral submucous fibrosis, and certain variants of lichen planus (Rivera, 2015). These conditions may exhibit varying

degrees of dysplasia and require close clinical monitoring to prevent or detect malignant transformation at an early stage (Tan et al., 2023).

Clinically, OSCC may initially present as a leukoplakic or erythroplakic plaque or as a painless ulcer, often underestimated by the patient (Bagan et al., 2010). As the disease progresses, symptoms such as bleeding, severe pain, trismus, and regional lymph node metastases may develop (Montero & Patel, 2015). Histopathologically, the neoplastic epithelium invades beyond the basement membrane, forming tumour cords or islands; the degree of differentiation (well, moderately, or poorly differentiated) and the presence of specific variants (e.g., verrucous or spindle cell carcinoma) influence prognosis (Speight & Farthing, 2018).

The five-year survival rate for OSCC varies significantly depending on the stage at diagnosis, being markedly higher for early-stage tumours (Rivera, 2015). In this context, numerous studies emphasize the importance of early screening techniques, including vital staining (e.g., toluidine blue), oral autofluorescence, and salivary biomarker tests (Bugshan & Farooq, 2020). These methods aim to identify early signs of dysplasia or microinvasion, enabling prompt and less invasive interventions.

From a therapeutic perspective, surgery often remains the primary approach, followed by postoperative radiotherapy or adjuvant chemoradiotherapy in cases with positive resection margins or multiple lymph node metastases (Montero & Patel, 2015).

2.3. Oral Cancer Radiotherapy

Radiotherapy is one of the main therapeutic pillars for head and neck tumours, including those arising in the oral cavity (Gomez et al., 2009; Lin, 2017). Specifically, in cases of Oral Squamous Cell Carcinoma (OSCC), radiotherapy is often used in combination with surgery or, in selected situations, as a primary treatment or palliative care (Mendenhall et al., 2021). The choice of approach depends on various factors, including tumour stage, patient condition, anatomical location, and the possibility of preserving oral function and quality of life (Bhide et al., 2012; Membreno et al., 2021).

Postoperative radiotherapy is applied when pathological analysis identifies risk factors for locoregional recurrence, such as positive or close surgical margins (≤1cm), a high number of metastatic lymph nodes, extracapsular lymph node extension, and perineural invasion (Gomez et al., 2009; Lin, 2017). In the presence of high-impact risk factors (e.g.,

positive margins or extensive extracapsular spread), chemotherapy (often cisplatin-based) is commonly added, constituting post-operative chemoradiotherapy (POCRT) (Millsop et al., 2017). The goal is to maximize the cure of residual disease control and reduce the likelihood of recurrence.

For patients with inoperable tumours or those with high surgical risk (e.g., due to significant comorbidities), radical radiotherapy is often used alone or in combination with chemotherapeutic drugs (cetuximab or cisplatin), forming a chemoradiotherapy regimen (Bhide et al., 2012). The objective is to achieve local control comparable to surgical treatment alone while preserving oral structures and minimizing functional impairment. In some advanced stages, an "organ preservation" approach may be attempted. Although more commonly applied to oropharyngeal or laryngeal tumours, this strategy is sometimes considered for specific oral sites, provided that the tumour remains resectable at a later stage if the response is unsatisfactory (Mendenhall et al., 2021).

When oral cancer is metastatic or locally advanced and not curable, palliative radiotherapy aims to alleviate symptoms (such as pain, bleeding, or obstruction) and slow down clinical deterioration (Membreno et al., 2021). In some cases, short-course hypofractionation or brachytherapy techniques may be considered for rapid local control.

Three-dimensional conformal radiotherapy (3D-CRT) utilizes planning based on tumour volume and at-risk tissues but lacks the dose-modulation precision of Intensity-Modulated Radiotherapy (IMRT) (Lin, 2017). Although it was the standard for many years, 3D-CRT carries a higher risk of late side effects (e.g., xerostomia, osteoradionecrosis) due to the extensive irradiation of salivary glands and the mandibular or maxillary bone (Brennan et al., 2017).

IMRT allows for differential modulation of beam intensity across various tumour subregions, enabling a more personalized dose distribution (Gutiontov et al., 2016). This technique allows:

• Sparing of critical structures such as the parotid and submandibular glands, spinal cord, and mandible;

• Reduction in xerostomia incidence and other tissue toxicities;

• Maintenance of efficacy in high-risk disease areas.

Both retrospective and prospective studies indicate that IMRT significantly improves

quality of life by reducing glandular damage and, consequently, dry mouth symptoms (Bhide et al., 2012; Brennan et al., 2017). IMRT requires precise definition of treatment volumes (Gross Tumour Volume, Clinical Target Volume, Planning Target Volume) in collaboration with radiologists and maxillofacial surgeons (Gutiontov et al., 2016).

Brachytherapy involves the placement of radioactive sources near or in direct contact with the tumour bed. In oral neoplasms, this technique is particularly advantageous for localized lesions of the tongue or floor of the mouth (Gomez et al., 2009). Brachytherapy can be used as monotherapy (for early-stage tumours) or in combination with surgery (in cases of high-risk margins) or external beam radiotherapy (Huang & O'Sullivan, 2013). However, this type of radiotherapy requires specialized expertise from the medical team and needs to be done in high-level centers.

In recent years, proton therapy has represented a significant innovation in the treatment of head and neck cancers, offering a promising alternative to conventional radiotherapy due to its ability to reduce radiation exposure to surrounding healthy tissues. The main drawback of this technique is its high cost, but it remains a highly promising option for the future (Bała et al., 2024).

2.4. Xerostomia

Xerostomia is defined as the subjective perception of oral dryness (Millsop et al., 2017). It can result from an objective reduction in salivary flow (hyposalivation), compositional alterations in saliva, or an imbalance in sensory perception of saliva (Cassolato & Turnbull, 2003; Guggenheimer & Moore, 2003). Epidemiological studies report a variable prevalence (generally between 5% and 46%), particularly among the elderly population, where systemic factors and the use of multiple medications (many with anticholinergic effects) increase the likelihood of developing symptoms (Turner, 2016).

From a clinical perspective, xerostomia is of great importance as it significantly impacts patients' quality of life, interfering with daily functions such as eating, speaking, and sleeping. Social interactions are also affected, as oral dryness may be associated with conditions like halitosis or speech difficulties (Millsop et al., 2017).

The most common cause of xerostomia is polypharmacy, particularly in the elderly. Numerous drugs-including tricyclic antidepressants, antipsychotics, antiparkinsonian agents, first-generation antihistamines, certain antihypertensives, and sedatives-have

anticholinergic effects that significantly reduce salivary flow (Turner, 2016; Tanasiewicz et al., 2016). Given that the geriatric population is most affected by chronic diseases and thus takes multiple medications, the high incidence of xerostomia in this age group is understandable (Guggenheimer & Moore, 2003).

Sjögren's syndrome is one of the primary pathological conditions associated with xerostomia. In this autoimmune disorder, the salivary (and lacrimal) glands undergo lymphocytic inflammatory infiltration, damaging the glandular structure and reducing secretion (Millsop et al., 2017). Other autoimmune diseases (such as rheumatoid arthritis, systemic lupus erythematosus, and scleroderma), as well as endocrine disorders (diabetes mellitus, hyperthyroidism) or conditions such as renal failure, HIV infection, and hepatitis C, can contribute to the development of xerostomia (Tanasiewicz et al., 2016).

Smoking, alcohol, and excessive caffeine consumption can exacerbate the perception of oral dryness. Alcohol acts as an irritant and dehydrating agent, while nicotine and caffeine may alter saliva composition and production (Cassolato & Turnbull, 2003).

Patients with xerostomia report difficulties in swallowing, phonation, and chewing (especially dry or firm foods), as well as taste alterations or reduction, burning sensations, pain, and halitosis (Tanasiewicz et al., 2016). Additionally, inadequate salivary flow impairs the natural antibacterial and buffering functions of saliva, increasing the incidence of dental caries (particularly cervical caries) and opportunistic infections such as candidiasis (Kapourani et al., 2022). Oral mucosa also becomes more prone to trauma and ulceration, further deteriorating quality of life and increasing the risk of complications (Guggenheimer & Moore, 2003).

Radiotherapy in the head and neck region, for example, in the treatment of oral cavity, oropharyngeal, laryngeal, or salivary gland carcinomas, often causes irreversible damage to the glandular parenchyma, leading to hyposalivation (Turner, 2016). Exposure to cumulative radiation doses ≥60 Gy can result in severe and progressive damage to the salivary glands (Millsop et al., 2017).

Radiation-induced xerostomia is a severe morbidity for Head and Neck Cancer (HNC) survivors following targeted curative radiotherapy (RT). Oral health and quality of life (QOL) for HNC survivors are strongly influenced by RT (Kaae et al., 2020). It can begin early during treatment: a 50% to 60% decrease in salivary flow can be observed in the first week; and, after 7 weeks of conventional RT, salivary flow is reduced to about 20%

(Agrawal et al., 2022).Typical manifestations of this damage include reduced salivary secretion, which in turn can translate into a subjective sensation of dry mouth (xerostomia); oral discomfort; altered taste; difficulty speaking, swallowing, and chewing; and an increased risk of dental diseases (Rupe et al). Saliva composition alters and becomes viscous as salivary flow decreases due to irradiation of the major salivary glands (Kaae et al., 2020). Unfortunately, non-neoplastic tissues included in the RT also suffer damage. The effects depend mainly on RT factors such as dose per fraction, total radiation dose, irradiated volume, and dose distribution in the tissue volume. These effects can occur during and after RT, interfering with patients' oral functions and negatively affecting their social lives (Palma et al., 2017).

The first step in assessing xerostomia is medical history collection, investigating concomitant diseases, medication, cancer treatments and associated symptoms (Millsop et al., 2017). Sialometry (quantitative measurement of salivary flow, both at rest and stimulated) helps distinguish between patients with actual hyposalivation and those whose sensation of dryness does not correspond to a significant reduction in saliva production (Cassolato & Turnbull, 2003). Moreover, more specific examinations (such as sialoendoscopy and minor salivary gland biopsies) may be indicated in cases where an underlying autoimmune disease, such as Sjögren's syndrome, is suspected (Turner, 2016).

2.5. Questionnaires used to evaluate quality of life regarding xerostomia

The EORTC QLQ-C30 (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire) is a standardized tool for assessing the quality of life in cancer patients. It is widely used in clinical research and studies related to health-related quality of life. Consists of 30 questions divided into different scales that evaluate various aspects of the patient's quality of life. Each question has a response scale ranging from 1 to 4 (1 = not at all, 4 = very much), except for the global quality of life scale, which ranges from 1 to 7.

The scores are then converted to a 0 to 100 scale: Higher scores in the functional scales and global quality of life indicate a better quality of life. Higher scores in the symptom scales indicate a greater severity of symptoms and, consequently, a poorer quality of life.

There are additional versions specific to particular cancer types (e.g., QLQ-H&N35 for

head and neck cancer), which provide a more detailed assessment of symptoms and related issues.

The EORTC QLQ H&N35 is a questionnaire that analyzes patients QOL, using 35 items that can be grouped into 7 multi-item symptom scales, measuring pain in the mouth, swallowing problems, senses, language, social eating and contact social, and eleven single-item scales, which assess problems with the teeth, mouth opening, dry mouth, sticky saliva, cough, feeling sick, as well as use of analgesics, nutritional supplements, feeding tube and finally increased and weight loss. This questionnaire uses a 4-point Likert-type measurement scale, which allows patients to rate the intensity or frequency of the symptoms and problems they are experiencing.

The result ranges from 0 to 100, indicating 100 as a perfect quality of life on the functioning scale, while for the symptoms scale, a score of 100 will indicate a heavy burden.

The FACT-G (*Functional Assessment of Cancer Therapy – General*) is a standardized questionnaire used to assess the quality of life in cancer patients. It is utilized in both clinical research and medical practice to measure the impact of cancer and its treatments on patients' quality of life.

It consists of 27 questions divided into four main domains: Physical Well-Being; Social/Family Well-Being; Emotional Well-Being; Funcional Well-Being

Each question has a response scale ranging from 0 to 4 (0 = not at all, 4 = very much). The scores for each domain are summed to obtain the total FACT-G score, which ranges from 0 to 108: Higher scores indicate a better quality of life and Lower scores indicate a negative impact of the disease and its treatments on quality of life.

The University of Washington Quality of Life Questionnaire (UW-QOL) is a questionnaire specifically designed to assess the quality of life in patients with head and neck cancers. It is widely used in clinical research and medical practice to monitor the impact of the disease and its treatments on patients. The questionnaire consists of 12 main questions, divided into two sections: Specific Function Section (12 domains) and Two questions assessing the overall perception of quality of life before and after the disease. An additional question asks the patient to identify the two most problematic aspects of their quality of life. Each question has a 0 to 100 response scale, with higher scores indicating a better quality of life. Each domain is evaluated separately, with no combined

total score. The results are used to compare the impact of the disease and treatments among different patients or study groups.

The specificity for head and neck cancer patients, along with its simplicity and quick administration, are the main advantages of this questionnaire.

The OHIP-14 (Oral Health Impact Profile - 14) is a standardized questionnaire used to assess the impact of oral health on quality of life. It is a shortened version of the OHIP-49 and is commonly used in clinical research and dental practice to measure discomfort and functional limitations caused by oral health problems. It consists of 14 questions, divided into 7 dimensions of oral health-related quality of life. Each question follows a 5-point Likert scale: 0 = Never; 1 = Rarely; 2 = Sometimes; 3 = Often; 4 = Always.

The Zimmerman Xerostomia Questionnaire (ZXQ) is a rapid self-assessment tool developed in the late 1990s by R.P. Zimmerman and colleagues to quantify oral dryness (xerostomia) in patients undergoing radiotherapy for head-and-neck tumours. It comprises five questions (items) presented as visual-analogue scales (VAS) from 0 to 100 mm. The items assess: Dryness of the mouth; Dryness of the tongue / oral Comfort; Difficulty sleeping because of dry mouth; Difficulty speaking due to dryness; Difficulty eating / denture use. For each item, the patient marks a point on the 100-mm line (0 = no trouble; 100 = maximum trouble). The values (in mm) are summed or averaged to yield an overall score (range 0–500, or 0–100 if the mean is used); higher scores indicate more severe xerostomia. Because the scale is sensitive to changes over time, it is often administered at fixed intervals during and after radiotherapy. It is widely employed in trials evaluating pharmacological interventions (e.g., pilocarpine), parotid-sparing radiotherapy techniques, and complementary therapies. Its chief advantages are speed (< 2 min), ease of translation, and the absence of any commercial licensing requirements.

3. RESULTS

From the 10 articles included in this systematic review, the sample sizes ranged from a minimum of 29 patients (Palma et al., 2017) to a maximum of 258 (Cohen et al., 2024), and there was similar heterogeneity in terms of follow-up duration among all studies (ranging from 1 to 12 months) and outcome measures used to evaluated the improvement in xerostomia (salivary flow rate, xerostomia questionnaires, quality of life scales, etc.) Our analysis identified several categories of interventions, each with distinct mechanisms of action and varying levels of effectiveness. We examined approaches ranging from pharmacological treatments such as pilocarpine to non-pharmacological local and topical measures aimed at symptomatic relief and lubrication of the oral cavity, as well as laser therapy. In addition, we explored complementary therapies like acupuncture and innovative options such as mesenchymal/stromal cell therapy (ASC), which are emerging in the clinical landscape with promising though still maturing results.

The most recent study is by Cohen et al. (2024) present a multicenter study involving 258 head and neck cancer patients previously treated with RT and suffering from moderate-to-severe xerostomia for at least 12 months. They divided patients in 3 groups in orther to compared true acupuncture (TA), sham acupuncture (SA), and a standard oral hygiene (SOH) group. The large sample and three-arm design add methodological strength to the study disegn. Patient-reported outcomes including the XQ (primary outcome) and the Functional Assessment of Cancer Therapy–General [FACT-G] (secondary outcome) were completed at baseline and weeks 4, 8, 12, and 26, with follow-up extending to 26 weeks. There were no significant mean (SD) group differences in XQ at baseline. The ANCOVA (controlling for baseline XQ) at week 4 revealed a significant group effect ($P = 0.002$), with TA showing significantly lower XQ scores than SOH, marginal differences (after correction) between TA and SA, and no significant differences between SA and SOH. Mixed-model repeated measures analysis showed a significant group-by-time interaction, with group differences at each time point. As with the week 4 outcomes, the TA group continued to report significantly lower XQ scores at weeks 8 and 12 than the SOH group, but by week 26 only the SA group maintained lower XQ scores than SOH, with no other significant differences. Response distributions were significantly different between TA and SOH at weeks 4, 8, and 12 ($P = 0.03$), with twice as many patients in the TA group showing a partial response at week 4. Similarly, the proportions of patients with clinically

significant xerostomia (XQ > 30) were significantly different between TA and SOH at weeks 4 and 12. No other differences were observed in rates of clinically significant xerostomia. The mixed-model repeated-measures analysis of FACT-G scores followed a similar pattern to the XQ, showing significant differences at week 4 (TA vs SOH) and at week 12 (TA vs SA and TA vs SOH), with no between-group differences at week 26. The results show a significant improvement in the acupuncture group, especially during the first 4–8 weeks, including benefits in quality of life (FACT-G). No serious adverse events occurred. Six adverse events were reported across all groups (SOH: 0; SA: 3; TA: 3). Adverse events with SA included 1 patient, facial edema, 1 patient, flulike symptom, and 1 patient, joint pain (all grade 3). Adverse events with TA included 1 patient whit hypertension (grade 3), 1 patient whit headache (grade 1), and 1 patient whit bruising (grade 1).

However, the lack of marked differences compared to SA after multiple-comparison corrections suggests further confirmation is needed.

Jakobsen et al. (2024) took a regenerative approach: ultrasound-guided injection of mesenchymal stem cells (ASCs) into the submandibular glands in a phase II RCT with 120 patients. Two groups were created in order to evaluate if the treatment was effective: the intervention group, treated with ASCs and the placebo group. Placebo consisted of CyroStor 10 (BiolifeSolutions), the freeze media for ASCs, containing 10% of dimethyl sulfoxide (DMSO). Patients treated with ASCs showed a mean increase in unstimulated salivary flow (UWS) of 0.04 (95% CI, 0.02–0.06) mL/min from baseline to 4 months, compared to an insignificant increase of 0.01 (95% CI, -0.007 to 0.036) mL/min in the placebo group. This corresponded to a 37.9% increase (95% CI, 18.06–57.79) in the ASC group and 20.89% (95% CI, 1.02–40.75) in the placebo group. No significant increase in stimulated salivary flow (SWS) was detected in patients treated with ASCs. Overall, no statistically significant difference in salivary gland function was found between the ASC-treated and placebo groups. The primary endpoint (increase in UWS and SWS) was achieved only for unstimulated flow; no significant differences were observed in subjective symptoms or QoL. However, given the safety and absence of adverse events, the study opens the door to future trials with expanded protocols. No deaths occurred during the 4-month study period. Fifteen patients experienced AE related to the intervention: 9 patients (7.5%) had temporary swelling of the submandibular glands, and all of these patients had received ASCs. The swelling remained for 1 day to 3 weeks, but

thereafter, disappeared in all patients. Two patients (1.7%) had a temporary haematoma after the injections; one received ASCs and one received placebo.

Porangaba et al. (2024), with 40 patients, tested an enzymatic saliva substitute spray versus placebo for 30 days. In phase 1, most patients in the Bioxtra Spray® group already reported some degree of xerostomia, with Grade 2 (n = 11; 52.4%) or Grade 3 (n = 10; 47.6%). After 30 days of treatment, there was a decrease in Grade 3 xerostomia (n = 7; 33.3%) and an increase in Grade 1 (n = 2; 9.5%; $p > 0.05$). In the placebo arm, most patients initially had Grade 2 or 3 xerostomia, and after 30 days most remained at Grade 2 (n = 11; 64.7%), with no statistical differences ($p > 0.05$). No significant differences were found between groups ($p > 0.05$). In phase 1, the mean SWS was 0.00 mL/min in Bioxtra Spray® patients treated with RTC3D vs 0.03 mL/min for IMRT patients ($p = 0.023$), and similarly in phase 2 (0.01 vs 0.04 mL/min; $p = 0.009$). No significant differences were seen in the placebo arm. At baseline, global QoL scores showed no significant differences. Among the 12 UW-QoL domains, the saliva domain had the worst scores (37.2 placebo, 26.8 Bioxtra®; $p > 0.05$). After treatment, global scores increased in both groups, but were lower in the Bioxtra® group (76.0 vs 85.7; $p < 0.05$). No significant difference was seen in the saliva domain (41.6 placebo, 30.0 Bioxtra®; $p > 0.05$). Although differences in xerostomia scores were not statistically significant, the product showed good acceptability and usability, suggesting that a longer follow-up or larger sample could better clarify its potential. The study does not evaluate the safety of the Bioxtra spray® and does not report whether there were any adverse events due to its administration

Rupe et al. (2023) offered a more promising option with a sodium-hyaluronate mouthwash in a cross-over design (2 × 30 days, with washout). Each participant received both the sodium-hyaluronate mouthwash (Hydral®) and the placebo (water + xylitol) for 30 days, separated by a 30-day washout period. Assessments (T0, T30, T61, T90) included: modified Xerostomia Questionnaire (XQ), EORTC-QLQ-C30, QLQ-H&N35, and unstimulated/stimulated salivary flow. A marked improvement in subjective xerostomia scores and high patient satisfaction were reported. The main results were: Group A, modified XQ = 70.1 at baseline vs 63.2 after washout; Group B, 58 at baseline vs 59.9 after washout. No significant differences were found between groups or timepoints. However, when comparing pre- and post-treatment scores with sodium-hyaluronate, significant improvements were observed (baseline: 65, post-treatment: 48.4;

p = 0.01). Satisfaction scores were higher for sodium-hyaluronate vs placebo (64.1 vs 31.9; p = 0.001), and the reduction in modified XQ was also significantly better (16.7 vs 4.9; p = 0.001). No treatment-related adverse events were observed in either period, confirming the mouthwash's high safety profile.

Agrawal et al. (2022) used oral pilocarpine (5 mg TID) in a prospective trial with 60 patients, with follow-up up to 12 months post-RT. The mean age was 47 years in the pilocarpine arm (ARM-A) and 49 years in the control arm (ARM-B); 86 % of the patients were male. Stage III–IV accounted for roughly 80 % of cases. Outcomes were assessed at 1, 3, 6 and 12 months using the Zimmerman Xerostomia Questionnaire (ZXQ) and the EORTC QLQ-HN35 quality-of-life questionnaire. The global ZXQ score, where higher values indicate better salivary function, was consistently higher in the pilocarpine group. At the first post-RT assessment (≈ 1 month), the mean global score was 50 mm in ARM-A versus 45 mm in ARM-B (P < 0.00001). The difference persisted at 3 months (59 vs 52 mm; P < 0.00001) and at 6 months (64 vs 57 mm; P < 0.01), while at 12 months it remained but was only borderline significant (71 vs 68 mm). Quality-of-life parameters confirmed the benefit: at 1 month the mean scores for pain, dysphagia and fatigue were 52.6, 65 and 55 in ARM-A versus 64, 76 and 58 in ARM-B. Differences favouring pilocarpine persisted at 3 months (reduced analgesic use 58 vs 65; improved sleep 25 vs 30) and at 6 months. No serious adverse events attributable to pilocarpine were reported; minor side-effects (sweating, mild gastrointestinal discomfort) did not lead to treatment discontinuation.

Kaae et al. (2020) explored a “mechanical” approach for the treatment of xerostomia: chewing gum. In a phase III RCT, 109 HNC survivors were randomized, with 91 completing the study (Arm A: gum, n = 55; Arm B: standard care, n = 36). The categorical reduction in dry-mouth symptoms (Dry mouth, Q41 EORTC QLQ-H&N35) was greater in Arm A (38 %) than in Arm B (19 %) , while symptom worsening occurred in 13 % versus 6 % of patients, respectively. The median score fell by 10.3 points in Arm A (74.5 → 64.2; P = 0.005) and by 5.6 points in Arm B (75.0 → 69.4). Significant improvements in Arm A were also observed for “Sticky saliva” (-9.7 points; P = 0.02) and for the GRIX domains “Daytime xerostomia” (-9.2 points; P = 0.001) and “Daytime thick saliva” (-4.9 points; P = 0.01). The “Social eating” domain improved in both study arms. Chewing for 5 minutes increased salivary flow (UWS 0.10 → 0.54 mL/min in Arm A and 0.09 → 0.70 mL/min in Arm B; P < 0.001 within arms) and reduced viscosity (non-sticky saliva after

stimulation: 93 % vs 89 %), but there were no significant between-arm differences. Resting hyposalivation persisted in roughly 50 % of participants. These findings suggest that chewing can alleviate symptoms without altering objective saliva production. No adverse events were reported.

De Sousa Pereira et al. (2020) evaluated topical pilocarpine (1.54% spray) in a crossover RCT. Saliva production was measured by the stimulated whole saliva flow (SWSF) method, using a sialometry kit (Halitus). The test consisted of chewing a mechanical sialogogue (silicone) for 5 min and the saliva produced was collected in a tube; saliva volumes were measured and the salivary flow rate (ml/min) calculated. Post-treatment SWFS was not statistically different between pilocarpine and placebo regardless of treatment sequence ($p > .05$), except at 2 months where the SWSF rates were statistically higher. what happend?. No significant differences were found in QoL or xerostomia index (XI) at any time point, but improvements over time were noted in the pilocarpine group. Efeitos adversos? The most common adverse side effects of oral pilocarpine includeb diaphoresis, frequent urination, and nausea. Moreover, patients may have dizziness, headache, and cardiovascular effects. However, the study does not evaluate the safety of pilocarpine and does not report adverse events.

Paterson et al. (2019) tested Visco-ease™, a spray based on lamellar body mimetics, in a double-blind RCT. No significant difference was found between groups for mean clinic GRIX (Groningen Radiotherapy-Induced Xerostomia Questionnaire) score at any time point. Regression adjusted for baseline GRIX also found no significant effect (effect = −1.26, CI −21.77 to 19.24, $p = 0.90$). Serious adverse events that were “at least possibly device-related” were monitored throughout the study. There werenone in either group.

Palma et al. (2017) investigated low-level laser therapy (LLLT). In a sample of 29 patients treated twice a week for 3 months, the mean age was 61 years and 72 % of participants were male. They underwent 24 sessions of low-level laser therapy (LLLT) with an InGaAlP diode (808 nm, 30 mW, 7.5 J/cm², 10 s per point), delivered twice a week for 3 months: six extra-oral points for each parotid gland, three for each submandibular gland and two intra-oral points for each sublingual gland, for a total of 22 points per session.

The mean unstimulated salivary flow rate (SFR) increased from 0.11 ± 0.10 to 0.19 ± 0.26 mL/min (+73 %; $P = 0.0012$), while the stimulated SFR rose from 0.19 ± 0.17 to 0.35 ± 0.26 mL/min (+84 %; $P < 0.0001$). The global UW-QoL score improved by about 35 % on average (from 671 ± 217 to 906 ± 185; $P < 0.0001$). No relevant adverse events

emerged, indicating the safety of this technique. The main limitation is the small sample size.

Chung et al. (2016) used an antioxidant complex of vitamin C/E. The trial group showed significant improvement in xerostomia questionnaire and scores at 6 months post-RT vs 1 month (P = .007 and .008), unlike the control group. No differences were observed in salivary scintigraphy, but the trial group maintained better oral indices (prestimulatory: P = .01; poststimulatory: P = .009). At the final follow-up, there was no difference in overall survival and disease-free survival between the 2 groups. No significant adverse events or side effects related to study medication were noticed or reported throughout the trial.

The data derived from the analyzed studies and their respective results have been synthesized and presented in three separate tables. The first table illustrates the demographic and clinical characteristics of the patients (cf. Table 3). The second table details the characteristics of the neoplasms and the radiotherapy doses used (cf. Table 4). The third table summarizes the main study outcomes (cf. Table 5).

Table 3

Demographics and patients characteristics

Author / Year	Study Type	Country	N. pacients	Gender	Mean Age	Median Age
Cohen et al.**, 2024**	Multicenter RCT	USA	258	201 M, 57 W	65.0 years	65,2 years (IQR)
Jakobsen et al.**, 2024**	Phase II RCT, double-blind	Denmark	120	NA	61.0 years	NA
Porangaba et al.**, 2024**	Double-blind RCT (2:1)	Brazil	40	34 M, 40 W	60.09 years (Bioxtra®) 59.94 years (Placeno)	62 years / 60 years (Range 40-72 / 30-69)
Rupe et al.**, 2023**	Cross-over RCT, double-blind	Italy	32	18 M, 14 W	54.6 years	NA
Agrawal et al.**, 2022**	Prospective RCT	India	60	51 M, 9 W	47.0 years (Pilocarpine) 49.0 years (control)	NA
Kaae et al.**, 2020**	Phase III RCT	Denmark	91	60 M, 31 W	NA	61 years (range 34-80)
De Sousa Pereira et al.**, 2020**	Cross-over RCT, double-blind	Brazil	40	29 M, 11 W	58,10 years	NA
Paterson et al.**, 2019**	Double-blind RCT (2:1)	United Kingdom	39	35 M, 4 W	59 years	NA
Palma et al.**, 2017**	Prospective study (controlled)	Brazil	29	21 M, 8 W	61 years	NA
Chung et al.**, 2016**	Double-blind RCT	South Korea	45	40 M, 5 W	56.6 years (Vit C/E) 61.6 years (Control)	NA

Subtitles: M Man, W Woman; RCT Randomized controlled trial; IQR Inter-Quartile Range; NA not available; USA United States of America

Table 4

Characteristics of cancers and radhioterapy dose

Author / Year	Cancer Type	Cancer Stage	Cancer Localization	Cancer Treatment	Radiotheraphy Dose (Gy)	Side Effects
Cohen et al.**, 2024**	NA	III – IV	NA	Radiotherapy	70 Gy	Xerostomia
Jakobsen et al.**, 2024**	NA	I – II	Oropharynx / Oral Cavity	Radiotherapy + Chemotherapy	66 Gy	Xerostomia
Porangaba et al.**, 2024**	Squamous cell carcinoma	II – III - IV	Oropharynx / Nasopharynx	Radiotherapy + Chemotherapy	65 Gy	Xerostomia
Rupe et al.**, 2023**	Squamous cell carcinoma	III – IV	Oropharynx	Radiotherapy	64 Gy	Xerostomia
Agrawal et al.**, 2022**	Squamous cell carcinoma	III – IV	Oral Cavity / Oropharynx Hypopharynx	Radiotherapy + Chemotherapy	70 Gy	Xerostomia, Dysphagia
Kaae et al.**, 2020**	NA	III – IV	Oropharynx	Radiotherapy + Surgery	60 Gy	Xerostomia, Mucositis
De Sousa Pereira et al.**, 2020.**	Squamous cell carcinoma	NA	Oral cavity / Oropharynx Hypopharynx	Radiotherapy	66 Gy	Xerostomia
Paterson et al.**, 2019**	Squamous cell carcinoma	III – IV	Oropharynx / Larynx Hypopharynx	Radiotherapy	70 Gy	Xerostomia
Palma et al.**, 2017**	Squamous cell carcinoma	III – IV	Oral Cabity / Pharynx Larynx	Radiotherapy + Chemotherapy	66 Gy	Xerostomia, Mucositis
Chung et al.**, 2016**	NA	I- II - III – IV	Larynx / Oropharynx Oral Cavity	Radiotherapy + Chemotherapy	70 Gy	Xerostomia

Subtitles: N/A not available; Gy Gray

Table 5

Table of results

Author / Years	Treatment	Primary Outcome	QoL Questionnaire	Adverse Events (AEs)	Results	Follow -Up
Cohen et al., **2024**	Acupuncture	Reduction in xerostomia (Xerostomia Questionnaire)	Quality of life (FACT-G)	No serious AEs reported	Significant improvement in the acupuncture group, especially during the first 4–8 weeks, including a benefit in quality of life (FACT-G)	6 months
Jakobsen et al., **2024**	Mesenchymal Stem/Stroma Cell	Improvement in salivary flow (UWS)	Quality of life (EORTC QLQ-H&N 35)	15 patients experienced AE	Significant increase in UWS, no differences in (SWS-QoL)	4 months
Porangaba et al., **2024**	Salivary substitute	Reduction in xerostomia (UWS-SWS)	Quality of life (UW-QoL)	NA	No significant reduction in xerostomia, good tolerability	2 months
Rupe et al., **2023**	Sodium-hyaluronate mouthwash	Improvement in xerostomia (modified XQ)	Quality of life (EORTC QLQ-C30/H&N35)	No AEs reported	Significant improvements in xerostomia and QoL	3 months
Agrawal et al., **2022**	Oral Pilocarpine	Reduction of xerostomia symptoms (Zimmerman, EORTC QLQ-HN35)	Quality of life (EORTC QLQ H&N 35)	No AEs reported	Significant reduction in symptoms, improved QoL with pilocarpine	12 months
Kaae et al., **2020**	Chewing gum	Reduction of xerostomia symptoms QLQ-H&N35	Quality of life (EORTC QLQ H&N 35)	No AEs reported	Improved subjective symptoms of xerostomia but no significant changes in salivary flow or viscosity	1 month

Author / Years	Treatment	Primary Outcome	QoL Questionnaire	Adverse Events (AEs)	Results	Follow -Up
De Sousa Pereira et al., **2020**	Topical Pilocarpine	SWSF (Stimulated Whole Saliva Flow) using a sialometry Halitus)	Quality of life (QoL OHIP-14)	No AEs reported	Post-treatment stimulated salivary flow was not significantly different between pilocarpine and placebo except at 2 months. No significant differences in QoL or XI, but improvements over time were observed in the pilocarpine group	3 months
Paterson et al., **2019**	Oral spray	Change in GRIX score	Quality of life (GRIX)	No AEs reported	No significant differences were observed between groups in mean GRIX scores	6 months
Palma et al., **2017**	Low-level Laser	Increased salivation (sialomertry unstimulated/stimulated) pH Assessment (pH-Fix-manchery-nage GmbH&Co)	Quality of life (UW-QoL)	No AEs reported	Increased salivary flow, both unstimulated and stimulated. Mean pH increased, and improvement in quality of life (UW-QoL)	3 months
Chung et al., **2016**	Vitamin C/E	Prevention of xerostomia (questionnaires)	Salivary scintigraphy, oral indices	No AEs reported	Significant improvement in xerostomia score and questionnaire at 6 months post-RT compared to 1 month. No differences in salivary scintigraphy	6 months

Subtitles: EORTC QLQ-C30 European Organisation for Research and Treatment of Cancer Quality of life Questionnaire; EORTC QLQ H&N35 European Organisation for Research and Treatment of Cancer Head and Neck Cancer Quality of life Questionnaire. FACT-G Functional Assessment of Cancer Therapy – General; UW-QOL University of Washington Quality of Life Questionnaire; QoL OHIP-14 Oral Health Impact Profile – 14; GRIX Groningen Radiotherapy-Induced Xerostomia Questionnaire; SWSF stimulated whole saliva flow; N/A not available; AE Adverse Events

4. DISCUSSION

Radiation-induced xerostomia (RIX) is one of the most frequent and debilitating complications for patients undergoing radiotherapy (RT) for head and neck cancer (HNC), significantly impacting quality of life (QoL). This systematic review examined evidence from ten randomized clinical trials (RCTs) and prospective studies assessing the efficacy and safety of various interventions aimed at preventing or treating RIX. The investigated therapeutic approaches were heterogeneous, with surgycal and non-surgycal approaches that included acupuncture, cellular therapies (mesenchymal stem cells - ASCs), low-level laser therapy (LLLT), pharmacological agents (oral and topical pilocarpine, vitamin C/E complex), saliva substitutes/stimulants (Visco-ease™ oral spray, Bioxtra® enzymatic system spray, sodium hyaluronate-based mouthwash), and mechanical stimulation (chewing gum).

The overall analysis of the studies presents a varied picture of the effectiveness of the different strategies. The heterogenecity of the observed results reflects the complexity of RIX and the diversity of therapeutic approaches that has been used to try to solve this complex clinical situation. A frequent discrepancy between subjective and objective measures (e.g., salivary flow) is evident among these authors. Many studies reported significant symptomatic improvements (e.g., Cohen et al., 2024; Rupe et al., 2023; Agrawal et al., 2022) even in the absence of a corresponding measurable increase in salivary flow, or vice versa. This underscores the importance of evaluating both aspects, considering patient-reported outcomes as primary or co-primary endpoints due to the subjective nature of xerostomia (Cohen et al., 2024; Paterson et al., 2019).

Another relevant aspect is the placebo effect, markedly observed in several studies, particularly those using sprays or mouthwashes (Jakobsen et al., 2024; Paterson et al., 2019; Pereira et al., 2020; Rupe et al., 2023). This phenomenon, combined with the potential intrinsic activity of some placebos (e.g., DMSO in Jakobsen et al., 2024 trial or the hydration provided by saline solution in Paterson et al., 2019 trial), complicates result interpretation and necessitates rigorous study designs, preferably with inert placebos and double-blinding.

The timing of intervention (prevention during RT vs. treatment of chronic RIX) could influence effectiveness, but current data do not allow definitive conclusions. The clinical

significance of statistically significant results warrants attention: for instance, Cohen et al. (2024) noted an average difference below the clinically significant threshold of 10 points on the XQ, yet a higher percentage of responders in the acupuncture group.

Most included studies were RCTs, many of which were double-blinded (Jakobsen et al., 2024; Porangaba et al., 2024; Rupe et al., 2023; De Sousa Pereira et al., 2020; Paterson et al., 2019; Chung et al., 2016), some multicentric or with crossover designs (Cohen L. et al., 2024; Rupe et al., 2023), representing a good level of evidence. The use of validated questionnaires for QoL and specific symptoms (XQ, FACT-G, EORTC QLQ-C30/H&N35, GRIX, UW-QoL, OHIP-14, Zimmerman) and the inclusion of objective measures (salivary flow, pH, viscosity, scintigraphy) constitute additional strengths. Safety assessment was also considered in nearly all studies.

All included studies reported no serious adverse events directly related to the tested interventions. For pilocarpine oral or spray (Agrawal S. et al., 2022; De Sousa Pereira RM et al., 2020), potential cholinergic effects were mild or absent; chewing gum and acupuncture had no clinical complications; topical therapies (mouthwashes or sprays) were well tolerated, and LLLT showed no relevant toxicity. Several studies reported improved QoL, although evidence levels varied due to the use of different and non-comparable questionnaires (EROTC QLQ C-30, EORTC QLQ-H&N35, FACT-G, UW-QoL, OHIP-14; GRIX).

However, several common limitations emerge. Many studies had small sample sizes (e.g., Palma et al. 2017) and short follow-up periods (e.g., Jakobsen et al., 4 months; Porangaba et al. (2024), 30 days; Chung et al. (2016) 6 months; Kaae et al. (2020) 1 month; Rupe et al. (2023) 3 months total), limiting the evaluation of long-term effects. As previously discussed, placebo choice and difficulties in maintaining blinding (e.g., Kaae et al., 2020) are significant limitations. Palma et al. (2017) study lacked a control group. Challenges in collecting objective data (e.g., compliance with scintigraphy in Chung et al., 2016) and occasionally high dropout rates were reported. Finally, population representativeness was limited in some studies.

Based on the analysed evidence given by the articles in this systematic review, the main conclusion are:

-Acupuncture (Cohen et al., 2024) emerges as a supported option for chronic RIX management in a large-scale RCT.

-Sodium hyaluronate-based mouthwash (Rupe et al., 2023) and chewing gum (Kaae et al., 2020) show potential for symptomatic relief.

-Oral pilocarpine (Agrawal et al., 2022) may be beneficial during and after RT to reduce symptoms and improve tolerance, whereas the topical form (Pereira et al., 2020) requires further confirmation.

-The vitamin C/E complex (Chung et al., 2016) and LLLT (Palma et al., 2017) show promising results but need validation in larger controlled studies.

-Stem cell therapy (Jakobsen et al., 2024) remains experimental and requires further investigation regarding efficacy, long-term safety, and placebo control.

-Some saliva substitutes (Visco-ease™, Bioxtra®) did not demonstrate benefits superior to placebo in the included trials (Paterson et al., 2019; Porangaba et al., 2024).

4.1. Further directions

Current evidence highlights several areas for future research:

-High-quality RCTs with larger samples and long-term follow-ups are needed to confirm the effectiveness of Low-Level Laser Therapy (LLLT), vitamins, stem cells, and topical pilocarpine.

-Direct comparative studies (head-to-head) among the most promising interventions would be useful for guiding therapeutic choices.

-Standardization of primary and secondary outcomes would facilitate study comparison and meta-analyses. Stratifying patients based on baseline salivary function would be beneficial.

-Studies optimizing intervention protocols (timing, dosage, duration) for vitamins, pilocarpine, acupuncture, and Low-Level Laser Therapy (LLLT) are needed.

-Stem cell research should focus on optimizing administration, minimizing immunogenicity, and using inert placebos while investigating the effects of dimethyl sulfoxide (DMSO).

-Mechanistic studies are needed to better understand how acupuncture, Low-Level Laser Therapy (LLLT), and stem cells exert their effects on salivary glands.

-Better understanding and control of the placebo effect in RIX studies are crucial.

4.2. Limitations of the study

Further research is needed to evaluate the impact of different RT techniques and doses that the salivary tissues absorb (IMRT vs. 3D-CRT, gland-sparing strategies) on treatment response for RIX.

Long-term safety assessment is essential, particularly for vitamins (oncologic risk) and stem cells (immunogenicity).

5. CONCLUSION

RIX remains a significant clinical issue that compromises the quality of life of HNC survivors. This systematic review has highlighted several interventions (acupuncture, sodium hyaluronate mouthwash, chewing gum, oral pilocarpine, potentially vitamins C/E, and LLLT) that show varying degrees of effectiveness in managing symptoms or preserving salivary function. However, the evidence is often limited by methodological factors, heterogeneity among studies, and a significant placebo effect. Stem cell therapy appears promising but requires further validation. Some saliva substitutes have not demonstrated superiority over placebo in these studies. Future research should focus on rigorous, large-scale trials with prolonged follow-up and standardized outcomes to establish the definitive effectiveness of these interventions and guide clinical practice in managing RIX.

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ANNEXES

Annex A. EORTC QLQ-C30

ENGLISH

eortc 1.png

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊_⌊_⌊_⌊_⌋

Your birthdate (Day, Month, Year): ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋

Today's date (Day, Month, Year): 31 ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Annex B. EORTC QLQ-H&N35

ENGLISH

EORTC QLQ - H&N35

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:		Not at all	A little	Quite a bit	Very much
31.	Have you had pain in your mouth?	1	2	3	4
32.	Have you had pain in your jaw?	1	2	3	4
33.	Have you had soreness in your mouth?	1	2	3	4
34.	Have you had a painful throat?	1	2	3	4
35.	Have you had problems swallowing liquids?	1	2	3	4
36.	Have you had problems swallowing pureed food?	1	2	3	4
37.	Have you had problems swallowing solid food?	1	2	3	4
38.	Have you choked when swallowing?	1	2	3	4
39.	Have you had problems with your teeth?	1	2	3	4
40.	Have you had problems opening your mouth wide?	1	2	3	4
41.	Have you had a dry mouth?	1	2	3	4
42.	Have you had sticky saliva?	1	2	3	4
43.	Have you had problems with your sense of smell?	1	2	3	4
44.	Have you had problems with your sense of taste?	1	2	3	4
45.	Have you coughed?	1	2	3	4
46.	Have you been hoarse?	1	2	3	4
47.	Have you felt ill?	1	2	3	4
48.	Has your appearance bothered you?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:		Not at all	A little	Quite a bit	Very much
49.	Have you had trouble eating?	1	2	3	4
50.	Have you had trouble eating in front of your family?	1	2	3	4
51.	Have you had trouble eating in front of other people?	1	2	3	4
52.	Have you had trouble enjoying your meals?	1	2	3	4
53.	Have you had trouble talking to other people?	1	2	3	4
54.	Have you had trouble talking on the telephone?	1	2	3	4
55.	Have you had trouble having social contact with your family?	1	2	3	4
56.	Have you had trouble having social contact with friends?	1	2	3	4
57.	Have you had trouble going out in public?	1	2	3	4
58.	Have you had trouble having physical contact with family or friends?	1	2	3	4
59.	Have you felt less interest in sex?	1	2	3	4
60.	Have you felt less sexual enjoyment?	1	2	3	4

During the past week:		No	Yes
61.	Have you used pain-killers?	1	2
62.	Have you taken any nutritional supplements (excluding vitamins)?	1	2
63.	Have you used a feeding tube?	1	2
64.	Have you lost weight?	1	2
65.	Have you gained weight?	1	2

Annex C. FACT-G

FACT-G (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box and go to the next section.*	☐				
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-G (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Somewhat	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Somewhat	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Annex D. UW-QOL

University of Washington Quality of Life Questionnaire (UW-QOL)

This questionnaire asks about your health and quality of life **over the past seven days**. Please answer all of the questions by checking one box for each question.

1. **Pain**. (Check one box: ☑)

   - ☐ I have no pain.
   - ☐ There is mild pain not needing medication.
   - ☐ I have moderate pain - requires regular medication (codeine or nonnarcotic).
   - ☐ I have severe pain controlled only by narcotics.
   - ☐ I have severe pain, not controlled by medication.

2. **Appearance**. (Check one box: ☑)

   - ☐ There is no change in my appearance.
   - ☐ The change in my appearance is minor.
   - ☐ My appearance bothers me but I remain active.
   - ☐ I feel significantly disfigured and limit my activities due to my appearance.
   - ☐ I cannot be with people due to my appearance.

3. **Activity**. (Check one box: ☑)

   - ☐ I am as active as I have ever been.
   - ☐ There are times when I can't keep up my old pace, but not often.
   - ☐ I am often tired and have slowed down my activities although I still get out.
   - ☐ I don't go out because I don't have the strength.
   - ☐ I am usually in bed or chair and don't leave home.

4. **Recreation**. (Check one box: ☑)

   - ☐ There are no limitations to recreation at home or away from home.
   - ☐ There are a few things I can't do but I still get out and enjoy life.
   - ☐ There are many times when I wish I could get out more, but I'm not up to it.
   - ☐ There are severe limitations to what I can do, mostly I stay at home and watch TV.
   - ☐ I can't do anything enjoyable.

5. **Swallowing**. (Check one box: ☑)

   - ☐ I can swallow as well as ever.
   - ☐ I cannot swallow certain solid foods.
   - ☐ I can only swallow liquid food.
   - ☐ I cannot swallow because it "goes down the wrong way" and chokes me.

6. **Chewing**. (Check one box: ☑)

   - ☐ I can chew as well as ever.
   - ☐ I can eat soft solids but cannot chew some foods.
   - ☐ I cannot even chew soft solids.

7. **Speech**. (Check one box: ☑)

- ☐ My speech is the same as always.
- ☐ I have difficulty saying some words but I can be understood over the phone.
- ☐ Only my family and friends can understand me.
- ☐ I cannot be understood.

8. **Shoulder**. (Check one box: ☑)

- ☐ I have no problem with my shoulder.
- ☐ My shoulder is stiff but it has not affected my activity or strength.
- ☐ Pain or weakness in my shoulder has caused me to change my work.
- ☐ I cannot work due to problems with my shoulder.

9. **Taste**. (Check one box: ☑)

- ☐ I can taste food normally.
- ☐ I can taste most foods normally.
- ☐ I can taste some foods.
- ☐ I cannot taste any foods.

10. **Saliva**. (Check one box: ☑)

- ☐ My saliva is of normal consistency.
- ☐ I have less saliva than normal, but it is enough.
- ☐ I have too little saliva.
- ☐ I have no saliva.

11. **Mood**. (Check one box: ☑)

- ☐ My mood is excellent and unaffected by my cancer.
- ☐ My mood is generally good and only occasionally affected by my cancer.
- ☐ I am neither in a good mood nor depressed about my cancer.
- ☐ I am somewhat depressed about my cancer.
- ☐ I am extremely depressed about my cancer.

12. **Anxiety**. (Check one box: ☑)

- ☐ I am not anxious about my cancer.
- ☐ I am a little anxious about my cancer.
- ☐ I am anxious about my cancer.
- ☐ I am very anxious about my cancer.

Which issues have been the most important to you during the past 7 days?
Check ☑ up to 3 boxes.

☐ Pain	☐ Swallowing	☐ Taste
☐ Appearance	☐ Chewing	☐ Saliva
☐ Activity	☐ Speech	☐ Mood
☐ Recreation	☐ Shoulder	☐ Anxiety

Annex E. QoL OHIP-14

Number	OHIP-14 Domain	Question
1.	Functional Limitation	1. Have you ever had difficulty pronouncing words / sentences because of problems with your oral cavity? 2. Have you ever felt unable to taste well because of problems with your oral cavity?
2.	Physical Pain	3. Have you ever had pain in your mouth? 4. Have you ever felt uncomfortable when chewing because of problems in the oral cavity?
3.	Psychological Discomfort	5. Have you ever felt worried/anxious because of problems with your oral cavity? 6. Have you ever felt tense because of problems with your oral cavity?
4.	Physical Disability	7. Have you ever felt dissatisfied with the food you consumed because of problems with your oral cavity? 8. Have you ever had to stop suddenly while chewing food because of problems in the oral cavity?
5.	Psychological Disability	9. Have you ever had difficulty feeling relaxed because of problems in the oral cavity? 10. Have you ever felt embarrassed because of problems with your oral cavity?
6.	Social Disability	11. Have you ever become irritable because of problems in the oral cavity? 12. Have you ever had difficulty carrying out your daily activities because of problems with your oral cavity?
7.	Handicap	13. Have you ever felt that your life is unsatisfactory because of problems with your oral cavity? 14. Have you ever found it difficult to do anything because of oral problems?

Annex F. GRIX

Question	Original Version (GRIXQ)
1	*Have you had a dry mouth during the day*
2	*Have you had a dry mouth outdoors*
3	*Have you had difficulties with eating due to a dry mouth*
4	*Have you had a dry mouth during activities*
5	*Have you had difficulties with talking due to a dry mouth*
6	*Did you drink more during the day due to a dry mouth*
7	*Have you had a dry mouth during the night*
8	*Have you had difficulties with sleeping due to a dry mouth*
9	*Did you need to drink during the night due to a dry mouth*
10	*Have you had sticky saliva during the day?*
11	*Have you had difficulties with eating due to sticky saliva*
12	*Have you had difficulties with talking due to sticky saliva*
13	*Have you had sticky saliva during the night*
14	*Have you had difficulties with sleeping due to sticky saliva*
Scoring	*Not at all* (1) *A little* (2) *Quite a bit* (3) *Very much* (4)