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REVIEW ARTICLE

A systematic review of salivary gland hypofunction and xerostomia induced by cancer therapies: management strategies and economic impact

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Abstract
Purpose This systematic review aimed to assess the literature for management strategies and economic impact of salivary gland hypofunction and xerostomia induced by cancer therapies and to determine the quality of evidence-based management recommendations.

Methods The electronic databases of MEDLINE/PubMed and EMBASE were searched for articles published in English since the 1989 NIH Development Consensus Conference on the Oral Complications of Cancer Therapies until 2008 inclusive. For each article, two independent reviewers extracted information regarding study design,

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study population, interventions, outcome measures, results, and conclusions.

Results Seventy-two interventional studies met the inclusion criteria. In addition, 49 intensity-modulated radiation therapy (IMRT) studies were included as a management strategy aiming for less salivary gland damage. Management guideline recommendations were drawn up for IMRT, amifostine, muscarinic agonist stimulation, oral mucosal lubricants, acupuncture, and submandibular gland transfer.

Conclusions There is evidence that salivary gland hypofunction and xerostomia induced by cancer therapies can be prevented or symptoms be minimized to some degree, depending on the type of cancer treatment. Management guideline recommendations are provided for IMRT, amifostine, muscarinic agonist stimulation, oral mucosal lubricants, acupuncture, and submandibular gland transfer. Fields of sparse literature identified included effects of gustatory and masticatory stimulation, specific oral mucosal lubricant formulas, submandibular gland transfer, acupuncture, hyperbaric oxygen treatment, management strategies in pediatric cancer populations, and the economic consequences of salivary gland hypofunction and xerostomia.

Keywords Cancer therapy · Salivary gland hypofunction · Xerostomia · Management strategies · Economic impact

Introduction

The profound salivary gland hypofunction (i.e., diminished salivary flow) and xerostomia (i.e., the subjective sensation of a dry mouth) often observed in response to external radiotherapy in the head and neck region may have a massive

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impact on patient's oral health and oral health-related quality of life (QoL) [1]. Importantly, the impact of salivary gland hypofunction and xerostomia on oral health and QoL is both acute and life-long. The adverse effects of other radiation regimens (e.g., interstitional radiotherapy, radioactive iodine) and chemotherapy on salivary gland function has been shown to be much less severe and chemotherapy-induced xerostomia to be reversible after the end of treatment [1].

Treatment of salivary gland hypofunction and xerostomia induced by cancer therapies is primarily symptomatic by stimulation of residual secretory capacity of the salivary glands or by the use of lubricating and/or moisturizing agents when saliva secretion cannot be stimulated. Although these treatment approaches have been shown to provide some relief of patients' dryness-related complaints, the continuing development of certain irradiation techniques to limit the dose to the salivary glands, agents to reduce the radiation injury to salivary gland tissue, and approaches to repair the radiation damage to the salivary gland will bear the largest potential to reduce post-radiotherapy salivary gland hypofunction and xerostomia. Patients may benefit from these approaches, thus providing patients with bearable xerostomia-related adverse effects after cancer treatment, since effects of symptomatic treatment in general is of short duration, lacks the properties of natural saliva, or may have significant side effects.

This systematic review represents a search and evaluation of the literature appearing since the 1989 NIH Development Consensus Conference on the Oral Complications of Cancer Therapies [2] and the publication of the National Cancer Institute (NCI) Monographs 1990 [3] evaluating management strategies of salivary gland hypofunction and xerostomia as sequelae of cancer therapies.

The 1989 NIH consensus

Consensus from the 1989 NIH Development Consensus Conference [2] relevant for management strategies of salivary gland hypofunction and xerostomia included:

- All cancer patients should have an oral examination before initiation of cancer therapy. Some clinicians may wish to include volumetric assessment of resting and stimulated whole saliva.
- No agreed-upon pretreatment strategies to prevent or minimize xerostomia.
- Currently, the best treatments for chronic xerostomia include regular use of topical fluorides, attention to oral hygiene, and sialagogues.

Directions for future research from the 1989 NIH Development Consensus Conference [2] applicable to management strategies of salivary gland hypofunction and xerostomia were directed towards:

- Development of accurate, quantifiable, reproducible criteria for assessing and classifying oral complications of cancer therapy.
- Development of radioprotective and chemoprotective agents.
- Development of more effective sialagogues and saliva substitutes and to evaluate their effectiveness in preventing the complications of xerostomia.
- Determination of the most effective strategies to ensure patient compliance with therapeutic regimens.

Historical summary of the literature before 1990 on management of salivary gland hypofunction and xerostomia as oral complications of cancer therapies

Before 1990, radiation techniques such as 3D-conformal radiotherapy and intensity-modified radiotherapy (IMRT) that currently are applied in head and neck cancer to reduce radiation damage to normal tissues (including salivary glands) were in development. At that time, the focus of research was on prevention and treatment of salivary glands from post-radiotherapy functional loss applying sialogogues, radioprotective agents, and/or saliva substitutes.

Regarding sialogogues, the observation that drug-induced depletion of submandibular serous cell granules before irradiation resulted in a decreased radiosensitivity of rodent submandibular glands linked the radiosensitivity of these cells to the content of secretory granules [4–6]. In rodents, these granules contain high amounts of proteolytic enzymes and transition metals [4]. Based on this phenomenon, it was reasoned that metal-catalyzed induction of lipid peroxidation of the membranes surrounding the granules will result in rupture of the granular membranes. Next, the resulting release of lytic enzymes within the cell would lead to cell lysis. In addition, in clinical studies the administration of sialogogues, in particular pilocarpine, was applied to stimulate any residual function of the salivary gland post-radiotherapy. This approach was shown to be worthwhile to a limited extent because the functional gain ceased as soon as the administration of the sialogogue was stopped [7]. Finally, to obtain a more persisting effect of pilocarpine, a pilot study was performed on the effect of administration of pilocarpine during radiotherapy. This study indicated that this approach might result in less radiation-induced reduction of salivary flow [8].

Regarding radioprotectors, animal studies showed that WR-2721 (amifostine) and its active metabolite WR-1065 accumulated in oral mucosa and salivary glands [9]. Next, the radioprotective effect of WR-2721 on rat parotid gland tissue

morphology and function could be shown in a rat model [10, 11]. Notwithstanding the radioprotective effect WR-2721 may have on tumor tissue too, in a pilot study it was shown that amifostine might have a radioprotective effect on chronic radiation injury to salivary gland tissue [12].

As before 1990 there were no effective, clinically available preventive measures, the treatment of hyposalivation was mainly palliative. This treatment consisted of oral hygiene practices, stimulation of residual salivary gland tissue (sialogogues), and symptomatic relief of oral dryness. Many rinsing solutions were tested, but an important disadvantage of all these mouthwashes was the necessity of frequent applications because of poor retention properties. For this reason, complex saliva substitutes were developed that contain agents not only to impart viscosity and to keep soft tissues moist but also include inorganic substances to retard enamel solubility. These substitutes were based on carboxymethylcellulose (CMC) [13, 14] or mucin [15]. Mucin-containing saliva substitutes were usually preferred over CMC-containing and placebo substitutes [16–19]. When compared to CMC substitutes, mucin-containing substitutes were shown to have superior rheological and wetting properties [20, 21].

Management strategies of salivary gland hypofunction and xerostomia induced by cancer treatments other than irradiation of the head and neck, such as radioactive iodine treatment, total body irradiation/hematopoietic stem cell transplantation, and chemotherapy, had been very sparsely covered in the literature before 1990.

Aims

To extend on the 1989 NIH Development Consensus Conference on the Oral Complications of Cancer Therapies [2], the goals of the present systematic review were the following:

1. Assess the management strategies for salivary gland hypofunction and xerostomia and determine the quality of recommendations for different treatment strategies.
2. Determine the economic impact of salivary gland hypofunction/xerostomia.

Systematic review methodology

Search strategy and criteria for selecting studies

The systematic review methodology has been described in detail elsewhere [1, 22]. In brief, a systematic literature search was conducted with assistance from a research librarian in the databases MEDLINE/PubMed and EMBASE for articles published between January 1, 1990 and December 31, 2008. The primary outcome was to identify all literature containing original data describing (1) prevalence of salivary gland hypofunction and/or xerostomia, (2) impact on oral health-related QoL, (3) management strategies of salivary gland hypofunction and xerostomia in cancer patients undergoing radiotherapy, chemotherapy, or combined treatment modalities as well as (4) the economic burden of such therapy.

An initial literature search targeting salivary gland hypofunction and xerostomia was performed in the electronic databases of MEDLINE/PubMed and EMBASE in March 2008 and updated in April 2009 using combinations of the MeSH terms of: [Saliva] OR [Salivary Glands] OR [Salivation] OR [Salivary Gland Diseases] OR [Xerostomia] OR [Dry Mouth] OR [Oral Dryness] AND [Neoplasms] OR [Head and Neck Neoplasms/Radiotherapy] OR [Radiotherapy] OR [Antineoplastic Agents] OR [Antineoplastic Combined Chemotherapy Protocols] OR [Combined Modality Therapy] OR [Whole-Body Irradiation] OR [Bone Marrow Transplantation] OR [Hematopoietic Stem Cell Transplantation] AND [Humans] AND [1990/01/01:2008/12/31]. The search results were imported into a computerized database (Reference Manager Version 12). The following publication types were eliminated: systematic and non-systematic reviews; studies not reporting actual data on xerostomia/salivary gland hypofunction; studies reporting data from previous publications or with a relevant later follow-up publication; phase I and II studies, opinion papers, and case reports; articles published before 1990; and articles from the 1990 NCI Monographs [3] based on the 1989 NIH Development Consensus Conference on the Oral Complications of Cancer Therapies [2]. Regarding xerostomia-related QoL, studies were included if they specifically related salivary gland hypofunction or xerostomia to QoL domains. Thus, single-item questions of dry mouth symptoms, i.e., the subjective amount or consistency of saliva without correlation to QoL domains, was interpreted as a measure of xerostomia and not included as xerostomia-related QoL. Furthermore, the search was limited to the English language. Gender and age were not limited.

Studies addressing management strategies are reported in the present paper, whereas observational studies dealing with prevalence, severity, and QoL related to salivary gland hypofunction and xerostomia as sequelae of anticancer therapies have been reported in a separate paper [1].

Review method

The abstract of each article was reviewed by the salivary gland hypofunction/xerostomia section head (SBJ) and the systematic review organizer (MTB). Irrelevant citations were removed according to the abovementioned criteria. The selected full-text articles were distributed to the

reviewer team along with an evaluation form customized for reviewing salivary gland hypofunction/xerostomia data modified from "Form T. Evaluation of studies assessing the effects of intervention" [22, 23]. The reviewers had been calibrated at teleconferences, by email correspondences, and/or at the Salivary Gland Hypofunction/Xerostomia Group Meeting at the MASCC/ISOO Symposium, Houston, Texas, June 2008. Two independent reviewers extracted information regarding study design, study population, interventions, outcome measures, methods, results, and conclusions for each article, and the evaluation results were compared and re-evaluated until consensus was reached (for further methodology details, see Brennan et al. [22]).

The review team was recruited from the Oral Care Study Group (chair, FKLS), Multinational Association of Supportive Care in Cancer (MASCC)/International Society of Oral Oncology (ISOO) and included expertise in the topic area of salivary gland hypofunction and xerostomia covering oral medicine, oral pathology, clinical oral physiology, oral oncology, oncology nursing, radiation oncology, oral immunology, pediatric dentistry, oral and maxillofacial surgery, palliative oncology, periodontology, epidemiology, and biostatistics.

Results

Description of studies

The electronic searches identified over a thousand titles and abstracts, and from these, 255 articles satisfied the inclusion criteria. Seventy-two interventional studies are described in the present systematic review, whereas 184 observational/cancer treatment studies are included in Jensen et al. [1]. Forty-nine studies addressing IMRT are included both in this paper as a management strategy and in the estimation of prevalence and severity of salivary gland hypofunction and xerostomia induced by cancer therapies in Jensen et al. [1]. For details regarding interventions, number of studies, and study designs of the included studies, see Table 1. None of the studies dealing with management strategies included pediatric/adolescent cancer populations.

Assessment of management strategies

IMRT

IMRT [1] allows a more accurate delivery of specific radiation dosage and dose distribution to the tumor and thereby brings about the possibility of better sparing of surrounding tissues, e.g., major salivary glands. As such, IMRT can be classified as a management strategy aiming for less salivary gland hypofunction and less xerostomia compared to conventional radiation regimens. IMRT was evaluated in 49 studies; two randomized controlled trials (both nasopharyngeal cancer), 38 cohort studies, two case–control, and seven cross-sectional studies. Thirty-three studies were not controlled. Eighteen studies reported data on salivary gland hypofunction (13 salivary flow rate, five by scintigraphy), and 44 studies assessed xerostomia. One study included a pediatric population [24]. General consen-

Table 1 Prevention and management strategies of salivary gland hypofunction and xerostomia associated with cancer therapies

Treatment strategy	Number of studies	RCT	Before and after	Cohort	Case–control	Cross-sectional
IMRT	49[a]	2		41	2	4
Amifostine	16[a]	9		6		1
Muscarinic agonist stimulation						
Pilocarpine after RT	16[b,c]	9	7			
Pilocarpine during RT	13[b]	11	2			
Cevimeline	2	1	1			
Bethanechol	1	1				
Gustatory and masticatory stimulation	4	1	2	1		
Mucosal lubricants/saliva substitutes	12[c]	8	4			
Submandibular gland transfer	4		4			
Acupuncture	4	2	1	1		
HBO treatment	2		2			

RCT randomized controlled trial, *IMRT* intensity-modulated radiation therapy, *RT* radiation therapy, *HBO* hyperbaric oxygen

[a] One study included both IMRT and amifostine

[b] One study included pilocarpine both during and after RT

[c] One study included both saliva substitutes and pilocarpine

sus from the randomized controlled trials, cohort, case–control, and cross-sectional studies provided supporting evidence that parotid-sparing IMRT has the potential to decrease the prevalence and severity of salivary gland hypofunction and xerostomia [25–56]. In addition, saliva secretion from spared salivary glands has the potential of increasing over time after therapy, unlike when similar tumors were treated by conventional radiation therapy [27, 36, 40, 47, 57–64]. As such, the benefits from IMRT on salivary gland function, xerostomia, and xerostomia-related QoL are most pronounced late (≥6 months) after radiotherapy and results in improvement of xerostomia-related QoL over time (assessed up to 2 years after therapy) [25–27, 31, 36, 37, 40, 47, 50, 52, 55, 57, 58, 60, 62–69]. To preserve salivary gland function, mean radiation doses ≤26–30 Gy [25, 57, 59, 60, 64, 67], <38 Gy [62], or <40 Gy [70] to the parotid glands have been suggested as well as submandibular/sublingual-sparing IMRT can be of relevance in selected patients [71] with a mean dose of ≤39 Gy to the submandibular/sublingual glands for potential recovery of gland function over time [72].

IMRT and salivary gland hypofunction/xerostomia-related QoL

Eleven studies specifically assessed the impact of xerostomia or salivary gland hypofunction on QoL aspects in relation to IMRT [25, 27, 31, 32, 34, 40, 44, 56, 58, 59, 73]. An association was found between xerostomia and QoL after parotid-sparing IMRT, with a decline in QoL in the 6-month period after radiation therapy and then followed by improvement of xerostomia-related QoL up to 24 months after RT [27, 31, 32, 34, 44, 58]. Regarding the impact of salivary gland hypofunction on QoL, whole saliva flow rates were related to oral comfort, speech, chewing/swallowing, and sleep [25]. Salivary gland hypofunction also demonstrated an impact on a combined QoL score of xerostomia's impact on daily activities, sleeping patterns, speech, swallowing [59], and to emotional function [40]. On the other hand, whole saliva as well as parotid and submandibular flow rates could not be shown to be associated with QoL scores up to 2 years after radiotherapy [27, 40, 58, 73], except for one report showing a correlation between stimulated parotid flow rate and speech problems [40].

Amifostine

Direct radioprotection in a classical way may be achieved by the use of amifostine, a radical scavenger, when systemically administered during radiation treatment [74–76]. Amifostine is preferentially accumulated in certain tissues, including the salivary glands, making these tissues less sensitive for radiation damage. Amifostine was assessed in 16 studies; nine randomized controlled trials, six cohort studies (two retrospective), and one cross-sectional study. Fifteen studies were performed in patients receiving radiotherapy or chemoradiation for a head and neck tumor; in one study, high dose ^{131}I treatment was used for differentiated thyroid cancer. Three studies reported data on salivary gland hypofunction (one by salivary flow rate, three by scintigraphy), seven studies assessed xerostomia, and six studies evaluated both parameters [all xerostomia, hypofunction was assessed either by salivary flow rate (five studies) or scintigraphy (two studies)].

The various cohort studies and randomized clinical trials performed revealed that amifostine has a potential to reduce complaints of xerostomia during and post-radiation treatment. The results of the various studies included were not consistent, however, as some studies showed a significant benefit of amifostine treatment on patients' experience of acute and late xerostomia, although the effect may be clinically minor [77] and in some of the studies the effect just reached significance [74, 75, 78–80], while other studies showed such a beneficial effect only for some acute and late time points assessed [81, 82]. Intravenous administration of amifostine has also been shown to reduce radiation-induced xerostomia and salivary gland dysfunction (scintigraphy) in patients treated with radioiodine [83].

Although many studies showed a beneficial effect on xerostomia, most studies failed to show that amifostine treatment also resulted in a smaller reduction in salivary flow rate in response to radiotherapy [74, 75, 82, 84, 85]. Secondary analyses of the salivary flow results of a few studies, which did not show a difference in salivary flow rate, reported that significantly more patients treated with amifostine than controls had meaningful unstimulated whole saliva secretion [74, 75]. One study mentioned that salivary gland functional data were collected, but no results were provided [79]. Scintigraphic studies showed that amifostine pretreatment may reduce radiation damage to salivary glands [48, 85, 86]. Moreover, in one of these studies, such a beneficial effect was only observed in salivary glands being irradiated with a cumulative dose <40 Gy [48].

A frequent documented major drawback of the use of amifostine is its severe adverse effects (e.g., hypotension, vomiting, nausea, allergic reaction), particularly when administered intravenously. Recent studies indicated that these adverse effects might be reduced by subcutaneous administration of amifostine because subcutaneous injection seems to be better tolerated by patients than intravenous administration [87, 88]. The main adverse effect after subcutaneous administration was nausea/vomiting, while more severe adverse effects such as hypotension and allergic reactions were not observed.

Finally, there is still the concern that amifostine might have an undesirable effect of tumor protection, raising questions about the appropriateness of amifostine in cancer patients [89]. The various trials included in this systematic review did not show this undesirable effect, although non-significant differences in survival and tumor control between amifostine-treated and control groups are present in the various studies.

Amifostine and salivary gland hypofunction/xerostomia-related QoL

QoL data related to xerostomia or salivary flow rates were very sparsely available in studies assessing the effect of amifostine on post-radiotherapy salivary gland functioning and xerostomia. Only one study showed a tendency that administration of amifostine had a beneficial effect on QoL related to salivary gland function as overall scores approached significance at the 1- and 2-year evaluation [75].

Muscarinic agonist stimulation

Pilocarpine

Pilocarpine is a cholinergic parasympathomimetic agent with mainly non-selective muscarinic action but also mild beta-adrenergic activity. Pilocarpine has been shown to enhance salivary secretion by stimulating muscarinic receptors on the surfaces of the salivary gland cells, and thereby reduces the sensation of dry mouth in patients in whom some functional salivary gland tissue has been preserved [90]. Pilocarpine hydrochloride (HCl) is approved in several countries for the treatment of xerostomia induced by radiotherapy in the head and neck region [91]. The present review includes 31 studies in which the efficacy of using oral pilocarpine *during* and *after* radiotherapy was evaluated.

Treatment with pilocarpine after radiation therapy

Sixteen studies evaluated the effect of pilocarpine after radiation therapy. Nine studies were randomized controlled trials (one was cross-over with patients as their own controls) [92–100] and seven were before and after studies (one controlled) [101–107]. Seven studies assessed xerostomia [94, 99–102, 104, 105] and nine studies evaluated both xerostomia and salivary flow rate [92, 93, 95–98, 103, 106, 107].

The dosage of pilocarpine HCl varied between studies; from 5 mg single dose and up to 30 mg daily (in dose titration studies). However, mainly a fixed dose of 5 mg three times daily was used. Also, the treatment period varied and only one study assessed the efficacy and safety of long-term treatment with oral pilocarpine HCl (36 months) [101]. Most studies reported a radiation dose to the parotid glands above 40 Gy, but one study related the level of xerostomia and salivary gland function to the dose/volume radiotherapy parameters and found that the response to pilocarpine HCl could not be predicted from radiation dose/volume [104]. Nevertheless, patients with some sparing of the major salivary gland and/or cumulative doses of <50 Gy on the major salivary glands were among the best responders to pilocarpine [104].

Data from the randomized clinical trials and before and after studies indicate that oral administration of pilocarpine HCl is effective in the treatment of radiation-induced xerostomia in patients with head and neck cancer [92–95, 99, 101, 104]. The effect of oral pilocarpine were also assessed after total body irradiation and radioactive iodine treatment reporting improvement of xerostomia [102] and a moderate although transient increase in whole saliva flow rates [106, 107] with no improvement of xerostomia [100], respectively, but the small number of patients included in these studies limits interpretation of the results.

Results from randomized, placebo-controlled trials suggest that oral pilocarpine HCl is more effective than a placebo treatment and that approximately 50% of the patients will benefit from oral pilocarpine treatment post-radiotherapy [92, 93, 95]. Optimum results were obtained with continuous treatment for more than 8 weeks with doses higher than 2.5 mg three times a day [92, 93, 95]. The time to response could be up to 12 weeks in some patients. Moreover, in two placebo-controlled clinical trials, topical oral administration of pilocarpine HCl suspended in a candy-like pastille [96] and a lozenge [98] has been shown to be more effective than placebo treatment in alleviating symptoms of post-radiation xerostomia (response rate 74% and 70%, respectively). An additional randomized cross-over study revealed that pilocarpine administered as a mouthwash improved xerostomia in 12 out of 17 patients with head and neck cancer who had received radiotherapy, and this was more effective than mucin-based artificial saliva [94].

Regarding salivary gland hypofunction, data from randomized clinical studies suggest that use of oral pilocarpine HCl increases unstimulated whole salivary flow rates [92, 93, 95], stimulated whole salivary flow rates [92], and unstimulated [92, 93, 95] and stimulated parotid saliva flow rates [92, 95] and mucous palatal secretion [103]. However, in the latter study, the parotid saliva flow was not significantly improved by stimulation with pilocarpine HCl [103]. Furthermore, variations in parotid flow throughout the pilocarpine treatment period as well as a lack of persistency of an initial increase in flow in response to pilocarpine were noted [92].

In a number of studies, the improvement in oral dryness did not correlate with the improvement in whole salivary and/or parotid flow rates [92, 96, 104], which

could be ascribed to a significant stimulatory action of pilocarpine HCl on minor (predominantly mucous) salivary glands and/or a more preserved functional capacity of these glands. This is further substantiated by a study in which it was shown that the palatal glands exhibit greater resistance to radiotherapy than the major salivary glands, and that the function of the palatal glands was partially restored to about 40–50% of the baseline function after radiotherapy [103].

Adverse effects were common in relation to treatment with pilocarpine but generally reported as being mild or of moderate severity [92, 93, 95, 101]. Nevertheless, some patients had to withdraw from trials due to adverse effects (6–15%). While the adverse effects were dose dependent, the response rates were not [92, 93]. The most common adverse effects at a standard dose of 5 mg three times daily included sweating (15–55%), headache (15%), urinary frequency (14%), vasodilatation (12%), dizziness (10%), dyspepsia (10%), lacrimation (10%), and nausea (6–20%) [92, 93, 95, 99, 101]. Although often not very prominent, the adverse effects of pilocarpine are of clinical relevance as the observed improvement of radiation-induced xerostomia and salivary gland function declines after the cessation of treatment with pilocarpine [92, 93]. Consequently, pilocarpine has to be administered life-long, which can be problematic due to its adverse effects. Oral pilocarpine HCl should be administered with caution and close medical monitoring is required in patients with cardiovascular disease like hypertension and arrhythmia as well as pulmonary disease like asthma, chronic bronchitis, or chronic obstructive pulmonary disease. Contraindications for pilocarpine HCl include narrow-angle glaucoma, uncontrolled asthma, and gastric ulcers [108, 109]. The interaction of pilocarpine HCl with other medications especially with agents with parasympathetic and beta-adrenergic effects may also preclude its use.

Treatment with pilocarpine during radiation therapy

It has been suggested that oral pilocarpine HCl given during radiotherapy may reduce salivary gland impairment and xerostomia both during and after radiotherapy [110]. Furthermore, it has no effect on tumor regrowth [111]. A total number of 13 studies assessed the protective effect of oral pilocarpine HCl being administered concomitantly with radiotherapy in patients with head and neck cancer; 11 randomized controlled trials (one was cross-over with patients as their own controls) [97, 110, 112–120] and two controlled before and after studies [121, 122]. Xerostomia was evaluated in all studies, whereas salivary gland function was measured in six studies, parotid and submandibular/sublingual salivary flow rates (unstimulated and stimulated) in three studies [110, 112, 120], unstimulated whole salivary flow rates in four studies [97, 116, 117, 119], and stimulated whole salivary flow rates in three studies [116, 117, 119] and salivary scintigraphy in one study [122]. Only one study was taking the radiation dose/volume parameter into account [120].

Seven studies found no statistical significant differences between patients treated with placebo and those treated with oral pilocarpine HCl during radiotherapy with regard to xerostomia [113, 115–117, 119, 120, 122]. A problem of most of these studies is that a wide range of cumulative doses was applied and thus the potential beneficial effect of pilocarpine can be confounded, i.e., patients subjected to a low cumulative dose (radiation effects are reversible) and patients subjected to a very high cumulative dose (radiation damage is so severe that no sparing effect of pilocarpine is to be expected). In a large study, unstimulated whole salivary flow rates significantly increased at 3 and 6 months in patients who received pilocarpine HCl, although there were no significant differences in xerostomia [119]. On the other hand, no improvement of salivary gland function (unstimulated/stimulated whole salivary flow rates and scintigraphy) has been observed in patients taking pilocarpine HCl during radiotherapy [117, 122]. In addition, no significant differences were found between patients who had received oral pilocarpine HCl and a placebo group with regard to submandibular/sublingual flow rates [120]. Importantly, the submandibular glands in this study either where removed as a part of the head and neck dissection procedure or had been exposed to high cumulative doses (>60 Gy). However, the results from the latter study indicated that the efficacy of oral pilocarpine HCl was dependent on the dose distributed to the parotid glands; i.e., in patients in whom the mean parotid dose exceeded 40 Gy, pilocarpine HCl significantly spared parotid gland function flow and reduced xerostomia, which became particularly significant after 12 months [120]. The adverse effects reported in the various studies were generally mild to moderate.

The protective effect of pilocarpine HCl on the salivary gland function is not fully understood. It has been stated that pilocarpine HCl acts by causing depletion of secretory granules in serous cells and thereby reducing the extent of radiation-induced salivary gland damage [121]. Others suggest that pilocarpine has stimulatory actions on minor salivary glands outside the radiation field [104, 110].

Oral pilocarpine and salivary gland hypofunction/xerostomia-related QoL

Two studies assessed the effect of pilocarpine HCl on post-radiotherapy salivary gland functioning and xerostomia-related QoL [104, 105]. Although some patients displayed a moderate improvement in radiation-induced xerostomia due to pilocarpine, administration of pilocarpine still had a

significant influence on QoL [104], while others found that disease-specific, health-related QoL recovered after radiotherapy despite persistent xerostomia [105].

Four studies assessed the xerostomia-related QoL in patients who had taken pilocarpine HCl during radiotherapy, and results were diverging [97, 116, 117, 119]. Accordingly, a slight improvement in QoL has been reported in patients taking pilocarpine with no improvement of xerostomia and salivary gland function [117], whereas others found concomitant improvement in xerostomia, salivary gland function, and xerostomia-related QoL [97]. In contrast, no significant improvement in QoL has also been shown, although salivary gland function was improved in response to pilocarpine [116, 119].

Cevimeline and bethanechol

Cevimeline HCl is a relatively new cholinergic agonist with high affinity for muscarinic M3 receptors, which are predominantly present on the salivary gland cells. It has minimal adverse effects on organs like heart and lungs. This review includes two large studies concerning the use of cevimeline HCl in the treatment of post-radiation xerostomia in patients with head and neck cancer; one open label study and a randomized controlled trial [123, 124]. In these studies, cevimeline HCl was generally well tolerated and oral administration of 30–45 mg three times daily for 52 weeks improved xerostomia (response rate 59% at the final visit) [124] and significantly increased unstimulated, but not stimulated, whole salivary flow rate [123]. About 70% experienced adverse effects, and most of them were mild to moderate [123]. The most common adverse effect was sweating followed by dyspepsia.

Other systemic sialogogues include bethanechol HCl which is a carbamic ester of β-methylcholine resistant to the action of cholinesterase. Most of the effect of bethanechol HCl is due to M3 muscarinic activity. The efficacy of bethanechol HCl was tested in a randomized phase III study concomitant with radiotherapy in patients with head and neck cancer and revealed a significant increase in unstimulated whole flow rate and a tendency of xerostomia to decrease [125]. Further studies are needed to determine the long-term efficacy and safety of both cevimeline HCl and bethanechol HCl.

Gustatory and masticatory stimulation

Four studies assessed gustatory and/or masticatory effects on saliva secretion following different radiation regimens; one randomized controlled trial, one cohort study, and two before and after studies. Two studies were not controlled. Two studies reported data on salivary gland hypofunction (one by salivary flow rate, one by scintigraphy) and three studies assessed xerostomia. No general consensus can be extracted from the included studies, since the addressed topics are sporadic within the field of salivary gland hypofunction and xerostomia as sequelae of cancer therapies.

Small studies of sucking on acidic candy and salivary-stimulating lozenge resulted in an increase in whole saliva secretion and improvement of oral dryness, respectively [126, 127], whereas an oral antimicrobial lozenge administered to reduce acute radiation toxicity, i.e., mucositis, did not influence xerostomia during radiation treatment [128]. A study of ^{131}I treatment for post-surgical thyroid cancer reported that early use of a sialogogue, i.e., sucking of lemon candy (intervention starting 1 h after administration of radioactive iodine and continuing for 5 days) aggravated xerostomia and salivary gland hypofunction as measured by scintigraphy compared to postponed administration of lemon candy stimulation until 1 day after ^{131}I treatment [129]. The authors explained this by the high blood concentration of ^{131}I early period after administration and an increase in blood flow in the major salivary glands in response to the sialogogue causing a greater amount of ^{131}I to be accumulated in the salivary gland tissue [129]. None of the studies assessed xerostomia-related QoL.

Oral mucosal lubricants/saliva substitutes

Oral mucosal lubricants/saliva substitutes are mainly useful in patients who do not respond to pharmacological, gustatory, or masticatory stimulation. Various saliva substitutes or dry mouth systems with constituents resembling the physical properties of glycoproteins and antibacterial components of saliva have been developed and are commercially available in the form of moisturizing gels, mouthwashes, or sprays. Twelve studies assessed lubricating gels, sprays, and mouthwashes all following radiation treatment in the head and neck; seven randomized controlled trials (patients served as their own controls in a randomized cross-over design) and five before and after studies (four non-controlled; see also the historical summary of the literature study as many lubricant/substitute studies were performed before 1990). All studies assessed xerostomia and two studies reported salivary flow rate. Only studies addressing saliva substitutes in patients suffering from salivary gland hypofunction and xerostomia induced by cancer therapies were included in this systematic review. Generally, the various saliva substitutes were sporadically tested and the study designs included small study populations testing the saliva substitute for a short period of use. The saliva substitutes evaluated were based on animal mucin, carboxymethylcellulose (CMC), hydroxypropylmethylcellulose (HPMC), hydroxyethylcellulose (HEC), polyglycerylmethacrylate (PGM), polyeth-

ylene oxide, xanthan gum, linseed extract, rape oil, and aloe vera.

Three studies assessed gels containing HPMC applied ad libitum during post-radiation periods of 2 weeks or five times daily during and for 4 weeks after radiation treatment (the gel was supplemented by a mouthwash and/or toothpaste as part of the dry mouth regimen) [130–132]. HPMC gels showed potential of reducing xerostomia [130–132], and the reduction of oral discomfort was reported to be more pronounced compared to CMC gel [130, 132]. No changes were observed in unstimulated and stimulated whole saliva secretion in response to the use of HPMC or CMC gel [130].

Two studies evaluated HEC gels applied ad libitum for periods of 2–4 weeks in patients previously treated by irradiation in the head and neck region [131, 133]. It was reported that HEC significantly decreased xerostomia [131, 133] and was slightly superior to PGM gels in reducing xerostomia [131].

Five studies included CMC gels/fluid/spray in their testing administered ad libitum for 1-, 2-, and 3-week periods as well as five times a day during and for 4 weeks after radiation treatment (supplemented by toothpaste in two studies) [130, 132, 134–136]. They consistently reported CMC preparations to decrease xerostomia [130, 132, 134–136]. Additionally, some studies reported that CMC gel was slightly inferior to PGM gel [130, 132], polyethylene oxide [134], and linseed fluid [135] in reducing xerostomia, whereas on the other hand CMC spray was found to be equally effective to mucin (extracted from pig stomach) spray, aloe vera gel, and rape oil spray [136].

Three studies assessed linseed fluid used ad libitum for 1- and 3-week periods post-irradiation and found that it reduces xerostomia [135–137]. Also, it was noted that the effect tended to increase with increasing time of use of the fluid (during a 3-week period) [135], that generally the patients with the most severe symptoms experienced the greatest relief [137], and that linseed fluid was preferred to CMC fluid [135].

Three studies assessed a mucin spray for a 1-week study period or for a 3-month period following radiotherapy in the head and neck region [94, 136, 138]. A decrease in xerostomia was observed in two studies [136, 138], whilst the third study compared a mucin spray and found it inferior to a pilocarpine mouthwash [94]. It has to be mentioned, however, that a pilocarpine mouthwash is meant to stimulate salivary flow and the mucin spray is meant to relieve oral dryness in patients who do not respond to a stimulation therapy. Moreover, no difference was found in the potential to reduce xerostomia when mucin spray was compared to CMC spray, aloe vera gel, and rape oil spray [136]. Thus, aloe vera gel and rape oil spray may also relieve xerostomia [136].

One study assessed a xanthan gum-based spray compared to a placebo of similar composition except for the xanthan gum and found that they reduced xerostomia to the same degree [139].

One study of PGM found only a statistically significant reduction in oral dryness-related complaints in patients suffering from severe xerostomia compared to moderate xerostomia [140].

The major disadvantage of the saliva substitutes described in the included studies is the generally short duration of relief they provide, and patients may instead prefer frequent use of water [134]. However, the lubricating effect of some saliva substitutes were reported to last for longer than others, i.e., linseed longer (58 min) than CMC (31 min) [135], and polyethylene oxide up to 2 h [134].

The majority of studies on this topic were published before 1990 (see historical summary in the “Introduction” section) and indicated that salivary substitutes are more effective than a placebo. Moreover, it is worthwhile to try another substitute as patient preference may play a role in the success of this treatment. The following advice on the general use of oral mucosal lubricants is extracted from Regelink et al. [140]. If severe xerostomia, the application of a saliva substitute with gel-like properties may provide relief during the night and when daily activities are at a low level [140]. During daytime, a saliva substitute with less viscous properties resembling natural saliva based on, e.g., polyacrylic acid, xanthan gum, or mucin may provide relief [140]. If moderate xerostomia, saliva substitutes with a rather low viscoelasticity, such as substitutes based on CMC, hydroxypropylmethylcellulose, and mucin, or low concentrations of xanthan gum and polyacrylic acid are indicated, supplemented by a gel to provide relief during night or other periods of severe oral dryness [140]. At slight xerostomia, little alleviation is to be expected from the use of saliva substitutes [140].

Oral mucosal lubricants/saliva substitutes and salivary gland hypofunction/xerostomia-related QoL

Previous studies have shown that mucin spray increased the patients’ daily activities and health-related QoL [19]. Xerostomia-related functions of chewing/swallowing, speech, and taste have been shown to improve with the use of HEC gel, while swallowing and taste were improved by HPMC gel [131]. Also, these parameters demonstrated improvement during application of linseed fluid when compared to CMC fluid [135]. On the other hand, another study found neither HPMC spray nor CMC spray significantly influenced xerostomia-related QoL related to eating/swallowing, speech, dry mouth at night/on waking, or taste [130]. Along this line, neither CMC spray, mucin spray, rape oil spray nor aloe vera

gel were shown to relieve xerostomia-related difficulties with eating and taste, while xerostomia effects on speech and quality of sleep were improved by all of these compounds [136, 138]. When looking at subgroups of patients, a study of PGM spray found xerostomia-related complaints improved in patients suffering from severe xerostomia compared to patients with moderate xerostomia [140], and older patients to have greater benefit from mucin spray than younger patients with regards to quality of sleep [138]. The use of HEC gel has been shown to significantly improve xerostomia-related QoL, including restrictions of social life, daily activities, eating, taste, oral discomfort, and tension/level of mood [133].

Surgical transfer of submandibular gland

Early reports on surgical transfer of one submandibular gland to the submental space (outside the radiation portal) have shown preservation of submandibular gland function and reduction of radiation-induced xerostomia to some extent in selected patients followed up to 2 years after treatment [141–144]. If all major salivary glands are to be included in the radiation portal, this management strategy may potentially be of relevance in strictly selected oropharyngeal and hypopharyngeal cancer patients who are to undergo surgery as the primary treatment before irradiation and where the contralateral submandibular gland, or the side with clinically negative cervical lymph nodes in midline primaries, can be surgically translocated to the submental space [141, 143]. A prerequisite is that the submental space, now containing the submandibular gland, is not included in the radiation portal. After the inclusion date was set as a criterion for selecting the literature eligible for inclusion in this systematic review, data from a phase III study comparing surgical transfer of the submandibular gland and oral pilocarpine were published. The results of that phase III study showed better preservation of salivary flow rate 3 to 6 months after radiotherapy with the surgical transfer of the submandibular gland procedure when compared to the administration of oral pilocarpine during and for 3 months after irradiation [145]. These new results will be addressed in future work and the management guidelines revised accordingly.

Acupuncture

Results of a preliminary before and after study including 18 patients with head and neck cancer who had received radiotherapy and who did not respond to oral pilocarpine treatment indicated that acupuncture (using auricular points and in some cases supplemented with electro-stimulation) is effective in alleviating xerostomia [146]. However, some residual functional capacity of the remaining salivary gland tissue is needed [146]. A randomized clinical trial using acupuncture (twice weekly for 6 weeks using the acupoints ST-6, LI-4, ST-36, and SP-6) in patients with post-radiotherapy xerostomia revealed a significant increase in the unstimulated whole salivary flow rates in both patients treated with real acupuncture and sham-treated patients [147]. However, in acupuncture-treated patients, xerostomia-related problems were significantly improved. The effects of acupuncture treatment on unstimulated and stimulated whole salivary flow rates and xerostomia were shown to last up to 6 months and with additional acupuncture therapy presumably for up to 3 years [148]. Finally, in a recent single-blind randomized clinical trial using manual acupuncture, dry mouth measures improved and unstimulated whole salivary flow rates tended to increase [149]. Furthermore, the improvement of xerostomia was closely related to QoL [149]. Unfortunately, the sample size of this study was small.

In summary, acupuncture treatment appears to offer a potential future intervention for the treatment of radiation-induced xerostomia [146–149]. Moreover, acupuncture is a treatment modality without serious adverse effects. Further clinical trials including sham acupuncture are needed to substantiate the clinical benefits of acupuncture and to understand the underlying mechanisms behind its actions on salivary gland function.

Hyperbaric oxygen treatment

Two studies reported on irradiated head and neck cancer patients receiving hyperbaric oxygen treatment as part of the treatment/prevention of osteoradionecrosis and suggested that there may be a decrease in xerostomia following hyperbaric oxygen treatment [150, 151]. Either the hyperbaric oxygen treatment was applied perioperative [151] or the mean time between application of hyperbaric oxygen treatment and the end of radiation therapy was 23 months (range 4–82 months) [150]. Moreover, both studies did not include a control group. In addition, it has to be kept in mind when interpreting these trials that recovery of xerostomia following radiation therapy may be achieved up to 2 years after cancer treatment [152]. Also, patients may have accepted that salivary gland hypofunction and xerostomia are unavoidable after cancer treatment and therefore have adjusted their expectations. Any potential improvement within this period, therefore, may possibly not be completely attributed to hyperbaric oxygen treatment.

Management guidelines and quality of recommendations (according to the ASCO clinical practice guidelines) [22]

IMRT

If oncologically feasible, IMRT is recommended as a standard approach in head and neck cancer to limit the cumulated

radiation dose to critical normal tissues. IMRT can reduce the dose to parotid, submandibular/sublingual, and minor salivary glands while helping maintain adequate whole saliva flow rates and reducing xerostomia. This recommendation is based on consensus of two randomized controlled trials and supporting consistent evidence from 41 cohort studies, two case–control trials, and four cross-sectional studies.

Guideline The panel recommends the use of parotid-sparing IMRT for prevention of salivary gland hypofunction and xerostomia in head and neck cancer patients (Level II evidence, grade A recommendation).

Amifostine

Phase III trials have shown amifostine reduced xerostomia after radiation therapy. However, the possibility of tumor protection remains a clinical concern. No consensus could be reached regarding recommendation as most clinical studies do not have the statistical power to evaluate the influence of amifostine on the therapeutic index. Also, the trial design of most amifostine studies is at least questionable and the outcomes subject to debate. Many trials failed to adequately document allocation concealment or the conduct of an intention-to-treat analysis, and the majority of the trials lacked a placebo in the control arms [76].

Guideline No guideline possible due to lack of consensus on the interpretation of existing evidence (Level II evidence, grade C recommendation).

Muscarinic agonist stimulation

After radiotherapy Administration of pilocarpine HCl following radiation therapy has shown reduced prevalence of xerostomia and improved salivary gland function to some extent. However, the effect is temporary and of relatively short duration, thus treatment needs to be lifelong. Pilocarpine is generally well tolerated but may induce mild to moderate systemic anticholinergic adverse effects, and medical monitoring of patients with cardiovascular and pulmonary diseases is recommended.

Guideline The panel recommends the use of oral pilocarpine following radiation therapy in head and neck cancer patients for improvement of xerostomia. The improvement of salivary gland hypofunction may be limited (Level II evidence, grade B recommendation).

During radiotherapy Regarding the use of pilocarpine HCl concomitantly with radiation therapy, results are inconsistent whether to reduce xerostomia and salivary gland hypofunction, but in some patients a beneficial effect has been shown on xerostomia.

Guideline The panel cannot recommend the use of oral pilocarpine during radiotherapy in head and neck cancer patients for improvement of xerostomia as the results of the various randomized clinical trials were not univocal (Level II evidence, grade C recommendation). In addition, the improvement of salivary gland hypofunction was shown to be limited. The dissimilar results on sparing of salivary gland function are thought to be highly dependent on the wide range of cumulative doses applied. The only trial providing an analysis of sparing of parotid gland function related to mean parotid dose indicated significant sparing of parotid gland function and reduced xerostomia for mean parotid doses exceeding 40 Gy, and is thus in favor of suggesting the use of pilocarpine during radiotherapy.

Gustatory and masticatory stimulation

Sugar-free lozenges, acidic candies, or chewing gum may potentially produce transitory relief from xerostomia by stimulating residual capacity of salivary gland tissue, but this has been sparsely addressed within the field of salivary gland hypofunction and xerostomia as sequelae of cancer therapies, so no recommendation can be given for this specific group of patients.

Guideline No guideline possible due to little evidence on which to base a guideline for patients suffering from xerostomia induced by cancer therapies (Level III evidence, grade D recommendation).

Oral mucosal lubricants/saliva substitutes

Oral mucosal lubricants/saliva substitutes are suggested for reducing xerostomia following radiation therapy including major salivary glands in the radiation field. It has been shown that these lubricants/substitutes are more effective than a placebo; however, they offer limited relief of the dry mouth feeling and of relatively short duration. Furthermore, they lack the protective effects of saliva, although some of them contain fluoride and electrolytes to prevent demineralization.

No specific mucosal lubricant formulas are recommended. It should be noted that the body of studies within this field are conducted before 1990 (see historical summary in the introductory chapter).

Guideline The panel recommends the use of oral mucosal lubricants/saliva substitutes for short-term improvement of xerostomia following radiation therapy in head and neck cancer patients (Level II evidence, grade B recommendation).

Surgical transfer of submandibular gland

Early results suggest that surgical transfer of one submandibular gland to the submental space potentially may be of relevance to preserve salivary gland function and reduce xerostomia in strictly selected oropharyngeal and hypopharyngeal cancer patients to be irradiated.

Guideline The panel suggests that the obtained level of sparing by submandibular salivary gland transfer might be of clinical significance (Level IV evidence, grade B recommendation).

Acupuncture

Acupuncture treatment appears to offer an intervention for the treatment of radiation-induced xerostomia in patients with a residual functional capacity of the salivary glands and is a treatment modality without serious adverse effects.

Guideline The panel suggests the use of acupuncture to stimulate salivary gland secretion and to alleviate xerostomia (Level II evidence, grade C recommendation).

Hyperbaric oxygen treatment

Insufficient data available so no recommendation possible regarding hyperbaric oxygen treatment.

Guideline No guideline possible due to no evidence on which to base a guideline (Level IV evidence, grade D recommendation).

Economic impact of salivary gland hypofunction and xerostomia as an oral complication of cancer therapies

A review of the literature revealed no data on inpatient or outpatient charges or resource utilization related specifically to the presence and/or severity of salivary gland hypofunction and xerostomia. When resource utilization was reported, e.g., mean treatment days, extra clinic visits, or days of parenteral nutrition, the resource utilization was reported to be due to parameters such as mouth pain, the inability to eat or drink, management of toxicity in general, extreme weakness, or fatigue. Furthermore, the resource utilization was reported during or in close proximity to the cancer treatment, and no studies covered this issue in a long-term perspective. Nevertheless, salivary gland hypofunction and xerostomia induced by cancer therapies may potentially have a direct economic impact of cancer treatment or be an aggravating factor with implications for some of the abovementioned parameters and thereby indirectly increase the financial costs of cancer therapies.

Epilogue

Salivary gland hypofunction and xerostomia are clinically significant adverse effects from cancer therapies and occur frequently. Since the 1989 NIH Development Consensus Conference on the Oral Complications of Cancer Therapies, the scientific approach to management strategies of salivary gland hypofunction and xerostomia as sequelae of radiotherapy in the head and neck region has focused on preservation of salivary gland function, primarily the parotid glands, by the advances in radiation techniques, including the appearance and optimizing of 3D treatment planning, conformal radiation techniques and IMRT, the development of cytoprotective agents and preservation by stimulation with cholinergic muscarinic agonists as well as the application of new lubricating or stimulatory agents, surgical transfer of submandibular glands, and acupuncture during and following cancer treatment. Salivary gland hypofunction and xerostomia management strategies were seldom addressed in other cancer treatments than radiation therapy of head and neck cancer.

In conclusion, IMRT currently shows the greatest potential as a management strategy by permanently preserving salivary gland function in head and neck cancer patients and other available management strategies of xerostomia are mainly symptomatic, of short duration, lack the protective effects of saliva, or may potentially have significant adverse effects. The systematic review found few reports dealing with effects of gustatory and masticatory stimulation, use of oral mucosal lubricants on xerostomia during and after cancer therapies, hyperbaric oxygen treatment, and management strategies in pediatric cancer populations in general. No studies addressed the economic consequences of salivary gland hypofunction and xerostomia on oral/general health and QoL, and such evaluations should be undertaken in future studies both during cancer treatment and in a life-long perspective. Furthermore, there are currently two new promising approaches, viz. gene therapy [153] and stem cell transfer [154] both aiming for regain of function after radiotherapy. New studies emerged after the inclusion criterion of this systematic review will be addressed in future work and the management guidelines revised accordingly.

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