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ORIGINAL ARTICLE

A systematic review of salivary gland hypofunction and xerostomia induced by cancer therapies: prevalence, severity and impact on quality of life

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Abstract
Purpose This systematic review aimed to assess the literature for prevalence, severity, and impact on quality of life of salivary gland hypofunction and xerostomia induced by cancer therapies.

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. Two independent reviewers extracted information regarding

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study design, study population, interventions, outcome measures, results and conclusions for each article.
Results The inclusion criteria were met by 184 articles covering salivary gland hypofunction and xerostomia induced by conventional, 3D conformal radiotherapy or intensity-modulated radiotherapy in head and neck cancer patients, cancer chemotherapy, total body irradiation/hematopoietic stem cell transplantation, radioactive iodine treatment, and immunotherapy.
Conclusions Salivary gland hypofunction and xerostomia are induced by radiotherapy in the head and neck region depending on the cumulative radiation dose to the gland tissue. Treatment focus should be on optimized/new approaches to further reduce the dose to the parotids, and particularly submandibular and minor salivary glands, as these glands are major contributors to moistening of oral tissues. Other cancer treatments also induce salivary gland hypofunction, although to a lesser severity, and in the case of chemotherapy and immunotherapy, the adverse effect is temporary. Fields of sparse literature included pediatric cancer populations, cancer chemotherapy, radioactive iodine treatment, total body irradiation/hematopoietic stem cell transplantation, and immunotherapy.

Keywords Cancer therapy · Radiotherapy · Chemotherapy · Salivary gland hypofunction · Xerostomia · Quality of life

Introduction

Saliva plays a crucial role in the maintenance of tooth integrity, dilution of food detritus and bacteria, and by

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mechanical cleansing of the oral cavity. Saliva also provides antimicrobial activity preventing oral infections and plays an important part in the upper gastrointestinal functions including taste perception, formation of food bolus, facilitation of mastication, swallowing and speech, as well as lubrication of oropharyngeal and upper esophageal mucosa (for review, see Pedersen et al. [1]). Whole saliva is the designation for the mixed fluid in the mouth, which derives from the major salivary glands (the parotid, submandibular, and sublingual glands, which account for 90% of the saliva production) and the minor salivary glands (which account for the remaining 10%). Under resting conditions, about two-thirds of the saliva is produced by the submandibular glands, which comprise both serous and mucous acinar cells and produce a viscous mucin-rich fluid, while the sublingual glands contribute with 1–2% and mainly consist of mucous acinar cells [2]. The serous parotid glands produce a watery and protein-rich fluid that, upon stimulation, accounts for about 50% of the total volume of saliva [3]. Even though the minor salivary glands produce only 10% of the total volume of saliva, they play a significant role in lubricating the mucosa [4]. The sensation of oral dryness may occur when a person's normal unstimulated flow rate is reduced by about 45–50% [5, 6]. Hyposalivation, a pathologic low saliva secretion, is commonly defined as a resting whole saliva flow rate of ≤0.1 ml/min and/or a stimulated whole saliva flow rate of ≤0.5 ml/min [7].

Salivary gland hypofunction, usually accompanied by a persistent feeling of a dry mouth, implies a seriously increased risk of development of oral infections and carious destruction of teeth, oral mucosal discomfort and pain, hampered oral functioning, and a worsened nutritional state. As a consequence, patients with salivary gland hypofunction usually are restricted in their daily activities, have a poorer general well being, and are handicapped in their social interactions [8]. Regarding head and neck cancer treatment, it is well accepted that salivary gland hypofunction (objective evidence of reduced salivary output) and xerostomia (subjective feeling of dry mouth) are significant morbidities during and following radiotherapy involving exposure of the major and minor salivary glands [9]. The salivary glands are superficially located compared to most head and neck tumors, and thus, the ionizing radiation has to pass through the salivary glands to effectively treat the tumor. In contrast, no firm conclusion has been reached in the literature regarding whether chemotherapy induces salivary gland hypofunction/xerostomia [10], and studies on this subject as well as other cancer treatments such as radioactive iodine treatment and total body irradiation/hematopoietic stem cell transplantation are sparse in comparison to the substantial number of publications on salivary gland sequelae induced by irradiation of the head and neck.

In 1989, a NIH Development Consensus Conference on Oral Complications of Cancer Therapies was held [11]. General consensus from this conference that applied to salivary gland hypofunction and xerostomia could be summarized as follows: (1) to establish baseline data with which all subsequent examinations can be compared and (2) to identify risk factors for the development of oral complications. These recommendations resulted in some directions for future research applicable to salivary gland hypofunction and xerostomia, viz., (1) to devise accurate, quantifiable, reproducible criteria for assessing and classifying oral complications of cancer therapy, (2) to determine incidence and prevalence of oral complications related to different types of anticancer therapies and related risk factors, and (3) to study the mechanisms of cancer treatment injury to the hard and soft oral tissues at the molecular and cellular level and determine how these affect the oral environment.

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 [11] and the related publication of the National Cancer Institute (NCI) monographs 1990 [12] in order to clarify the impact of newer cancer therapies on the prevalence and severity of salivary gland hypofunction and xerostomia. The aims of the current review were (1) to assess the prevalence and severity of salivary gland hypofunction and xerostomia by cancer therapy regimen and (2) to assess the impact of salivary gland hypofunction and xerostomia on quality of life (QoL).

Systematic review methodology

Search strategy and criteria for selecting studies

A systematic literature search was conducted with assistance from a research librarian in the databases MEDLINE/PubMed and EMBASE for articles published between 1 January 1990 and 31 December 2008. The primary outcome was to trace all literature containing original data on prevalence of salivary gland hypofunction and/or xerostomia as well as the economic burden, impact on oral health-related QoL, or management strategies of salivary gland hypofunction and xerostomia in cancer patients undergoing head and neck radiotherapy, chemotherapy, or combined treatment modalities.

The literature search including 31 December 2007 was performed in March 2008 and an update including 31 December 2008 was performed in April 2009 using combinations of the MeSH terms of [Saliva] OR [Salivary Glands] OR [Salivation] OR [Salivary Gland Diseases] OR [Xerostomia] AND [Neoplasms] OR [Head and Neck Neoplasms/Radiotherapy] OR [Radiotherapy] OR [Anti-

neoplastic Agents] OR [Antineoplastic Combined Chemotherapy Protocols] OR [Combined Modality Therapy] OR [Total Body Irradiation] OR [Bone Marrow Transplantation] OR [Hematopoietic Stem Cell Transplantation] AND [Humans] AND [1990/01/01:2008/12/31]. In MEDLINE/PubMed, the MeSH term [Xerostomia] is presently defined as "decreased salivary flow" and not as the subjective feeling of having a dry mouth (decreased salivary flow should be hyposalivation or salivary gland hypofunction); therefore, the search was exploded to include the text words of [dry mouth] and [oral dryness]. The search results were imported into a computerized database (Reference Manager Version 12). The search results from each of the electronic databases of MEDLINE/PubMed and EMBASE were combined, and duplicate publications were eliminated.

The following publication types were eliminated from the present systematic review: 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 [12] based on the 1989 NIH Development Consensus Conference on the Oral Complications of Cancer Therapies [11]. Furthermore, the search was limited to English language. Gender and age were not limited. Studies addressing prevalence, severity, and QoL related to different types of anticancer therapies are reported in the present paper, whereas interventional studies addressing management strategies and the search for economic impact are reported in Jensen et al. [13].

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 criteria mentioned above (publication types) creating a preliminary set of potentially relevant publications. Then, the full text articles were distributed to the reviewer team along with an evaluation form customized for reviewing salivary gland hypofunction/xerostomia data [14]. This form was modified by the review group during calibration sessions from "Form T. Evaluation of studies assessing the effects of intervention" [15]. Each reviewer then independently evaluated a number of allocated articles. Two independent reviewers extracted information regarding study design, study population, interventions, outcome measures, methods, results, and conclusions for each article. The evaluation results were compared and re-evaluated until consensus was reached between two reviewers.

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 calibrated at teleconferences, by email correspondences and/or at the Salivary Gland Hypofunction/Xerostomia Group Meeting at the MASCC/ISOO Symposium, Houston, TX, June 2008. The reviewers included experts in the areas of salivary gland hypofunction and xerostomia and included the following disciplines: 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.

Statistical estimation of salivary flow rate and prevalence/severity of xerostomia

Results of salivary flow rates and prevalence and severity of xerostomia were extracted when available from the included studies. The data were weighted and pooled. Quality weighting of the data included in the estimation of saliva flow rate and prevalence and severity of xerostomia was based on sources of bias, representativeness, scale validity, and sample size. Further details of the quality weighting and data handling have been reported elsewhere [14].

Results

Description of studies

The electronic searches identified over a thousand titles and abstracts and from which a total of 356 potentially relevant publications were selected according to the defined criteria. After examination of the abstracts and full-text articles by the review group, 101 articles were excluded for reasons summarized in Table 1, and 255 articles satisfied the inclusion criteria. Regarding cancer treatment, number of studies, and study designs of the included studies, see Table 2.

Of the 255 trials included, 238 (93%) assessed adult populations, six (2%) assessed mixed adult and pediatric populations, and 11 (4%) included populations of children and adolescents.

Methodological issues of included studies

Regarding evaluation of salivary gland function, discrepancies in the definitions of salivary gland hypofunction and xerostomia were observed. Xerostomia, i.e., the subjective feeling of dry mouth, was at times being confused with and used as a synonym of salivary gland hypofunction or hyposalivation, i.e., the objective measure of decreased saliva secretion.

Table 1 Reasons for exclusion identified during reviewing (not apparent from literature search)

Reason for exclusion	Number of articles
Review	2
Case report	1
Phase I-II trials	41
Not sufficient data on salivary gland hypofunction or xerostomia	18
No data presented on salivary gland hypofunction or xerostomia	27
Salivary gland hypofunction/xerostomia not induced by cancer therapy	6
Data from previous publication or later follow-up publication relevant	2
Anecdotal intervention, not relevant	3
Published before 1990	1

Between studies, considerable variation was found regarding saliva collection procedures [whole saliva, selective parotid saliva (single or both glands pooled), or submandibular/sublingual saliva, all major glands pooled after collection], stimulatory state of the glands (unstimulated, stimulated by chewing paraffin wax, parafilm, rubber, rubber ring, surgical latex tube, vitamin C tablets, corn chips, chewing gum, sucking on lemon candy, or oral application of 1%, 2%, or 5% citric acid) and flow rate units, i.e., ml/min, ml/2 min, ml/5 min, ml/10 min, g (no time unit), g/2 min, g/5 min, g/10 min, and percent change with/without reporting of baseline values. Furthermore, assessments were carried out at a wide range of different time points during and after cancer treatment and, in some cases, ranges from a few months to several years after cancer therapy were pooled within studies.

Great diversity existed in data reporting, i.e., incidence/prevalence, mean, standard deviation, standard error of the mean, median, range, 95% confidence interval, no indications of variability, and reporting of actual data in tables or reporting in figures (not always readable from figures). When reporting descriptive statistics and estimates based on salivary flow rate data, these data tend not to be normally distributed, but may be skewed to the lower end.

Furthermore, multiple different validated or unvalidated assessment scales of xerostomia and xerostomia-related QoL were used. Within studies, heterogeneity of cancer diagnoses and cancer treatment regimens was found.

Another general characteristic was that studies lacked reporting on confounding factors known to influence salivary gland function, e.g. co-morbidities and medication intake (xerogenic medications and polypharmacy).

The above mentioned methodological issues made comparing results challenging both within study groups and between studies.

Salivary gland hypofunction and prevalence of xerostomia by cancer therapy regimen

Radiation therapy in head and neck cancer

The systematic review of the literature of radiation therapy in head and neck cancer is presented for separate radiation

Table 2 Cancer treatments associated with salivary gland hypofunction and xerostomia

Treatment strategy	Number of studies	RCT	Cohort	Case–control	Cross-sectional
Conventional RT	82[a]		59	1	22
3D conformal RT	14[b]		13		1
IMRT	49[b]	2	38	2	7
Mixed head and neck RT regimens	1		1		
Radioactive iodine treatment	10		8		2
Conditioning TBI/CT and HSCT	11[c]		9[c]		3[c]
CT	16[a]		10		6
Immunotherapy	3		3		

RCT randomized controlled trials, *RT* radiation therapy, *3D* three-dimensional, *IMRT* intensity-modulated RT, *TBI* total body irradiation, *CT* chemotherapy, *HSCT* hematopoietic stem cell transplantation

[a] One study included both conventional RT and CT

[b] One study was counted in both 3D conformal RT and IMRT

[c] One study included both cohort and cross-sectional design

regimens, i.e., conventional radiation therapy, 3D conformal radiotherapy and intensity-modulated radiation therapy (IMRT). However, regarding the extraction of data for our estimates of prevalence and severity of xerostomia and salivary gland hypofunction, the numbers available on grading of xerostomia and salivary flow rates were not sufficient to split by type of radiation regimen.

Xerostomia data could be determined from 79 studies and salivary flow rate data from 46 studies.

For all head and neck radiation regimens pooled, the weighted xerostomia prevalence and severity [by visual analog scale (VAS) and grades 1-4), and the salivary flow changes are presented in Table 3 and Figs. 1, 2 and 3. The results showed a 93% prevalence of xerostomia during irradiation followed by slightly lower prevalences in the range of 73.6–85.3% from 1 month to more than 2 years post-treatment compared to 6.0% before treatment (Table 3 and Fig. 1). Along this line, the severity of xerostomia measured by VAS (1–100) showed an unchanged medium score from 1 month to more than 2 years post-treatment (Fig. 2). The severity grading of xerostomia (grades 1–4) demonstrated a pattern with grade 2 as the most prevalent (43.6–46.0%) during treatment and in the early period from 1–6 months after radiotherapy and grade 1 as the second most prevalent (24.3–37.5%) (Table 3). Hereafter, a shift was demonstrated, with grade 1 xerostomia as the most prevalent (39.2–41.7%) in the late period 6 months to more than 1 year post-treatment and grade 2 as the second most prevalent (23.9–37.8%; Table 3). Grade 2 was at its lowest more than 2 years after irradiation (Table 3). Grade 3 xerostomia showed some fluctuation with 11.5% during treatment, 3.9% at the lowest 1–3 months after radiotherapy and 15.6% at the highest more than 2 years after treatment (Table 3). Grade 4 xerostomia was not introduced until late after radiation therapy and only affected a few percentages of the cancer population treated by head and neck irradiation (Table 3).

The weighted and pooled whole saliva secretions showed profoundly lower unstimulated and stimulated whole salivary flow rates during radiation therapy with a further reduction at 1–3 months post-treatment (Fig. 3). However, slightly higher unstimulated and stimulated whole saliva flow rates were shown from 1 year and 6 months, respectively, and up to 2 years after radiotherapy (Fig. 1). The period from 1 year following radiotherapy with slightly higher salivary flow rates corresponds to the period with a shift toward higher prevalences of grade 1 and lower grade 2 xerostomia (Table 3). In addition, the stimulated secretion was consistently higher than the unstimulated secretion, implying a residual capacity of the salivary gland tissue and a potential of stimulatory management of xerostomia following head and neck irradiation (Fig. 3).

Conventional radiotherapy

Eighty-two studies assessed salivary gland function in relation to conventional radiation therapy (studies included accelerated, hyperfractionated, and boost radiotherapy, concomitant chemotherapy, and chemotherapy boost). Fifty-nine were cohort studies, 22 were cross-sectional studies, one was a case–control study, and 24 studies were controlled. Twenty-six studies measured salivary gland hypofunction (25 salivary flow rate and one scintigraphy) and 66 studies assessed xerostomia (only ten studies combined assessments of salivary gland hypofunction and xerostomia).

Xerostomia is the most frequent and permanent complaint after conventional radiotherapy [16–63] and is related to the cumulative dose of irradiation and the volume of salivary gland tissue that has been included in the treatment portals [57, 64–68]. When all salivary glands are included (e.g., nasopharyngeal carcinoma), the highest prevalence and severity of salivary gland hypofunction and xerostomia has been reported, followed by radiation treatment of oropharyngeal carcinoma, while the least dryness complaints and loss of salivary gland function were reported for radiation treatment of laryngeal/epilaryngeal cancer [18, 20, 25, 28, 50, 69–72].

For our estimates of prevalence, data on xerostomia induced by conventional radiotherapy could be extracted from 38 studies, but there were not sufficient data to report separately on the grading of xerostomia or salivary flow rates in response to conventional radiation therapy. The weighted prevalence of xerostomia showed some fluctuation with 81.4% during treatment, 70.9% at the lowest 1–3 months after radiotherapy, and 90.9% at the highest more than 2 years after treatment (Table 3 and Fig. 1). Thus, no improvement was shown when comparing the prevalence during treatment and more than 2 years post-treatment (Table 3 and Fig. 1).

The literature review showed that unstimulated and stimulated saliva secretion decreases dramatically after conventional radiation therapy, with the major salivary glands included within the radiation portal [40, 52, 73–78]. The severity of this damage is dependent on the cumulative radiation dose and the proportion of the major salivary glands included within the treatment portal and is thus less pronounced in unilaterally irradiated patients [66, 69, 79–85]. The early response to irradiation results in decreased salivary flow rates within the first week of treatment, and a second phase of decrease in secretion may be noted after completion of radiation therapy, with no significant recovery after high-dose (~60 Gy to the salivary gland tissue) radiotherapy [40, 66, 74, 79, 80, 83, 84, 86, 87]. This was also seen in our estimates of whole saliva flow rates (Fig. 1). Unfortunately, few studies assessed the actual

Table 3 Weighted prevalence of xerostomia and severity grade by post-treatment phase and type of radiation therapy

Type of cancer therapy	Pre-tx	During RT	1-3 months post-RT	3-6 months post-RT	6-12 months post-RT	1–2 years post-RT	>2 years post-RT
All studies							
Prevalence	6.0%	93.0%	73.6%	79.0%	82.9%	77.6%	85.3%
Std. err.	0.03	0.05	0.07	0.05	0.05	0.06	0.04
95% CI	0–3.9	82.9–100	58.9–88.4	68.1–89.9	72.6–93.2	64.7–90.6	77.6–93.0
Grade 1							
Prevalence	5.4%	37.5%	24.3%	31.4%	39.2%	44.1%	41.7%
Std. err.	0.04	0.05	0.04	0.08	0.06	0.10	0.09
95% CI	0–62.6	26.5–48.5	14.4–34.2	13.6–49.2	24.9–53.4	18.9–69.2	22.4–61.0
Grade 2							
Prevalence	0%	43.7%	46.0%	43.6%	35.0%	37.8%	23.9%
Std. err.	NA	0.07	0.09	0.09	0.03	0.14	0.06
95% CI	NA	28.4–59.1	27.0–65.0	22.7–64.5	28.8–41.2	3.1–72.5	10.4–37.4
Grade 3							
Prevalence	0%	11.5%	3.9%	7.2%	5.7%	6.1%	15.6%
Std. err.	NA	0.07	0.02	0.03	0.03	0.03	0.05
95% CI	NA	0–26.7	0–9.9	1.2–13.2	0–11.8	0.3–11.9	4.3–26.8
Grade 4							
Prevalence	0%	0%	0%	0%	2.6%	0%	1.7%
Std. err.	NA	0	0	0	0.03	0	0.03
95% CI	NA	0–0	0–0	0–0	0–10.0	0–0	0–8.4
References, see conventional RT, 3D conformal RT and IMRT							
Conventional RT							
Prevalence	10.4%	81.4%	70.9%	83.2%	71.5%	83.8%	90.9%
Std. err.	0.07	0.09	0.09	0.06	0.09	0.09	0.03
95% CI	0–4.2	57.5–100	50.2–91.7	67.6–98.9	47.3–95.6	63.9-100	83.4–98.4
References [16, 17, 19, 22, 23, 26, 28, 29, 31, 32, 35, 37–39, 41, 44, 46–48, 50, 53, 55, 58–60, 62–64, 67, 68, 71, 89–91, 93, 104, 120, 199]							
3D conformal RT							
Prevalence	0%	NR	46.7%	74.5%	90.3%	75.4%	69.4%
Std. err.	NA		NA	NA	NA	0.05	NA
95% CI	NA		NA	NA	NA	10.1–100	NA
References [95, 99, 104, 105, 107]							
IMRT							
Prevalence	11.8%	100%	89.4%	72.7%	90.1%	66.0%	68.1%
Std. err.	NA	0.04	0.10	0.10	0.04	0.11	0.06
95% CI	NA	90–100	61.0–100	39.5–100	81.0–99.2	34.3–97.7	40.4–95.7
References [109, 118–122, 124, 126–129, 131, 133, 136–139, 142, 144–146, 149, 151–153]							

Tx treatment, *Std. err.* standard error, *CI* confidence interval, *NR* none reported, *NA* not applicable, since data derived from one study only, *RT* radiation therapy, *3D* three-dimensional, *IMRT* intensity-modulated RT

flow rate. Only one study assessed the flow rate of the buccal and labial minor salivary glands and found both to be significantly decreased after conventional radiation therapy (head and neck cancer diagnoses not specified) compared to healthy controls [76]. Furthermore, only one study assessed sequelae of childhood irradiation. The study population had been treated for head and neck rhabdomyosarcoma from 7.5 to 33 years previously and 12% (2/17) of

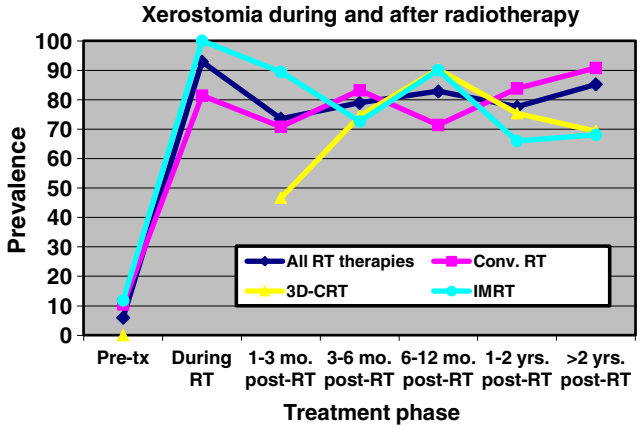

Fig. 1 Pooled and weighted prevalences of xerostomia induced by head and neck radiotherapy. *RT* radiotherapy, *Conv.* conventional, *3D-CRT* 3-dimensional conformal RT, *IMRT* intensity-modulated RT, *Tx* treatment, *Mo.* months, *Yrs.* years. Based on references in Table 3

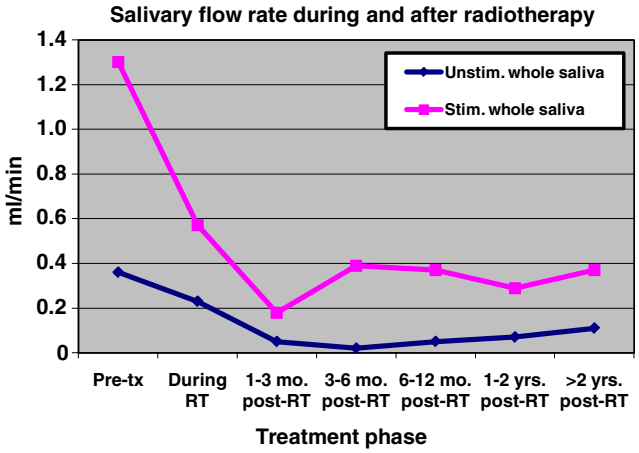

Fig. 3 Pooled and weighted data of unstimulated and stimulated whole saliva flow changes during and after head and neck radiotherapy. *Tx* treatment, *RT* radiotherapy, *Mo.* months, *Yrs.* years, *Unstim.* unstimulated, *Stim.* stimulated. Based on references [27, 31, 40, 54, 64, 66, 67, 69, 73, 74, 76–80, 83, 84, 86, 97, 102, 110, 115, 118, 122]

survivors reported suffering from xerostomia [88]. This lower prevalence of xerostomia in the latter patient group compared to patients treated for head and neck cancer is also due to the lower cumulative radiation dose applied in the treatment of rhabdomyosarcoma.

Concomitant chemotherapy usually had been administered in a proportion of the radiation patients included in the various studies, and data on salivary flow rate and xerostomia were generally not reported separately for this patient group. Thus, no firm conclusion can be drawn if concomitant chemotherapy and radiation therapy has a potential additive effect on salivary gland hypofunction [24, 36, 48, 67, 72, 89–94].

3D conformal radiotherapy

Fourteen studies assessed 3D conformal radiotherapy and effects on salivary gland function: 13 cohort studies and one cross-sectional study. Three studies were controlled. Eight studies reported data on salivary gland hypofunction (seven salivary flow rates and one scintigraphy), and 11 studies assessed xerostomia. The studies demonstrated consensus that reduced radiotherapy dosages by 3D conformal radiotherapy to contralateral parotid glands resulted in less loss of salivary gland function post-radiotherapy up to 2 years after completion of radiotherapy [95–102] and 3D conformal radiotherapy to have a

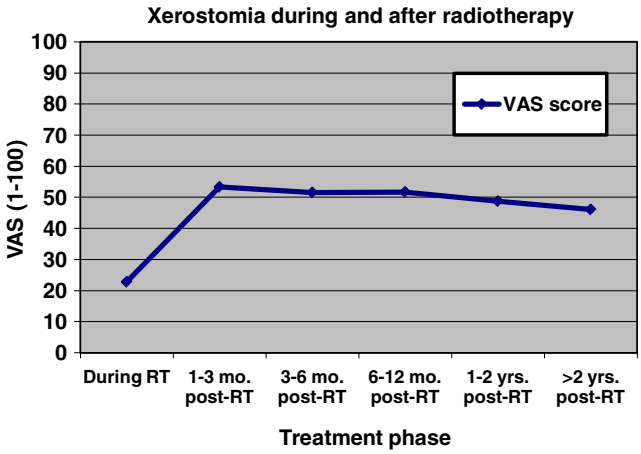

Fig. 2 Pooled and weighted data of xerostomia assessed by visual analog scale (VAS) during and after head and neck radiotherapy. *RT* radiotherapy, *Mo.* months, *Yrs.* years. Based on references [20, 25, 27, 33, 37, 42–45, 49, 51, 52, 54, 55, 58, 61, 67, 70, 72, 92, 100, 108, 110, 113, 116, 122, 130, 132]

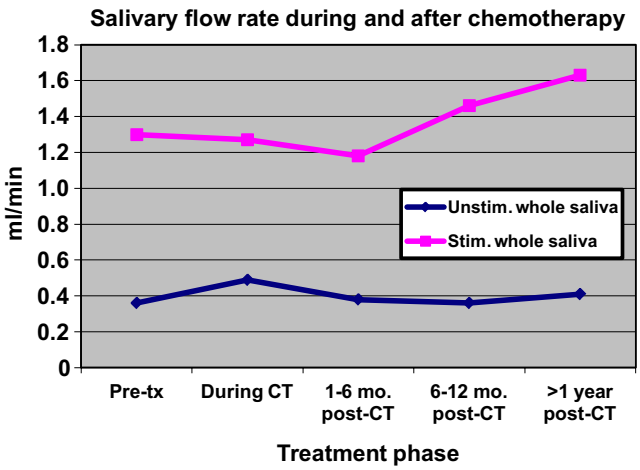

Fig. 4 Pooled and weighted data of unstimulated and stimulated whole saliva flow changes with chemotherapy. *Tx* treatment, *CT* chemotherapy, *Mo.* months, *Unstim.* unstimulated, *Stim.* stimulated. Based on references [27, 179–184, 186, 188, 190, 192]

potential to decrease the prevalence and severity of xerostomia [95, 99, 100, 103–107]. As was shown for conventional radiotherapy, xerostomia was also shown to be significantly worse following bilateral 3D conformal radiotherapy compared to unilateral treatment [108].

For our estimates of prevalence, data on xerostomia induced by 3D conformal radiotherapy could be extracted from five studies, but there were not sufficient data to report separately on the grading of xerostomia or salivary flow rates. The weighted prevalence of xerostomia is seen in Table 3 and Fig. 1. Since very few data were available, results are only reported for some assessment time points. The result at 1–3 months after irradiation showed a low prevalence of xerostomia, but this was based on only one study of mixed cancer diagnoses not including nasopharyngeal cancers (Table 3 and Fig. 1). At 6–12 months post-treatment, the xerostomia prevalence was at the same level as the results of IMRT and higher than conventional radiotherapy, while more than 1 year post-treatment, the prevalence was lower than after conventional radiotherapy and approaching the same level as IMRT (Table 3 and Fig. 1).

Intensity-modulated radiation therapy

IMRT allows more accurate delivery of specific radiation dosage and dose distribution to the tumor mass according to tumor location and severity, with sparing of the normal tissue and organs at risk, e.g., salivary glands. 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 and five scintigraphy), and 44 studies assessed xerostomia. Finally, only one study assessed IMRT and xerostomia in a pediatric population [109].

Based on the two randomized controlled trials, IMRT of early stage nasopharyngeal carcinoma compared to conventional/2D radiotherapy resulted in sparing of salivary gland function one year after treatment [110, 111]. Regarding xerostomia 1 year after treatment, one of the randomized controlled trials found lower prevalence of physician-assessed grades 2–4 oral dryness with IMRT, but no difference in patient-assessed oral dryness between patients treated with IMRT or 2D radiotherapy [111], and the other found no difference in physician-assessed oral dryness between IMRT and conventional radiotherapy, but the symptom of sticky saliva to be significantly lower with IMRT than conventional radiotherapy [110].

In summary, from the various cohort, case–control and cross-sectional studies several consensus conclusions can be drawn. Parotid-sparing IMRT have the potential to decrease the prevalence and severity of salivary gland hypofunction [110–114], and the saliva secretion from spared salivary glands may also have the potential of increasing over time after therapy, unlike when treated by high-dose conventional radiation therapy [110, 111, 113, 115–123]. Furthermore, a large variety in mean cumulative radiation doses to parotid gland tissue has been reported above, which radiation damage to parotid glands has become irreversible. These cumulative doses range from ≤26–30 Gy [112, 115, 117, 118, 123, 124] and <38 Gy [121] to <40 Gy [82]. The differences in the reported dose ranges may partly be due to few cases with a low mean parotid dose, thus rendering dose–response curves with greater statistical uncertainty [125].

For our estimates of prevalence, data on xerostomia induced by IMRT could be extracted from 25 studies, but there were not sufficient data to report separately on the grading of xerostomia or salivary flow rates. The weighted prevalence of xerostomia is seen in Table 3 and Fig. 1. The results showed a 100% prevalence of xerostomia during IMRT, which was higher than during conventional irradiation (Table 3 and Fig. 1). At 6–12 months post-treatment, the xerostomia prevalence was at the same level, as the results of 3D conformal radiotherapy and higher than conventional radiotherapy, while more than 1 year post-treatment, the prevalence was lower than after conventional radiotherapy (Table 3 and Fig. 1). The results at 6–12 months after IMRT showed a peak in the prevalence of xerostomia; likewise, the results 6–12 months after conventional radiotherapy showed a slope down (Fig. 1). Accordingly, when interpreting the data, it has to be taken into consideration that different head and neck cancer diagnoses are pooled both within and between studies, and the distribution of nasopharyngeal cancers and laryngeal cancers in the included studies may significantly impact the prevalence of xerostomia to a higher or lower level, respectively.

The literature review showed that parotid sparing IMRT have the potential of decreasing the prevalence and severity of xerostomia [103, 110–113, 120, 126–150]. After an initial post-IMRT decline (1–3 months), salivary secretion and xerostomia gradually recover over time (1–2 years) [110–113, 115, 116, 118, 120–124, 126, 130, 134, 144, 146, 149, 151–154]. Nevertheless, incomplete improvement in xerostomia by sparing of the parotid gland via IMRT emphasizes the need to enhance protection of the submandibular glands as the greatest contributors to whole saliva during rest as well as the sublingual and minor salivary glands. As such, submandibular/sublingual sparing IMRT can be of relevance in selected patients [155] also because the seromucous submandibular saliva is a better moistener for the oral tissues than the pure serous parotid secretion. Comparable to data on parotid gland sparing, a mean dose of ≤39 Gy has been found for potential recovery of submandibular/sublingual gland function over time [156].

In addition, sparing minor salivary glands might be very useful and applicable; as with IMRT, the mean radiation dose to the oral cavity can be reduced [113].

Radioactive iodine treatment

Ten studies assessed effects of radioactive iodine treatment of thyroid cancer on salivary glands: eight cohort studies and two cross-sectional studies of which three studies were controlled. Radioactive iodine is actively accumulated in salivary gland tissue, and sialadenitis is a common sequela [157–162] along with decreased salivary secretion and xerostomia [157–159, 161–163]. Salivary gland hypofunction and xerostomia following radioactive iodine treatment has, by most authors, been reported to be dependent on cumulative activity [157, 158, 163], while others did not find this coherence [161]. A low prevalence of xerostomia (5%) has been observed within a few days after low-dose radioactive iodine treatment [164], which is comparable with the prevalence of xerostomia in the normal population [165], while higher prevalences have been found after high-dose iodine treatment.

For our prevalence calculations, data on xerostomia induced by radioactive iodine treatment could be extracted from only six studies, and there was insufficient data available to report on the grading of xerostomia or salivary flow rates. The weighted prevalence of xerostomia was 0.5% (0.01; 0–7.7) (standard error; 95% confidence interval) before treatment [161, 162], and 33.6% (0.1; 0–75)–37.8% (0.07; 15.8–59.8) at 1–2 years after treatment [158, 162, 163, 166].

The literature review showed that only four studies reported data on salivary gland hypofunction. Assessment was done by scintigraphy in two studies [158, 163] and by sialometry in another two [166, 167]. The scintigraphy studies revealed a higher impairment in salivary gland function in parotid glands than in submandibular glands. A sialometry study showed unstimulated and stimulated whole saliva flow rates to be reduced by 27–41 and 27–36%, respectively, in a small cohort study of only four patients and a larger cross-sectional study within a time span of 4 months to 20 years after radioactive iodine treatment [167]. Another study assessing unstimulated whole saliva flow rate did not find any difference between patients at 8.4±7 years after radioactive iodine treatment compared to thyroid cancer patients only treated surgically [166].

Conditioning total body irradiation/chemotherapy and hematopoietic stem cell transplantation

Eleven studies were included, examining effects of conditioning total body irradiation and/or chemotherapy and hematopoietic stem cell transplantation on salivary gland function (the specific effects of graft versus host disease is not included in the present systematic review, although some patients in the included studies developed graft versus host disease at some time point of the study period). The saliva-related end point was salivary flow rate in nine studies and xerostomia in three studies; three studies were cross-sectional (one study was controlled) and nine were cohort studies (three were controlled and one study included both a cohort and cross-sectional design).

It was reported that patients may suffer from xerostomia after conditioning by total body irradiation prior to high-dose chemotherapy and bone marrow transplantation [168, 169].

For our prevalence calculations, very few numbers on the prevalence of xerostomia induced by conditioning total body irradiation/chemotherapy and hematopoietic stem cell transplantation could be extracted from three studies. There were not sufficient data available to report on neither the grading of xerostomia, salivary flow rates nor pretreatment for comparison. The weighted prevalence of xerostomia during treatment was 40.2% (0.15; 0–100) [168, 169], and one study reported 79% at 6.9 years after treatment [170].

The biological effects of radiation on salivary gland tissue are greatly dependent on how the physical dose is delivered. A higher radiation dose per fraction, as in total body irradiation, with a lower cumulative dose results in less salivary tissue damage when compared to a radiation fractionation scheme with lower radiation dose per fraction but much higher cumulative dose in head and neck cancer patients.

With regards to salivary flow rate, stimulated whole saliva flow rate has been reported to be significantly more reduced within 3 months after bone marrow transplantation in children (before the age of 12 years) preconditioned by total body irradiation combined with chemotherapy compared to children preconditioned by chemotherapy only [171]. This is consistent with findings of other studies of unstimulated and stimulated whole saliva and stimulated parotid saliva in mixed pediatric/adolescent and adult populations [172–174]. However, one study examining unstimulated whole saliva flow rate did not find a difference from before hematopoietic stem cell transplantation compared to up to 3 months after treatment in a small adult population when the conditioning regimen consisted of high-dose chemotherapy only [175].

After bone marrow transplantation (4–12 years after treatment), normal stimulated whole saliva secretion has been reported in children conditioned with chemotherapy, while conditioning regimens including total body irradiation may result in a permanent reduction [171, 176]. Normal unstimulated and stimulated whole salivary flow rates have also been reported in a small group of adult patients a few years after total body irradiation, high-dose chemotherapy, and bone marrow transplantation [172]. The prevalence of hyposalivation (unstimulated whole saliva)

has been reported to be about 26% of pediatric and adult study populations at cross-sectional examination at a mean of 1.5 and 6.9 years after bone marrow transplantation in study populations with pooled conditioning regimens of chemotherapy as well as chemotherapy/total body irradiation, and hyposalivation (stimulated whole saliva) was reported to affect 31% and 61% of the patients in the respective studies [170, 177].

When looking separately at conditioning with chemotherapy or total body irradiation, hyposalivation of stimulated whole saliva has been reported to be present in 26% and 54–70% of the pediatric patients, respectively [176, 178]. Furthermore, stimulated whole salivary flow rate has even been reported to exceed the baseline level 4 years after bone marrow transplantation in children preconditioned with chemotherapy while still decreased in total body irradiated patients [171].

Finally, it has been reported that significant risk factors for low stimulated whole saliva secretion in children after bone marrow transplantation were conditioning with total body irradiation, recipient female sex, and seropositivity for at least three herpes viruses [178]. If none of the risk factors was present, the estimated probability of stimulated whole saliva hyposalivation was 1%, whereas the probability was 68% when all risk factors were present [178].

Cancer chemotherapy

Sixteen studies were identified assessing salivary gland function in relation to cancer chemotherapy. The saliva-related end point was salivary flow rate in 11 studies, xerostomia in two studies, and another three studies assessed both parameters. Ten of the studies were cohorts and six were cross-sectional of which six and four were controlled, respectively. The results show divergence likely due to few and heterogeneous studies regarding underlying cancer diagnoses, chemotherapy regimens, different study periods in relation to administration of chemotherapeutics, and number of previous chemotherapy cycles. Therefore, it is not possible to draw any consistent conclusion on the effects of cancer chemotherapy on prevalence of salivary gland hypofunction and xerostomia.

Reports of salivary flow rate in adult acute leukemia patients suggest that whole saliva flow rates decreases within a few days following induction therapy and then returns toward baseline level within 1–2 weeks [179–182]. Along this line, hyposalivation of stimulated whole saliva (i.e., <0.7 ml/min) was found in up to 75% of acute leukemia patients during chemotherapy [179]. Furthermore, significantly decreased unstimulated and stimulated whole saliva flow rates and significantly increased prevalence of xerostomia also has been found during and 6 months following adjuvant moderate standard dose chemotherapy (cyclophosphamide, epirubicin/methotrexate, and 5-fluorouracil) for solid tumors (i.e., breast cancer) [183, 184]. Cross-sectional examinations during or 1/2–7 years after chemotherapy of adult and childhood solid and hematological malignancies also suggested decreased saliva secretion and xerostomia [185–187]. On the contrary, other studies of moderate and intensive chemotherapy regimens in the treatment of hematological malignancies did not reveal changes in unstimulated and stimulated whole saliva secretion during [27, 188, 189], within a few weeks after [190] or up to several years after treatment [191, 192]. Finally, it has been reported that patients having low salivary secretion before cancer treatment seem to be at higher risk of developing hyposalivation in response to chemotherapy and to have prolonged recovery [184, 193].

For our prevalence calculations, data on xerostomia induced by chemotherapy could be extracted from four studies, but there were not sufficient data to report on the grading. The weighted prevalence of xerostomia showed a prevalence of 49.9% (0.04; 33.6–66.2) during chemotherapy [185, 187, 190], while a single study reported prevalences before treatment of 7% and after treatment, i.e., 47% at 6 months and 48% at 1 year after chemotherapy [184]. The weighted unstimulated and stimulated whole salivary flow rates were based on data extracted from 11 studies [27, 179–184, 186, 188, 190, 192], and the pooled flow rates seemed mainly unchanged during chemotherapy. From 6 to 12 months after chemotherapy, the stimulated whole salivary flow rates tended to be higher than during and up to 6 months after chemotherapy (Fig. 4).

Thus, data suggest that some patients temporarily may suffer from distinct hyposalivation and xerostomia during and following cancer chemotherapy, while others are not affected to any noticeable extent. Unfortunately, most studies assessed salivary gland function only during chemotherapy with no long-term follow-up. Furthermore, because the treatment regimens differ depending on cancer diagnoses and since different antineoplastic medications are likely to have different mechanisms of action on a cellular level, it is necessary to distinguish between individual chemotherapy regimens in the study designs to arrive at any useful conclusions regarding adverse drug effects on salivary gland function.

Immunotherapy

Three cohort studies reported on the effect of immunotherapy as a cancer treatment modality and its effects on salivary gland function; one study was controlled. The saliva-related end points were salivary flow rates, although dryness of the mouth was also briefly addressed. Salivary gland tissue is thought to

be a target organ for IL-2-mediated immunological reactions, inducing lymphocytic infiltration and cytokine production leading to salivary gland hypofunction. Thus, intravenous or subcutaneous administration of IL-2 in patients with metastatic cancer and in patients treated with autologous blood stem cell transplantation for hematological malignancies resulted in xerostomia and salivary gland hypofunction; yet, salivary gland hypofunction returned to baseline within 2 weeks after treatment, e.g., secretion of glandular saliva was decreased by 83–95 and 73–83% for unstimulated parotid and submandibular flow rates, respectively, and decreased by 48–65 and 52–56%, respectively, during stimulated conditions [194–196]. IL-2-mediated salivary gland hypofunction may resemble graft versus host disease induced hyposalivation, which may point to similar pathophysiologic mechanisms [195].

Salivary gland hypofunction and xerostomia-related QoL

Since the 1989 NIH Development Consensus Conference, there has been increasing focus on the impact of oral complications of cancer therapies on QoL. QoL, as it applies to cancer patients, may be defined as a patient's appraisal and satisfaction with their current level of functioning compared to what is perceived to be possible or ideal [197]. Thus, the impact of salivary gland hypofunction and xerostomia on QoL may be affected by patient expectations, coping strategies, and changes in the way in which a patient evaluates overall well-being and satisfaction over time. Accordingly, patients may have accepted that salivary gland hypofunction and xerostomia are unavoidable after cancer treatment and therefore have adjusted their expectations. Hence, this may partly explain if a lack of coherence is observed between QoL aspects, decreased salivary flow rates, and xerostomia following cancer treatment.

The QoL instruments used in the studies included in the present review generally assessed symptoms or functional problems, such as ability to speak, chew, and swallow, to wear dentures, oral comfort/pain, or sleep disturbance. QoL domains assessed by the instruments included physical function, role function, social function, emotional function, cognitive function, and general health status and did not include the direct impact of xerostomia and salivary gland hypofunction. However, QoL may be significantly influenced by xerostomia and salivary gland hypofunction in addition to the presence of other major oral complications of cancer therapy, such as mucositis, soft tissue destruction, surgical sequelae, oral mucosal infection, pain, taste loss, trismus, or carious destruction of teeth [8, 9].

Accordingly, in our analysis of 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, that is, 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.

Conventional radiotherapy and salivary gland hypofunction/xerostomia-related QoL

Ten studies correlated xerostomia to QoL aspects following conventional radiotherapy. Studies have found that lower unstimulated and stimulated whole saliva flow rates and xerostomia worsen overall QoL and domains of senses, speech, sleep, eating, swallowing, social contact/eating, dyspnea, need for nutritional support, and deteriorates subjective vocal function and speech performance in heterogeneous head and neck cancers [58, 67, 198–200]. In line with this, xerostomia has also been shown to negatively affect physical, role, emotional and social function, symptoms of dyspnea, appetite loss, as well as overall QoL in laryngeal/hypopharyngeal cancer patients [201], although the latter patients are affected by xerostomia to a lesser degree than diagnoses of nasopharyngeal, oropharyngeal, and oral cavity cancers [18, 20, 25, 28, 50, 69–72]. The impact of xerostomia on general aspects of QoL following conventional radiotherapy has also been shown to be more pronounced in female and younger patients [53]. In patients with a diagnosis of cancer of the base of the tongue, a high percentage (89%) found that xerostomia caused moderate to severe distress 5 years after radiotherapy [17]. On the other hand, 1 year after chemoradiation in a cohort of heterogeneous head and neck cancer patients, xerostomia appeared to have little impact on performance, global QoL, or specific QoL aspects, although xerostomia was reported as a significant problem by over three quarters of patients [18]. Along this line, no significant relation was found between global QoL, stimulated parotid flow rate, and dry mouth symptoms. Patients experience normalized overall QoL in spite of the presence of moderate to severe xerostomia years after radiation therapy [52].

3D conformal radiotherapy and salivary gland hypofunction/xerostomia-related QoL

Four studies evaluated xerostomia-related QoL during and following 3D conformal radiotherapy. Two studies of invasive cancer of the head and neck (diagnoses not further specified) assessed xerostomia-related QoL by a validated 15-question scale [98, 100], one study of oro- and nasopharyngeal cancers by a five questions xerostomia-related QoL questionnaire [103], and one study of mixed

cancer diagnoses of oral cavity, nasopharynx, oropharynx, hypopharynx, and larynx assessed xerostomia by the RTOG/EORTC Late Radiation Morbidity Scoring System and correlated it to health-related QoL evaluated by the EORTC QLQ-C30 [105]. These studies found that xerostomia-related QoL had significantly worsened at the completion of the radiotherapy course compared to baseline but improved 1 month after treatment [98]. Six months after 3D conformal radiotherapy, xerostomia significantly has affected health-related QoL, although slight xerostomia did not have a clinically relevant impact, whereas severe xerostomia was shown to have a moderate impact on emotional function and fatigue and a large impact on social functioning and global QoL [105]. In addition, xerostomia-related QoL responses were reported to be markedly better at 1 year after radiotherapy than at the completion of the radiotherapy course but are still significantly worse than baseline [98, 100, 103]. Other authors reported the impact of xerostomia to be relatively low up to 18 months after radiation therapy and then increasing at 24 months after treatment [105]. Finally, individuals with higher unstimulated and stimulated parotid flow rates at completion of radiotherapy and up to 1 year after radiotherapy were shown to report better QoL scores than those with lower salivary secretion [98].

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 (Table 4) [103, 110, 112, 113, 116, 117, 130, 132, 140, 150, 202]. The results reported in this table suggest that decreasing xerostomia by partly sparing of parotid gland function by IMRT has the potential of improving some QoL domains compared to conventional or 3D conformal radiotherapy [103, 110, 112, 117, 130, 132, 140, 150]. The variation of results also clearly illustrates the diversity of assessment scales used and the challenge of drawing general conclusions (Table 4).

To summarize, after parotid sparing IMRT, an association was found between xerostomia and QoL (Table 4), with a decline in QoL in the 6-month period after RT and then followed by improvement of xerostomia-related QoL up to 24 months after radiation therapy [103, 113, 116, 130, 132, 140]. Thus, the potential benefits from IMRT on xerostomia-related QoL are most pronounced late (≥6 months) after therapy (Table 4).

Regarding the impact of salivary gland hypofunction on QoL (Table 4), whole saliva flow rates, both unstimulated and stimulated, were related to oral comfort, speech, chewing/swallowing, and sleep [112], to a combined QoL score of xerostomia's impact on daily activities, sleeping patterns, speech, and swallowing [117], and to emotional function [110]. On the other hand, unstimulated and stimulated whole saliva flow rate did not correlate to Medical Outcome Short Form 36 QoL scores [110, 202]. In addition, unstimulated and stimulated parotid and submandibular flow rates could not be shown to be associated with QoL scores up to 2 years after radiotherapy [113, 116], except for one report showing a correlation between stimulated parotid flow rate and speech problems [110].

Other cancer therapies and salivary gland hypofunction/xerostomia-related QoL

No studies assessed QoL in relation to salivary gland hypofunction or xerostomia as sequelae of cancer chemotherapy, conditioning total body irradiation/chemotherapy and hematopoietic stem cell transplantation, radioactive iodine treatment, and cancer therapies in children/adolescents.

Epilogue

Salivary gland hypofunction and xerostomia are frequently reported and clinically significant adverse effects of cancer therapies. Differences in tumor site, stage, and treatment regimens produce different severities of salivary gland hypofunction, xerostomia, and impact on QoL aspects. This is mainly related to the involvement of the major salivary glands in the radiation treatment portals, as radiotherapy is shown to be the major cause of salivary gland hypofunction and xerostomia in head and neck cancer patients. Within the radiation techniques that are currently routinely applied in the clinic, IMRT has the greatest potential of sparing salivary gland tissue resulting in a better preservation of salivary gland function in head and neck cancer patients. The future focus should be on optimized or new approaches to further reduce the cumulative radiation dose to the parotids and likely to the submandibular/sublingual and minor salivary glands with regards to reducing xerostomia and the potentially severe consequences of decreased saliva secretion on health. Particularly, a shift of the focus of preserving the parotid glands toward preserving the submandibular and minor salivary glands is of utmost importance, as the non-serous glands are the major contributors to the continuous moistening of the oral tissues. Probably, when the function of the latter glands can be better preserved, a better correlation between the level of salivary secretion remaining after cancer treatment and xerostomia-related QoL aspects can be perceived.

As was shown, the heterogeneity of diagnoses and treatment parameters within studies has resulted in difficul-

Table 4 Studies assessing quality of life (QoL) aspects related to salivary gland hypofunction and/or xerostomia after intensity-modulated radiation therapy (IMRT) for head and neck cancer

Authors	Cancer site	Treatment modality (*n*)	QoL questionnaire	Salivary gland secretion/ xerostomia	Time of assessment	Correlation of salivary gland function and QoL
Chao et al. [112]	Mixed H&N	IMRT (27) 3D-RT (14)	XQoLQ	UWS and SWS	6 months after RT	UWS and SWS correlated positively to scores of xerostomia, oral comfort, speech, chewing/swallowing and sleep (higher scores indicating less difficulty with oral dryness)
Eisbruch et al. [113]	Mixed H&N	IMRT, unilateral (48) and bilateral (84)	UM-XQ	UPS, SPS, USS and SSS Xerostomia	1, 3, 6, 12, 18 and 24 months after RT	The UM-XQ summary scores increased by 1 month after RT UM-XQ summary scores decreased by 18 and 24 months Little effect of RT on xerostomia-related sleeping problems Salivary flow rates not associated with UM-XQ scores
Lin et al. [116]	Mixed H&N	IMRT (36)	HN-QoL UM-XQ	UPS, SPS, USS and SSS Xerostomia	3, 6 and 12 months after RT	Xerostomia correlated to eating, communication, emotion and pain domains Xerostomia and QoL scores improved from 3-12 months after RT Salivary flow rates not associated with QoL scores
Blanco et al. [117]	Mixed H&N	IMRT (45) 3D-RT (14) and 3D-RT + IMRT boost (6)	XQoLQ	UWS and SWS	6 and 12 months after RT	SWS improved from 6 to 12 months after RT and correlated positively to QoL scores (higher scores indicating better QoL)
Jabbari et al. [130]	Mixed H&N	IMRT (30) Conv. RT (10)	HN-QoL UM-XQ	Xerostomia	1, 3, 6, 12, 18 and 24 months after RT	Xerostomia-related QoL declined in the period of 6 months after RT in both groups. Thereafter improvement after IMRT but not after conv. RT
Ng et al. [103]	Mixed H&N	IMRT (38) Conv. RT (44)	XQoLQ	Xerostomia	IMRT 14 (6–31) months after RT Conv. RT 20 (6–34) months after RT	IMRT had lower scores compared to conv. RT in overall XQoLQ score and regarding individual questions of xerostomia and impact of dry mouth on speech, chewing/swallowing and sleep
Pacholke et al. [132]	Mixed H&N	IMRT (27) 4 groups of conv. RT Larynx only (35) Ipsilateral (32) Bilateral partly (11) Bilateral total (105)	UM-XQ	Xerostomia	>12 months after RT	Low UM-XQ scores in laryngeal group and high in conv. bilateral RT (total irradiation of major salivary glands) compared to IMRT, conv. ipsilateral and bilateral (partly irradiation of parotid glands) RT Differences between the conv. ipsilateral, bilateral (partial irradiation of parotid glands) and IMRT groups were not statistically significant

Pow et al. [110]	Early stage nasopharyngeal	IMRT (24)	SF-36	SWS and SPS	2, 6 and 12 months after RT	No correlations between SF-36 subscale scores and salivary flow rates
		Conv. RT (21)	EORTC QLQ-C30	Xerostomia		SWS correlated negatively with EORTC QLQ-C30 global health (quotes that it might be due to statistical chance?) and positively with emotional function. SPS correlated positively with role function
			EORTC QLQ-H&N35			SPS correlated negatively with EORTC QLQ-H&N35 dry mouth, sticky saliva and speech problems
						IMRT better than conv. RT in terms of improved QoL
Daly et al. [140]	Mixed H&N	IMRT (29)	UM-XQ	Xerostomia	IMRT 18 (6–56) months after RT	IMRT had lower scores compared to conv. RT in overall UM-XQ scores and regarding individual questions of xerostomia-related talking and chewing difficulty, xerostomia with or without eating, and frequency of sipping liquid with and without eating
		Conv. RT (75)			Conv. RT 42 (7–148) months after RT	
Lin et al. [202]	Mixed H&N	Pooled IMRT (32) and 3D-RT (18)	SF-36, Taiwanese UM-XQ, Taiwanese	UWS Xerostomia	Before, and 2, 4, 6 and 8 weeks after starting RT	UWS correlated negatively to UM-XQ scores at all time points after starting RT, but did not correlate to SF-36 QoL scores
						UM-XQ scores correlated negatively to SF-36 scores before, 4 and 6 weeks after starting RT
Van Rij et al. [150]	Mixed H&N	IMRT (75)	Study-specific	Xerostomia	IMRT 2.3 years after RT	IMRT had less difficulty swallowing food, needed less water for a dry mouth during day, night and meals, had fewer problems with speech and eating in public compared to conv. RT
		Conv. RT (87)			Conv. RT 2.9 years after RT	Laryngeal cancer patients had fewer complaints than oropharyngeal cancer patients

RT radiation therapy, *3D* three-dimensional, *H&N* head and neck, *Conv.* conventional, *UWS* unstimulated whole saliva flow rate, *SWS* stimulated whole saliva flow rate, *UPS* unstimulated parotid flow rate, *SPS* stimulated parotid flow rate, *USS* unstimulated submandibular flow rate, *SSS* stimulated submandibular flow rate

Xerostomia-related QoL Questionnaire (XQoLQ): five questions addressing xerostomia and impact of dry mouth on oral comfort, speech, chewing/swallowing and sleep (a sixth question includes wearing dentures), VAS, higher score indicating better xerostomia-related QoL assessment. H&N cancer-related QoL Questionnaire (HN-QoL): 20 questions, four domains addressing eating, communication, emotion and pain, 0–100, higher scores indicating worse QoL assessment. University of Michigan Xerostomia Questionnaire (UM-XQ): eight questions addressing xerostomia and impact of dry mouth on oral comfort, speech, eating/chewing/swallowing and sleep, 11-point ordinal Likert scale from 0 to 10, final summary score 0–100, higher scores indicating worse level of xerostomia or discomfort due to xerostomia. Xerostomia-related QoL Scale (XQoLS): 15 questions, four domains addressing impact of salivary dysfunction and xerostomia on pain/discomfort, physical, personal/psychological and social functioning, 5-point scale, percentage of maximum score, higher scores indicating worse QoL assessment. Medical Outcome Short Form 36 (SF-36): 36 questions, eight subscales; physical, social, role limitation-physical, role limitation-emotional, mental health, vitality, pain and general health perception, final summary score 0–100, higher score indicating better health status. European Organization for Research and Treatment of Cancer Core Questionnaire [EORTC QLQ-C30 (+3)]: 33 questions, five functional scales: physical, role, emotional, cognitive and social functioning; three symptom scales: fatigue, pain, nausea/vomiting; a global QoL scale; and six single items concerning dyspnea, sleep disturbances and financial impact. Final summary score 1–100, higher score in functional scales and global QoL indicating high/healthy level of functioning, higher score in symptom scales/items indicating high level of symptoms/problems. European Organization for Research and Treatment of Cancer Head and Neck Cancer Module (EORTC QLQ-H&N35): 35 questions, seven multi-item scales assessing pain, swallowing, senses, speech, social eating, social contact, and sexuality; 11 single items about teeth, mouth opening, dry mouth, sticky saliva, and coughing. Final summary score 1–100, higher score in functional scales and global QoL indicating high/healthy level of functioning, higher score in symptom scales/items indicating high level of symptoms/problems

ties in interpretation of the outcomes, and genuine differences in effects may be obscured. Hence, site- and treatment-specific assessments could provide more precise knowledge of the impact of cancer treatment on salivary gland hypofunction and xerostomia. However, this approach would obviously increase the problem of small study sample sizes, meanwhile emphasizing the need for large, multi-institutional, randomized studies to assess cancer treatments. However, when performing such trials, these trials would greatly benefit from universal application of standardized saliva collection procedures, a validated xerostomia assessment scale (patient-assessed), and a validated questionnaire specifically addressing the impact of xerostomia on QoL aspects [54, 135, 203].

Fields with sparsely available literature as identified by this systematic review are salivary gland hypofunction and xerostomia in pediatric/adolescent cancer populations, salivary gland hypofunction/xerostomia as an oral complication of cancer chemotherapy, radioactive iodine treatment, and total body irradiation/hematopoietic stem cell transplantation. In addition, no firm conclusions could be drawn about the potential additive effect of concomitant chemotherapy and radiotherapy on salivary gland hypofunction.

The abovementioned recommendations would be beneficial to be implemented in future studies both during cancer treatment and in a life-long perspective.

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