University of Groningen

Xerostomia

Delli, K.; Spijkervet, F.K.L.; Kroese, F.G.M.; Bootsma, H.; Vissink, A.

Published in:
 Monographs in Oral Science

DOI:
[10.1159/000358792](https://doi.org/10.1159/000358792)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
 Publisher's PDF, also known as Version of record

Publication date:
 2014

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Delli, K., Spijkervet, F. K. L., Kroese, F. G. M., Bootsma, H., & Vissink, A. (2014). Xerostomia. *Monographs in Oral Science*, 24, 109-125. <https://doi.org/10.1159/000358792>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Xerostomia

Konstantina Delli^a • Fred K.L. Spijkervet^a • Frans G.M. Kroese^b •
Hendrika Bootsma^b • Arjan Vissink^a

Departments of ^aOral and Maxillofacial Surgery and ^bRheumatology and Clinical Immunology,
University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

Abstract

Xerostomia is the subjective feeling of oral dryness. The major causes are Sjögren's syndrome (SS), medication and radiotherapy to the head and neck. SS is a chronic systemic autoimmune disease characterized by infiltration of the exocrine glands, the salivary and lacrimal ones in particular. The pathogenesis involves systemic B cell hyperactivity and T cell lymphocytes targeting glandular epithelial cells. About 7.5% of patients with SS develop malignant B cell lymphoma, mostly mucosa-associated tissue lymphomas. Certain classes of drugs can induce hyposalivation and/or xerostomia by, e.g., targeting neurotransmitters and receptors. As a result, amongst others the production of fluid and electrolytes in salivary glands can be reduced and the salivary composition can change. During head and neck radiotherapy, the administration of high doses to the major salivary glands, which are located in the periphery of the head, leads to progressive loss of glandular function and a diminished salivary output. Reduction of the dose and the volume of irradiated salivary glands by advanced radiotherapy techniques can be highly beneficial for patients.

© 2014 S. Karger AG, Basel

Xerostomia is the subjective feeling of oral dryness. The term is derived from the Greek words *xeros* (ξηρός), meaning 'dry', and *stoma* (στόμα), meaning 'mouth'. The prevalence of xerostomia is estimated to be between 13 and 63% [1]. It is more prominent in women, in elderly subjects and in individuals housed in long-term care facilities. A number of factors has been associated with transient or persistent xerostomia (table 1). This paper will focus on the three most common causes: Sjögren's syndrome (SS), medication and radiotherapy of the head and neck.

Sjögren's Syndrome

SS was first described by the Swedish ophthalmologist Henrik Sjögren in 1930. It is a chronic inflammatory and lymphoproliferative disorder that is principally characterized by chronic infiltration of the exocrine glands. It commonly affects the salivary and lacrimal glands, resulting in xerostomia and dry eyes (keratoconjunctivitis sicca). These symptoms may be accompanied by extraglandular manifestations, evident in almost any or-

Table 1. Influence of conditions on salivary gland function

	Flow rate	Changed composition	Xerostomia
Xerogenic drugs	↓	+	+
Sjögren's syndrome	↓	+	+
Head and neck radiotherapy	↓	+	+
Chronic inflammatory connective tissue diseases			
Scleroderma	↓	?	+
Mixed connective tissue disease	↓	?	+
Chronic inflammatory bowel diseases			
Crohn's disease	→	+	+
Ulcerative colitis	→	+	–
Celiac disease	→	+	–
Autoimmune liver diseases	↓	?	+
Musculoskeletal disorders			
Fibromyalgia	↓	?	+
Chronic fatigue syndrome	↓	?	+
Amyloidosis	↓	?	+
Endocrine disorders			
Diabetes mellitus	↓	+/-	+
Hyperthyroidism	↑	+	–
Hypothyroidism	↓	?	+
Cushing's syndrome	→	+	–
Addison's disease	→	+	–
Neurological disorders			
CNS trauma	↓	?	?
Cerebral palsy	↓	+	?
Bell's palsy	↓	?	?
Parkinson's disease	↓	+	+
Alzheimer's disease	↓	+	+
Holmes-Adie syndrome	↓	?	+
Burning mouth syndrome	→	+	+
Infectious diseases			
Epidemic parotitis	?	?	?
HIV/AIDS	↓	+/-	+
Hepatitis C virus	↓	?	+
Epstein-Barr virus	?	?	?
Tuberculosis	?	?	?
Local bacterial salivary gland infections	↓	+	?
Genetic disorders			
Salivary gland aplasia	↓	?	?
Cystic fibrosis	↓	+	?
Ectodermal dysplasia	↓	+	–
Prader-Willi syndrome	↓	+	?
Metabolic disturbances			
Water and salt balance	↓	+	+
Sodium retention syndrome	↓	+	+
Malnutrition	↓	+	+
Eating disorders			
Bulimia nervosa	↓	+/-	+
Anorexia nervosa	↓	+	+
Cancer-associated disturbances			
Chemotherapy	↓	+/-	+
Graft-versus-host disease	↓	+	+
Advanced cancer/terminally ill patients	↓	?	+

Modified after Jensen et al. [62], 2010. ↓ = Reduced; ↑ = increased; → = same; + = yes; – = no; ? = unknown.

gan. According to the American-European Consensus Group (AECG) classification criteria [2], SS can be distinguished in primary SS, in case no other autoimmune disease is present, and secondary SS, in case additional connective tissue diseases are present, such as rheumatoid arthritis, systemic lupus erythematosus, scleroderma and mixed connective tissue disease.

Epidemiology

SS is one of the most common rheumatic diseases, with a prevalence of 0.5–1% in the total population. It affects mainly women (i.e. female-to-male ratio equals 9:1). The median age of occurrence is around 50 years, although it can arise in all ages. In rheumatoid arthritis, the prevalence of SS is around 30% and approximately 20% of patients with systemic lupus erythematosus fulfil the criteria for secondary SS.

Clinical Features

Glandular Manifestations

SS primarily affects lacrimal and salivary glands. With respect to the eyes' symptoms, dryness may result in a sensation of itching, grittiness and soreness; nevertheless, the eyes' appearance can be normal. Ocular complaints may include photosensitivity/photophobia, erythema, eye fatigue, decreased visual acuity, discharge from the eyes, and the sensation of a film across the visual field [3] (fig. 1). Progressive keratitis may result in loss of vision in patients with SS. Ocular complications may include corneal ulceration, vascularization, opacification and, rarely, perforation [4].

Another prominent symptom of SS is xerostomia. This symptom is often associated with dysgeusia, difficulty in eating dry food, problems in speaking for long periods of time, burning sensation of the mouth, discomfort while wearing dentures and increased risk of dental caries, especially cervically (fig. 2), and oral infection, in particular candidiasis. At the onset of SS, the mouth appears to be normally moisturized but while the disease progresses, saliva diminishes and becomes foamy,

Fig. 1. Dry eye due to diminished tear production, examined with Schirmer's test.

Fig. 2. Tender and dry oral mucosa, characteristically forming fine wrinkles.

lacking the usual pooling in the floor of the mouth. In advanced disease, the oral mucosa is tender and dry and characteristically forms fine wrinkles (fig. 3). The tongue, in particular, often becomes fissured and exhibits atrophy of the papillae.

Enlargement of especially the parotid and submandibular glands (fig. 4) is a common phenomenon in patients with SS. Swelling of the salivary glands is usually bilateral, may be nonpainful to slightly tender and intermittent to persistent in nature. The swelling is generally attributed to the presence of an autoinflammatory process in these glands, and stasis of saliva can result in secondary infection, encouraging further swelling. The development of lymphomas, in most cases in the pa-

Fig. 3. Red, fissured tongue with atrophy of the papillae.

Fig. 4. Enlarged parotid salivary gland due to the development of MALT lymphoma.

Fig. 5. Purpura is a common extraglandular manifestation in SS patients.

rotid gland, can also lead to more persistent unilateral glandular enlargement. Dryness can occur at the mucosal surfaces of upper and lower respiratory tracts resulting in nonproductive cough [5]. Dry skin affects about 55% of SS patients while in female patients with SS desiccation of the vagina results in dyspareunia [6].

Lymphoma Development

About 7.5% of patients with SS develop malignant B cell lymphoma, 48–75% of which is of the MALT-type (Mucosa Associated Lymphoid Tissue-type)

[7, 8]. SS patients also have an 18.8 (confidence interval 9.5–37.3) times increased risk in developing lymphomas [9]. B cell lymphomas are most frequently located in the parotid gland. The conversion from variable to persistent enlargement of the gland is an alarming clinical sign. The presence of palpable purpura (fig. 5), vasculitis (fig. 6), renal involvement and peripheral neuropathy, although not pathognomonic, should raise suspicion, especially when it is combined with monoclonal gammopathy, reduced levels of complement C4, CD4+ T lymphocytopenia, a sharp increase in IgG levels or cryoglobulinemia [7–12] (table 2).

Serological Findings

The most characteristic autoantibodies in SS are the anti-Ro/SSA and anti-La/SSB autoantibodies (table 3), which are present in 70 and 50% of cases, respectively. Their titers reflect disease activity, while high titers of particularly anti-La/SSB have been associated with extraglandular disease [13]. Despite the fact that anti-Ro/SSA and anti-La/SSB are not specific for SS, since they can also occur in e.g. patients with systemic lupus erythematosus, their presence should alert the clinician for the possibility of a diagnosis of SS.

Fig. 6. Raynaud's phenomenon in two different cases (**a** and **b**).

Table 2. Risk factors for the development of lymphoma

Clinical	Serological
Persistent enlargement of parotid gland	Monoclonal gammopathy
Persistent lymphadenopathy	Reduced levels of complement C4
Palpable purpura	CD4+ T lymphocytopenia
Vasculitis	Increase in IgG levels
Renal involvement	Cryoglobulinemia
Peripheral neuropathy	

Table 3. Serological findings in SS patients

Autoantibody	Frequency in SS patients, %	Specific for SS
Anti-Ro/SSA	70	no
Anti-La/SSB	50	no
Anti- α -fodrin	30	yes
Antimuscarinic acetylcholine receptor 3	71–90	no
Rheumatoid factor	50	no

Diagnostic Criteria

In 2002, a joint study of the AECG presented the revised AECG classification criteria for SS and to date they are the most widely accepted criteria [2]. These criteria successfully combine subjective symptoms, as well as objective signs of keratoconjunctivitis sicca and hyposalivation together with histopathological and serological findings. It must be underlined that SS can be present in a

patient who does not completely fulfil these classification criteria and that, since anticholinergic drugs are widely used by patients for many conditions, their exclusion should be carefully re-evaluated [1]. Recently, due to the emergence of biological agents, the American College of Rheumatology (ACR) proposed new classification criteria for SS, based merely on objective tests. The ACR classification criteria were developed from regis-

Table 4. Possible factors predisposing to SS

Endogenous	Immunological disturbance HLA-DR3/DQ2 Female gender
Exogenous	Virus infection Epstein-Barr virus Coxsackievirus Retroviruses (e.g. HTLV-10) HIV Hepatitis C

try data collected with standardized measures and are thought to be more suitable in situations where misclassification may present health risks [14].

Etiopathogenesis

SS is considered to be an autoimmune disorder but with a pathogenesis that is poorly understood. It is not clarified yet whether this disturbance of the immune system exists primarily or is a result of an infection, possibly viral, or has another cause. Several findings suggest that viruses, such as Epstein-Barr virus, coxsackievirus and retroviruses may be implicated. Possibly, their glandular persistence in salivary gland epithelial cells may lead to chronic lymphocytic sialoadenitis with formation of foci around the ducts [15]. Additionally, hepatitis C and HIV infections can produce both symptoms and pathological findings similar to those in SS, but for the time being the presence of these infections is an exclusion criterion for SS.

Moreover various endogenous factors may be involved (table 4). The strong female preponderance implies possible involvement of hormonal factors, while the extended haplotype HLA-DR3/DQ2 in combination with the C4null gene being present in 50% of SS patients probably evinces genetic factors too [16, 17].

The complexity of the pathogenetic pathways in SS involves both systemic B cell hyperactivity

and T cell lymphocytes targeting glandular epithelial cells:

- prolonged B cell survival and B cell hyperactivity lead to the presence of anti-Ro/SSA and anti-La/SSB antibodies, rheumatoid factor, type 2 cryoglobulins and hypergammaglobulinemia in SS patients;
- ductal epithelial cells are surrounded by activated T cells, predominantly CD4+ (70–80%); CD8+ T cells constitute around 10% of infiltrating cells in affected labial salivary glands [18].

Histopathology

Biopsy of the minor salivary glands of the lower lip is widely used for the diagnosis of SS, and its histopathology is considered as 1 of the 4 objective AECG classification criteria of SS as well as 1 of the 3 objective ACR criteria [2, 4]. The procedure is performed under local anesthesia. A lower lip mucosa incision of approximately 1.5 cm is made and at least 7 individual labial glands are collected [19]. Parotid biopsies are increasingly gaining broader acceptance and use as an alternative to minor salivary gland biopsies. Parotid biopsies are validated for the AECG classification criteria [20], but not yet for the ACR classification criteria. With this technique, parotid tissue is taken under local anesthesia, from the area around the lower ear lobe. A 1-cm incision is carried out, followed by blunt dissection to the parotid gland and an incisional biopsy. The remaining wound is closed in layers [21] (fig. 7). Several studies show a lower morbidity after a parotid gland biopsy compared to a lip biopsy [20, 22] with regard to loss of sensibility and pain. In none of the parotid gland biopsy studies was a disturbance of the facial nerve observed.

The most prominent microscopic finding in SS is periductal lymphocytic infiltration of salivary glands in combination with destruction of acini (fig. 8a). The infiltrates contain B and T lymphocytes as well as nonlymphoid cells and are located around the striated ducts. When these infiltrates are composed of more than 50 cells, they

Fig. 7. Incisional biopsy of the parotid gland. **a** The area is anesthetized with local infiltration anesthesia. **b** With a No 15 blade a small 1–2 cm incision is made just below and behind the earlobe near the posterior angle of the mandible. **c** The skin is incised and the parotid capsule is exposed by blunt dissection. The capsule of the gland is carefully opened and a small amount of superficial parotid tissue is removed. **d** The procedure is completed with a 2 to 3-layered closure with 4-0 gauge absorbable sutures (polyglycolic acid), while the skin layer is closed with 5-0 nylon sutures.

are called focus. The presence of more than 1 focus per 4-mm² area of glandular tissue is regarded as a positive criterion for the diagnosis of SS. Furthermore, if the major glands are enlarged, progression to a lymphoepithelial lesion (fig. 8b) can also be present. In major salivary glands characteristic epimyoepithelial islands in a background of lymphoid stroma are usually seen.

The sensitivity and specificity of the parotid biopsy are comparable with those of labial salivary glands [20] and additionally can provide evidence about lymphoepithelial lesions and well-formed lymphoid follicles or germinal centers. It is suggested that the presence of germinal center-like structures in primary SS salivary biopsies is a

highly predictive and easy-to-obtain marker for non-Hodgkin lymphoma development, allowing for risk stratification of patients and the possibility to initiate preventive B-cell-directed therapy [23]. The histopathological results of a parotid biopsy can be indicative of malignant lymphoma as MALT lymphomas often develop in the parotid gland and rarely in labial glands. Repeated biopsies from the same parotid gland offer information concerning the course of the disease.

Treatment

Evidence-based therapy for SS is limited, and the treatment of patients with SS is mainly supportive (table 5).

Fig. 8. a Parotid gland tissue showing a periductular lymphocytic infiltrate and deposition of fat between the serous acini. Magnification $\times 10$. **b** Lymphoepithelial lesions surrounded by a lymphocytic infiltrate (from Pijpe et al. [20]). Magnification $\times 20$.

Local treatment for dryness of eyes and mouth is helpful in many cases. Artificial tears lubricate dry eyes, and in case of keratoconjunctivitis local corticosteroids and local immunosuppressive agents may be used. Sealed glasses are also introduced in an attempt to prevent evaporation of tears and to conserve the tear film. Sealing the lacrimal punctum in the inner margin of the eyelid can also be helpful by blocking the normal drainage to the nose. To treat xerostomia, one

first has to estimate whether stimulating salivary secretion by gustatory (sugar-free sweets), mechanical (chewing gum) or sialagogue medication (pilocarpine, cevimeline) results in relief of xerostomia. When stimulation of salivary secretion is uneventful, one can try to treat xerostomia with mouthrinses, artificial saliva and/or oral gels. Antifungal therapy, such as local treatment with nystatin, myconazole or amphotericin B, is frequently needed to treat oral candidia-

Table 5. Treatment of SS

Supportive	Causal
(1) Local	(1) B cell depletion, e.g. rituximab
Eye	(2) Inhibition of costimulation of T cells, e.g. abatacept
Artificial tears	(3) Anti-tumor necrosis factor α , e.g. infliximab, etanercept
Corticosteroids	(4) Neutralization of interferon, e.g. rontalizumab
Immunosuppressives	
Sealed glasses	
Blocking the lacrimal punctum	
Mouth	
Artificial saliva	
Antifungal therapy	
Fluoride application	
(2) Systemic	
Pilocarpine	
Cevimeline	

sis. Due to the increased risk of dental caries, a weekly to daily use of topical neutral fluoride applications or mouthrinses is indicated in dentate patients.

During the past two decades biologicals have become available to target specific cells or cytokines that are fundamental in the immune response. Under this new perspective, inhibitors of tumor necrosis factor α , interferon α , B cell depletion therapies, B-cell-activating factor inhibitors and treatments targeting the costimulation of T cells have also been recruited in the treatment of SS [24, 25].

The therapeutic approach to the patients with SS and MALT lymphoma is a matter of debate [26].

Drugs

Drugs are the most common cause of dry mouth. A review of the 200 most frequently prescribed drugs in the USA revealed that the most common side effect was dry mouth (80.5%) followed by dysgeusia (47.5%) and stomatitis (33.9%) [27]. The exact relationship between dry mouth and

drugs is variably influenced by many factors, such as type of drug, number of drugs, drug combination, dose, form, time of intake, duration of use, drug interaction and reliability of the patient's report. The situation is even more complicated in diseases and disorders that contribute to the problem. Nonetheless, it is generally accepted that the prevalence of dry mouth increases with age and the number of drugs taken per day.

Interrelation with Age and Sex

Studies indicate that the average intake of drugs increases with age. In the USA for example, the intake of 1–2 drugs/day/person progressively increases from 24 to 87% from the age of 18 to the age of 65, respectively (fig. 9). The prevalence of dry mouth increases with the number of drugs taken per day (fig. 10). Furthermore, drug-induced dryness is greater in women than men [28].

Possible Mechanisms

This section will focus on the mechanisms by which the most commonly used therapeutic drugs (table 6) induce xerostomia [29]. More detailed lists about xerogenic medication can be found at www.drymouth.info.

Fig. 9. Prescription drug use in the USA, 2001–2004. Modified after Sreenby and Vissink [1].

Fig. 10. Prevalence of drugs and dry mouth. Modified after Sreenby and Vissink [1].

Table 6. Top 10 therapeutic classes by US dispensed prescriptions in 2011 (<http://www.imshealth.com>)

Ranking	Drug class	Xerogenic effect
1	Antidepressants	yes
2	Lipid regulators	no
3	Narcotic analgesics	yes
4	Antidiabetics	no
5	Angiotensin-converting enzyme inhibitors	yes
6	β-Blockers	uncommon
7	Respiratory agents	yes
8	Antulcerants	yes
9	Diuretics	yes
10	Antiepileptics	yes

Antidepressants

Antidepressants were the most common drug category prescribed in 2011 in the USA. Over 60% of patients prescribed antidepressants report taking these for more than 2 years, and 14% for 10 years or more. Antidepressants fall into 4 different classes, i.e. tricyclic antidepressants (TCAs),

selective serotonin reuptake inhibitors, monoamine oxidase inhibitors and atypical antidepressants. The xerogenic capacity of TCAs is high. A meta-analysis of the adverse effects of TCAs versus selective serotonin reuptake inhibitors revealed that dry mouth occurred in 28% of patients taking TCAs in comparison to 7% of patients on selective serotonin reuptake inhibitors [30].

Narcotic Analgesics

Narcotic analgesics in general reduce neuronal excitability in the pain-carrying pathway by binding to opioid receptors. Narcotic analgesics used to alleviate acute and chronic pain are morphine and its analogues as well as some synthetic derivatives. Glare et al. [31] reported a prevalence of 95% of dry mouth among patients who received morphine due to cancer pain. The symptom was persistent with a moderate to severe intensity in 57% of them [31].

Angiotensin-Converting Enzyme Inhibitors

Angiotensin-converting enzyme inhibitors are widely used for the treatment of hypertension. They inhibit the conversion of angiotensin I to

angiotensin II. Angiotensin II receptor antagonists block the binding of angiotensin II to the angiotensin receptors located in the vascular smooth muscle. Both angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists present similar actions and side effects. Reports suggest that about 1–13% of patients using these drugs complain of oral dryness [32, 33].

Respiratory Agents

Smidt et al. [34] reported that 27% of patients taking respiratory agents experience dry mouth. The main categories of respiratory agents associated with dry mouth are [34]:

drugs for obstructive airway diseases: the most commonly reported adverse event in patients on tiotropium (an antimuscarinic agent) was dry mouth (9.3 vs. 1.6%) relative to placebo [35], while overall 6–13% of patients receiving it complain of xerostomia [36, 37];

cough and cold preparations: stimulation of α - and β -adrenergic receptors in the mucous membrane of the respiratory tract by pseudoephedrine and phenylephrine results in the shrinking of the nasal mucous membranes and relieves nasal obstruction; studies demonstrated that pseudoephedrine induced oral dryness in 0.4–11% of patients [38, 39];

antihistamines: three antihistamines are commonly used, i.e. brompheniramine, clopheniramine and carbinoxamine; their frequent combination with decongestants as well as breathing through the mouth can cause dry mouth [38, 39].

Antiulcerants

Antiulcerants are used as part of the treatment of ulcers. The two basic types of antiulcerants are H_2 blockers and proton pump inhibitors. Dry mouth is found in 41% of patients receiving an H_2 receptor antagonist for eradication of *Helicobacter pylori* [40]. A subnormal parotid or whole-saliva flow rate is reported in patients treated with the proton pump inhibitor omeprazole [41].

Diuretics

Diuretics increase the formation and extraction of urine. As a result, there is a decrease in the volume of extracellular water and a consequent reduction in cardiac output and blood pressure. According to Smidt et al. [34], 17.8% of patients taking diuretics experience dry mouth. Habbab et al. [33] distinguished the frequency of dry mouth in patients taking thiazide, loop and potassium-sparing diuretics in 3, 8 and 16%, respectively.

Antiepileptics

Antiepileptics prevent rapid, repetitive stimulation of the brain that causes seizure activity. A selective dose-dependent pattern in the onset of dry mouth after the administration of pregabalin has been reported, which becomes evident after a dosage of 150 mg/day [42]. There are also sporadic reports of transient ‘sicca syndrome’ during phenobarbital treatment [43] or even phenytoin-induced pseudo-SS [44]. Mild xerogenic effects have been attributed to carbamazepine, oxcarbazepine, gabapentin, valproic acid, clonazepam, zonisamide, lamotrigine and topiramate (www.drymouth.info).

Management of Drug-Induced Xerostomia

Drug-induced xerostomia can be diminished by avoiding xerogenic drugs or minimizing their exposure to them. Substitution of a different agent with similar therapeutic properties can usually relieve the symptoms. If this is not possible, patients should be reassured that in most cases this condition is not permanent and salivary gland function will return to pretreatment levels after the end of the therapy. In order to support these patients, usage of salivary stimulants or artificial saliva, in particular substitutes with a stimulating additive such as malic acid (during daytime) and gel type substitutes (during the night), should be encouraged during their treatment with xerogenic drugs.

Radiotherapy

Radiotherapy plays a fundamental role in the treatment of the majority of patients with head and neck cancer. It can be used as a single modality or in combination with surgery and/or chemotherapy and typically involves administration of high doses to the major salivary glands. Ablation therapy of thyroid cancer with radioactive iodine treatment can also result in radiation damage to salivary gland tissue as, besides thyroid glands, salivary glands have a high uptake of this agent too.

In most cases radiation damage to salivary gland tissue results in progressive loss of glandular function and diminished salivary output. Patients complain of oral dryness, impairment of oral functions (speech, chewing and swallowing) because of insufficient lubrication of mucosal surfaces and of ingested food [45]. The oral mucosa can become dry and atrophic, leading to frequent ulceration and injury. The shift in oral microflora towards cariogenic bacteria in combination with the reduced saliva flow and altered saliva composition may lead to radiation caries [46, 47]. It must be noted that the subjective symptom of xerostomia does not always correlate with salivary flow rates; this not only applies to radiation-induced xerostomia, but also to xerostomia from other origins.

Pathophysiology

One week after the onset of conventional radiotherapy treatment, when 5–10 Gy are typically delivered, the salivary output declines by 60–90%. The acute phase of xerostomia is characterized by thick and sticky saliva, as a result of the faster decline in the serous, watery content of the saliva, compared to the decline of mucins and proteins. Late recovery is possible in cases of moderate radiation dose [48–50]. More recent studies revealed, however, that the serous parotid and seromucous submandibular gland are probably equally sensitive to ionizing radiation [51].

The mechanism of acute salivary damage is not fully understood, and to date several theories have been proposed, amongst others as described below.

(1) DNA damage caused by radiation impairs proper cell division, resulting in cell death or senescence of cells that attempt to divide. Since cells of salivary glands have a slow turnover rate (60–120 days), they are expected to be late responding tissue (>60 days) [52]. However, the changes in quantity and composition of saliva occur shortly after the radiation, indicating that salivary glands respond acutely [51, 53]. Radiation injury leads to the loss of saliva-producing acinar cells, but ducts, although deprived of function, remain intact [54]. The role of apoptotic cell death after radiotherapy is controversial. Paardenkooper et al. [55] did not observe a dose-related increase in apoptotic cells early after radiation therapy, whereas Avila et al. [56] found that early radiation-induced salivary gland dysfunction resulted from p53-dependent apoptosis. Currently, research focuses on very selectively blocking certain areas of the parotid gland from radiation injury meanwhile sparing those areas of the parotid gland where the stem cells reside (probably the main excretory ducts).

(2) The leakage of granules and subsequent lysis of acinar cells has been suggested as an alternative explanation for this phenomenon [57, 58]. Nevertheless, studies show no cell loss during the first days after irradiation [51, 59–61].

Management

Reducing the volume of irradiated salivary glands by advanced radiotherapy techniques in combination with salivary protectors and/or stimulators can be highly beneficial for patients.

Advanced Radiation Delivery Techniques

Prevalence rates of xerostomia after radiotherapy with conventional and more advanced techniques are shown in figure 11, of which 3-dimensional conformal radiotherapy (3-D-CRT) and intensity-modulated radiotherapy (IMRT) are currently most commonly applied.

Fig. 11. Stimulated parotid and submandibular/sublingual (SM/SL) saliva flow rates after conventional radiotherapy (RT) and parotid-sparing intensity-modulated radiotherapy (IMRT). Modified after Vissink et al. [45].

3-D-CRT is designed to deliver an exact dose of irradiation to a target volume. This is achieved by creating a 3-dimensional image of the tumor so that multiple radiation beams can be shaped exactly to the contour of the treatment area. There is evidence that reduced radiotherapy dosages by 3-D-CRT to contralateral parotid glands result in less loss of salivary gland function after radiotherapy up to 2 years after the completion of radiotherapy [62]. Albeit 3-D-CRT has the potential to decrease the prevalence and severity of xerostomia, xerostomia has been shown to be significantly worse after bilateral compared to unilateral treatment.

IMRT is currently recommended as a standard approach in head and neck cancer, as it allows a more accurate distribution of specific radiation dosage and dosage distribution to the tumor and therefore provides better sparing of the surrounding tissues. Since it reduces the dose to salivary glands, it can contribute to the maintenance of adequate saliva flow rates and the reduction of xero-

stomia [63–65]. IMRT compared to 2-dimensional radiotherapy results in a significant decrease in xerostomia (both patient- and observer-rated). Approximately 40% of patients still complain of dry mouth [66].

A rather new technique that is yet sparsely applied in the clinic is *proton radiotherapy*. This technique uses charged particles (protons) instead of photons. The physical and radiobiological properties of protons allow a better dose distribution, compared with photon radiotherapy. Thus, the dose to normal tissues as well as the late side effects are minimized. The existing literature shows that the dose to critical organs can be significantly reduced, especially in patients with tumors located in the pharynx [67, 68] and the paranasal sinuses [69, 70] as well as in the head and neck cancer patients treated with bilateral neck irradiation [71].

Agents for Prevention of Xerostomia or Restoration of Lubrication

Pilocarpine

Pilocarpine is a cholinergic parasympathomimetic agent, acting as an agonist at muscarinic receptors. One third to two thirds of patients with post-radiotherapy xerostomia can benefit from the administration of pilocarpine [72, 73]. A dose of 5 mg t.i.d. is recommended, and up to 4 weeks might be required before a maximum effect is visible. The possible mechanism involves stimulation of the residual function of the major salivary glands as well as the stimulation of the minor salivary glands, especially the ones in the palate, which have a greater resistance to irradiation [74].

The effects of postirradiation pilocarpine disappear when patients stop using it. In order to protect salivary glands during radiotherapy and to eliminate the long-term postirradiation effects, administration of pilocarpine during radiotherapy is an alternative choice [75, 76]. The beneficial effect of pilocarpine depends on the dose distribution in the parotid glands and when the parotid dose exceeds

40 Gy, administration of pilocarpine during radiotherapy can considerably spare parotid flow and reduce patient-rated xerostomia [77].

Amifostine

Direct radioprotection can be achieved by the use of amifostine, a scavenger of free radicals [78]. Although salivary flow is preserved when amifostine is concurrently delivered with radiation, patients continue to experience xerostomia. Intravenous administration is accompanied by several side effects (e.g. nausea, vomiting, hypotension). Furthermore amifostine might also have the undesirable effect of tumor protection. Thus, the debate continues whether it is safe to use it in cancer patients [79].

Tempol

Tempol is a stable nitroxide, providing radioprotection possibly by mimicking superoxide dismutase activity and scavenging free radicals. In a mouse model tempol significantly reduced salivary gland hypofunction [80], by protecting salivary glands, but not tumor tissue [81]. Thus, tempol could be considered for human clinical trials.

Keratinocyte Growth Factor

Keratinocyte growth factor can be administered prior to or during radiotherapy. It suppresses apoptosis and enhances survival and proliferation

of salivary acinar cells [82]. Postirradiation administration of keratinocyte growth factor most likely accelerates expansion of the pool of progenitor/stem cells that survived the treatment.

Oral Lubricants and Saliva Substitutes

A symptomatic approach of xerostomia is attempted when stimulation of residual secretion is insufficient or in cases where there is a contraindication in the administration of the aforementioned agents. The most commonly applied and best-studied saliva substitutes are based on carboxymethylcellulose [83], mucin [84] or xanthan gum [85]. Mucin- and xanthan gum-containing substitutes are usually preferred because they have superior rheological and wetting properties compared to carboxymethylcellulose-based saliva substitutes. During the night and when daily activities are at a low level, gel-like saliva substitutes are preferred [86].

Adult Salivary Gland Stem Cells

Supportive and palliative care does not address the source of the problem: a lack of functional saliva-producing cells, caused by radiation-induced stem cell sterilization. Recent identification of salivary gland stem and progenitor cell populations provides a basis for the development of a stem cell-based therapy for xerostomia [87].

References

- 1 Sreenby LM, Vissink A: Dry Mouth. The Malevolent Symptom: A Clinical Guide, ed 1. Iowa, Wiley-Blackwell, 2010.
- 2 Vitali C, Bombardieri S, Jonsson R, Moutsopoulos HM, Alexander EL, Carsons SE, Daniels TE, Fox PC, Fox RI, Kassan SS, Pillemer SR, Talal N, Weisman MH, European Study Group on Classification Criteria for Sjögren's Syndrome: Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis* 2002; 61:554–558.
- 3 Kassan SS, Moutsopoulos HM: Clinical manifestations and early diagnosis of Sjögren syndrome. More author information. *Arch Intern Med* 2004;164: 1275–1284.
- 4 Anaya JM, Talal N: Sjögren's syndrome; in Kassirer JP, Greene HL (eds): *Current Therapy in Adult Medicine*, ed 4. Baltimore, Mosby, 1997, pp 1291–1298.
- 5 Papiris SA, Maniati M, Constantopoulos SH, Roussos C, Moutsopoulos HM, Skopouli FN: Lung involvement in primary Sjögren's syndrome is mainly related to the small airway disease. *Ann Rheum Dis* 1995;58:61–64.
- 6 Al-Hashimi I, Khuder S, Haghighat N, Zipp M: Frequency and predictive value of the clinical manifestations in Sjögren's syndrome. *J Oral Pathol Med* 2001;30:1–6.
- 7 Theander E, Henriksson G, Ljungberg O, Mandl T, Manthorpe R, Jacobsson LT: Lymphoma and other malignancies in primary Sjögren's syndrome: a cohort study on cancer incidence and lymphoma predictors. *Ann Rheum Dis* 2006;65: 796–803.

- 8 Sutcliffe N, Inanc M, Speight P, Isenberg D: Predictors of lymphoma development in primary Sjögren's syndrome. *Semin Arthritis Rheum* 1998;28:80–87.
- 9 Zintzaras E, Voulgarelis M, Moutsopoulos HM: The risk of lymphoma development in autoimmune diseases: a meta-analysis. *Arch Intern Med* 2005;165:2337–2344.
- 10 Ioannidis JP, Vassiliou VA, Moutsopoulos HM: Long-term risk of mortality and lymphoproliferative disease and predictive classification of primary Sjögren's syndrome. *Arthritis Rheum* 2002;46:741–747.
- 11 Theander E, Manthorpe R, Jacobsson LT: Mortality and causes of death in primary Sjögren's syndrome: a prospective cohort study. *Arthritis Rheum* 2004;50:1262–1269.
- 12 Fox RI: Sjögren's syndrome. *Lancet* 2005;366:321–331.
- 13 Maran R, Dueymes M, Pennec YL, Casburn-Budd R, Shoenfeld Y, Youinou P: Predominance of IgG1 subclass of anti-Ro/SSA, but not anti-La/SSB antibodies in primary Sjögren's syndrome. *J Autoimmun* 1993;6:379–387.
- 14 Shiboski SC, Shiboski CH, Criswell L, Baer A, Challacombe S, Lanfranchi H, Schiødt M, Umehara H, Vivino F, Zhao Y, Dong Y, Greenspan D, Heidenreich AM, Helin P, Kirkham B, Kitagawa K, Larkin G, Li M, Lietman T, Lindegaard J, McNamara N, Sack K, Shirlaw P, Sugai S, Vollenweider C, Whitcher J, Wu A, Zhang S, Zhang W, Greenspan J, Daniels T; Sjögren's International Collaborative Clinical Alliance (SICCA) Research Groups: American College of Rheumatology classification criteria for Sjögren's syndrome: a data-driven, expert consensus approach in the Sjögren's International Collaborative Clinical Alliance cohort. *Arthritis Care Res (Hoboken)* 2012;64:475–487.
- 15 Triantafyllopoulou A, Tapinos N, Moutsopoulos HM: Evidence for coxsackievirus infection in primary Sjögren's syndrome. *Arthritis Rheum* 2004;50:2897–2902.
- 16 Price EJ, Venables PJ: The etiopathogenesis of Sjögren's syndrome. *Semin Arthritis Rheum* 1995;25:117–133.
- 17 Hansen A, Lipsky PE, Dörner T: Immunopathogenesis of primary Sjögren's syndrome: implications for disease management and therapy. *Curr Opin Rheumatol* 2005;17:558–565.
- 18 Tapinos NI, Polihronis M, Tzioufas AG, Skopouli FN: Immunopathology of Sjögren's syndrome. *Ann Méd Interne (Paris)* 1998;149:17–24.
- 19 Greenspan JS, Daniels TE, Talal N, Sylvestre RA: The histopathology of Sjögren's syndrome in labial salivary gland biopsies. *Oral Surg Oral Med Oral Pathol* 1974;37:217–229.
- 20 Pijpe J, Kalk WW, van der Wal JE, Vissink A, Kluin PM, Roodenburg JL, Bootsma H, Kallenberg CG, Spijkervet FK: Parotid gland biopsy compared with labial biopsy in the diagnosis of patients with primary Sjögren's syndrome. *Rheumatology (Oxford)* 2007;46:335–341.
- 21 Kraaijenhagen HA: Letter: technique for parotid biopsy. *J Oral Surg* 1975;33:328.
- 22 Marx RE, Hartman KS, Rethman KV: A prospective study comparing incisional labial to incisional parotid biopsies in the detection and confirmation of sarcoidosis, Sjögren's disease, sialosis and lymphoma. *J Rheumatol* 1988;15:621–629.
- 23 Theander E, Vasaitis L, Baecklund E, Nordmark G, Warfvinge G, Liedholm R, Brokstad K, Jonsson R, Jonsson MV: Lymphoid organisation in labial salivary gland biopsies is a possible predictor for the development of malignant lymphoma in primary Sjögren's syndrome. *Ann Rheum Dis* 2011;70:1363–1368.
- 24 Cummins MJ, Papas A, Kammer GM, Fox PC: Treatment of primary Sjögren's syndrome with low-dose human interferon alfa administered by the oromucosal route: combined phase III results. *Arthritis Rheum* 2003;49:585–593.
- 25 Meiners PM, Vissink A, Kallenberg CG, Kroese FG, Bootsma H: Treatment of primary Sjögren's syndrome with anti-CD20 therapy (rituximab). A feasible approach or just a starting point? *Expert Opin Biol Ther* 2011;11:1381–1394.
- 26 Pollard RP, Pijpe J, Bootsma H, Spijkervet FK, Kluin PM, Roodenburg JL, Kallenberg CG, Vissink A, van Imhoff GW: Treatment of mucosa-associated lymphoid tissue lymphoma in Sjögren's syndrome: a retrospective clinical study. *J Rheumatol* 2011;38:2198–2208.
- 27 Smith RG, Burtner AP: Oral side-effects of the most frequently prescribed drugs. *Spec Care Dentist* 1994;14:96–102.
- 28 Nederfors T, Isaksson R, Mörnstad H, Dahlöf C: Prevalence of perceived symptoms of dry mouth in an adult Swedish population – relation to age, sex and pharmacotherapy. *Community Dent Oral Epidemiol* 1997;25:211–216.
- 29 Scully C: Drug effects on salivary glands: dry mouth. *Oral Dis* 2003;9:165–176.
- 30 Wilson K, Mottram P: A comparison of side effects of selective serotonin reuptake inhibitors and tricyclic antidepressants in older depressed patients: a meta-analysis. *Int J Geriatr Psychiatry* 2004;19:754–762.
- 31 Glare P, Walsh D, Sheehan D: The adverse effects of morphine: a prospective survey of common symptoms during repeated dosing for chronic cancer pain. *Am J Hosp Palliat Care* 2006;23:229–235.
- 32 Mangrella M, Motola G, Russo F, Mazzeo F, Giassa T, Falcone G, Rossi F, D'Alessio O, Rossi F: Hospital intensive monitoring of adverse reactions of ACE inhibitors. *Minerva Med* 1998;89:91–97.
- 33 Habbab KM, Moles DR, Porter SR: Potential oral manifestations of cardiovascular drugs. *Oral Dis* 2010;16:769–773.
- 34 Smidt D, Torpet LA, Nauntofte B, Heegaard KM, Pedersen AM: Associations between oral and ocular dryness, labial and whole salivary flow rates, systemic diseases and medications in a sample of older people. *Community Dent Oral Epidemiol* 2011;39:276–288.
- 35 Casaburi R, Briggs DD Jr, Donohue JF, Serby CW, Menjoge SS, Witek TJ Jr: The spirometric efficacy of once-daily dosing with tiotropium in stable COPD: a 13-week multicenter trial. The US Tiotropium Study Group. *Chest* 2000;118:1294–1302.
- 36 Durham MC: Tiotropium (Spiriva): a once-daily inhaled anticholinergic medication for chronic obstructive pulmonary disease. *Proc (Bayl Univ Med Cent)* 2004;17:366–373.
- 37 Keam SJ, Keating GM: Tiotropium bromide. A review of its use as maintenance therapy in patients with COPD. *Treat Respir Med* 2004;3:247–268.
- 38 Kaiser HB, Banov CH, Berkowitz RR, Bernstein DI, Bronsky EA, Georgitis JW, Mendelson LM, Rooklin AR, Sholler LJ, Stricker WW, Harrison JE, Danzig MR, Lorber RR: Comparative efficacy and safety of once-daily versus twice-daily loratadine-pseudoephedrine combinations versus placebo in seasonal allergic rhinitis. *Am J Ther* 1998;5:245–251.

- 39 Wellington K, Jarvis B: Cetirizine/pseudoephedrine. *Drugs* 2001;61:2231–2242.
- 40 Kaviani MJ, Malekzadeh R, Vahedi H, Sotoudeh M, Kamalian N, Amini M, Massarrat S: Various durations of a standard regimen (amoxycillin, metronidazole, colloidal bismuth sub-citrate for 2 weeks or with additional ranitidine for 1 or 2 weeks) on eradication of *Helicobacter pylori* in Iranian peptic ulcer patients. A randomized controlled trial. *Eur J Gastroenterol Hepatol* 2001;13: 915–919.
- 41 Teare JP, Spedding C, Whitehead MW, Greenfield SM, Challacombe SJ, Thompson RP: Omeprazole and dry mouth. *Scand J Gastroenterol* 1995;30:216–218.
- 42 Zaccara G, Gangemi P, Perucca P, Specchio L: The adverse event profile of pregabalin: a systematic review and meta-analysis of randomized controlled trials. *Epilepsia* 2011;52:826–836.
- 43 Marino D, Malandrini A, Rocchi R, Selvi E, Federico A: Transient 'sicca syndrome' during phenobarbital treatment. *J Neurol Sci* 2011;300:164.
- 44 Chakravarty K, al-Jafari MS: Phenytoin-induced pseudo-Sjögren's syndrome. *Br J Rheumatol* 1996;35:1033–1034.
- 45 Vissink A, Mitchell JB, Baum BJ, Limesand KH, Jensen SB, Fox PC, Elting LS, Langendijk JA, Coppes RP, Reyland ME: Clinical management of salivary gland hypofunction and xerostomia in head-and-neck cancer patients: successes and barriers. *Int J Radiat Oncol Biol Phys* 2010;78:983–989.
- 46 Jensen SB, Pedersen AM, Reibel J, Nauntofte B: Xerostomia and hypofunction of the salivary glands in cancer therapy. *Support Care Cancer* 2003;11: 207–225.
- 47 Vissink A, Jansma J, Spijkervet FK, Burlage FR, Coppes RP: Oral sequelae of head and neck radiotherapy. *Crit Rev Oral Biol Med* 2003;14:199–212.
- 48 Shannon IL, Trodahl JN, Starcke EN: Radiosensitivity of the human parotid gland. *Proc Soc Exp Biol Med* 1978;157: 50–53.
- 49 Mossman KL: Quantitative radiation dose-response relationships for normal tissues in man. II. Response of the salivary glands during radiotherapy. *Radiat Res* 1983;95:392–398.
- 50 Ship JA, Eisbruch A, D'Hondt E, Jones RE: Parotid sparing study in head and neck cancer patients receiving bilateral radiation therapy: one-year results. *J Dent Res* 1997;76:807–813.
- 51 Coppes RP, Zeilstra LJW, Kampinga HH, Konings AW: Early to late sparing of radiation damage to the parotid gland by adrenergic and muscarinic receptor agonists. *Br J Cancer* 2001;85:1055–1063.
- 52 Stewart FA, Van der Kogel AJ: Volume effects in normal tissues; in Steel GG (ed): *Basic Clinical Radiology*, ed 3. London, Arnold, 2002, pp 42–51.
- 53 Burlage FR, Coppes RP, Meertens H, Stokman MA, Vissink A: Parotid and submandibular/sublingual salivary flow during high dose radiotherapy. *Radiother Oncol* 2001;61:271–274.
- 54 Konings AW, Coppes RP, Vissink A: On the mechanism of salivary gland radiosensitivity. *Int J Radiat Oncol Biol Phys* 2005;62:1187–1194.
- 55 Paardenkooper GMRM, Zeilstra LJW, Coppes RP, Coppes RP, Konings AW: Radiation induced apoptosis is not the cause of acute impairment of rat salivary gland function. *Int J Radiat Biol* 1998; 73:641–648.
- 56 Avila JL, Grundmann O, Burd R, Limesand KH: Radiation-induced salivary gland dysfunction results from p53-dependent apoptosis. *Int J Radiat Oncol Biol Phys* 2009;73:523–529.
- 57 Abok K, Brunk U, Jung B, Ericsson J: Morphologic and histochemical studies of the deferring radiosensitivity of the ductular and acinar cell of the rat submandibular gland. *Virchows Arch Cell Pathol* 1984;45:443–460.
- 58 Nagler RM, Marmary Y, Fox PC, Baum BJ, Har-El R, Chevion M: Irradiation-induced damage to the salivary glands: the role of redox-active iron and copper. *Radiat Res* 1997;147:468–475.
- 59 Vissink A, 's-Gravenmade EJ, Ligeon EE, Konings WT: A functional and chemical study of radiation effects on rat parotid and submandibular/sublingual glands. *Radiat Res* 1990;124:259–265.
- 60 Vissink A, Kalicharan D, 's-Gravenmade EJ, Jongebloed WL, Ligeon EE, Nieuwenhuis P, Konings AW: Acute irradiation effects on morphology and function of rat submandibular glands. *J Oral Pathol Med* 1991;20:449–456.
- 61 Zeilstra LJ, Vissink A, Konings AWT, Coppes RP: Radiation induced cell loss in rat submandibular gland and its relation to gland function. *Int J Radiat Biol* 2000;76:419–429.
- 62 Jensen SB, Pedersen AM, Vissink A, Andersen E, Brown CG, Davies AN, Duttil J, Fulton JS, Jankovic L, Lopes NN, Mello AL, Muniz LV, Murdoch-Kinch CA, Nair RG, Napeñas JJ, Nogueira-Rodrigues A, Saunders D, Stirling B, von Bültzingslöwen I, Weikel DS, Elting LS, Spijkervet FK, Brennan MT: Salivary Gland Hypofunction/Xerostomia Section, Oral Care Study Group, Multinational Association of Supportive Care in Cancer (MASCC)/International Society of Oral Oncology (ISOO): A systematic review of salivary gland hypofunction and xerostomia induced by cancer therapies: prevalence, severity and impact on quality of life. *Support Care Cancer* 2010;18:1039–1060.
- 63 Eisbruch A, Ten Haken RK, Hyungjin MK, Marsh LH, Ship JA: Dose, volume and function relationships in parotid salivary glands following conformal and intensity-modulated irradiation of head and neck cancer. *Int J Radiat Oncol Biol Phys* 1999;45:577–587.
- 64 Roesink JM, Moerland MA, Battermann JJ, Hordijk GJ, Terhaard CH: Quantitative dose-volume response analysis of changes in parotid gland function after radiotherapy in the head-and-neck region. *Int J Radiat Oncol Biol Phys* 2001; 51:938–946.
- 65 Murdoch-Kinch CA, Kim HM, Vineberg KA, Ship JA, Eisbruch A: Dose-effect relationship for the submandibular salivary glands and implications for their sparing by intensity modulated radiotherapy. *Int J Radiat Oncol Biol Phys* 2008;72:373–382.
- 66 Vergeer MR, Doornaert PA, Rietveld DH, Leemans CR, Slotman BJ, Langendijk JA: Intensity-modulated radiotherapy reduces radiation-induced morbidity and improves health-related quality of life: results of a nonrandomized prospective study using a standardized follow-up program. *Int J Radiat Oncol Biol Phys* 2009;74:1–8.
- 67 Steneker M, Lomax A, Schneider U: Intensity modulated photon and proton therapy for the treatment of head and neck tumors. *Radiother Oncol* 2006;80: 263–267.
- 68 Widesott L, Pierelli A, Fiorino C, et al: Intensity-modulated proton therapy versus helical tomotherapy in nasopharynx cancer: planning comparison and NTCP evaluation. *Int J Radiat Oncol Biol Phys* 2008;72:589–596.

- 69 Cozzi L, Fogliata A, Lomax A, Bolsi A: A treatment planning comparison of 3D conformal therapy, intensity modulated photon therapy and proton therapy for treatment of advanced head and neck tumours. *Radiother Oncol* 2001;61:287–297.
- 70 Lomax AJ, Goitein M, Adams J: Intensity modulation in radiotherapy: photons versus protons in the paranasal sinus. *Radiother Oncol* 2003;66:11–18.
- 71 Van de Water T, Lomax T, Bijl HP, Schilstra K, Hug E, Langendijk JA: Comparative treatment planning study between scanned intensity modulated proton therapy and photon therapy in complex oropharyngeal carcinoma. *Radiother Oncol* 2008;88:S77–S78.
- 72 Johnson JT, Ferretti GA, Nethery WJ, Valdez IH, Fox PC, Ng D, Muscoplat CC, Gallagher SC: Oral pilocarpine for post-irradiation xerostomia in patients with head and neck cancer. *N Engl J Med* 1993;329:390–395.
- 73 LeVeque FG, Montgomery M, Potter D, Zimmer MB, Rieke JW, Steiger BW, Gallagher SC, Muscoplat CC: A multicenter, randomized, double-blind, placebo-controlled, dose-titration study of oral pilocarpine for treatment of radiation-induced xerostomia in head and neck cancer patients. *J Clin Oncol* 1993;11:1124–1131.
- 74 Niedermeier W, Matthaeus C, Meyer C, Staar S, Müller RP, Schulze HJ: Radiation-induced hyposalivation and its treatment with oral pilocarpine. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1998;86:541–549.
- 75 Warde P, O'Sullivan B, Aslanidis J, Kroll B, Lockwood G, Waldron J, Payne D, Bayley A, Ringash J, Kim J, Liu FF, Maxymiw W, Sprague S, Cummings BJ: A phase III placebo-controlled trial of oral pilocarpine in patients undergoing radiotherapy for head-and-neck cancer. *Int J Radiat Oncol Biol Phys* 2002;54:9–13.
- 76 Scarantino C, LeVeque F, Swann RS, White R, Schulsinger A, Hodson DI, Meredith R, Foote R, Brachman D, Lee N: Effect of pilocarpine during radiation therapy: results of RTOG 97-09, a phase III randomized study in head and neck cancer patients. *J Support Oncol* 2006;4:252–258.
- 77 Burlage FR, Roesink JM, Kampinga HH, Coppes RP, Terhaard C, Langendijk JA, van Luijk P, Stokman MA, Vissink A: Protection of salivary function by concomitant pilocarpine during radiotherapy: a double-blind, randomized, placebo-controlled study. *Int J Radiat Oncol Biol Phys* 2008;70:14–22.
- 78 Wasserman TH, Brizel DM, Henke M, Monnier A, Eschwege F, Sauer R, Strnad V: Influence of intravenous amifostine on xerostomia, tumor control, and survival after radiotherapy for head-and-neck cancer: 2 year follow-up of a prospective, randomized, phase III trial. *Int J Radiat Oncol Biol Phys* 2005;63:985–990.
- 79 Brizel DM, Wasserman TH, Henke M, Strnad V, Rudat V, Monnier A, Eschwege F, Zhang J, Russell L, Oster W, Sauer R: Phase III randomized trial of amifostine as a radioprotector in head and neck cancer. *J Clin Oncol* 2000;18:3339–3345.
- 80 Cotrim AP, Hyodo F, Matsumoto K, Sowers AL, Cook JA, Baum BJ, Krishna MC, Mitchell JB: Differential radiation protection of salivary glands versus tumor by tempol with accompanying tissue assessment of tempol by magnetic resonance imaging. *Clin Cancer Res* 2007;13:4928–4933.
- 81 Cotrim AP, Sowers AL, Lodde BM, Vitolo JM, Kingman A, Russo A, Mitchell JB, Baum BJ: Kinetics of tempol for prevention of xerostomia following head and neck irradiation in a mouse model. *Clin Cancer Res* 2005;11:7564–7568.
- 82 Dreyer JO, Sakuma Y, Seifert G: Die Strahlen-Sialadenitis. Stadieneinteilung und Immunhistologie. *Pathologie* 1989;10:165–170.
- 83 Matzker J, Schreiber J: Synthetischer Speichel zur Therapie der Hyposalien insbesondere bei der radiogenen Sialadenitis. *Z Laryngol Rinol Otol* 1972;51:422–428.
- 84 's-Gravenmade EJ, Roukema DA, Panders AK: The effects of mucin-containing artificial saliva on severe xerostomia. *Int J Oral Surg* 1974;3:435–439.
- 85 Van der Reijden WA, Van der Kwaak H, Vissink A, Veerman ECI, Nieuw Amerongen AV: Treatment of xerostomia with polymer-based saliva substitutes in patients with Sjögren's syndrome. *Arthritis Rheum* 1996;39:57–69.
- 86 Regelink G, Vissink A, Reintsema H, Nauta JM: Efficacy of a synthetic polymer saliva substitute in reducing oral complaints of patients suffering from irradiation-induced xerostomia. *Quintessence Int* 1998;29:383–388.
- 87 Pringle S, Van Os R, Coppes RP: Concise review: adult salivary gland stem cells and a potential therapy for xerostomia. *Stem Cells* 2012;31:613–619.

Konstantina Delli
Department of Oral and Maxillofacial Surgery
PO Box 30001
NL-9700 RB Groningen (The Netherlands)
E-Mail k.delli@umcg.nl