

Pathophysiology and Management of Radiation-induced Xerostomia

Lawrence B. Berk, MD, PhD, Anand T. Shivnani, MD, and William Small, Jr., MD

Radiotherapeutic treatment of head and neck cancer patients often causes long-term detriment to their quality of life. The three most important problems resulting from use of this modality that have been cited by patients involve salivary function, swallowing, and taste. All three of these domains are affected by radiation-induced damage to the salivary glands [1].

Salivary Glands

ANATOMY

Within the mouth and throat are three paired sets of salivary glands: the parotid glands, the submandibular glands, and the sublingual glands plus multiple minor salivary glands (Figure 1) [2]. The largest of the salivary glands, the parotids, are located in the space between the outer ear canal and the mandibular ramus and extend in front of the posterior portion of the mandible. The facial nerve (cranial nerve VII) runs through the parotid gland. The path of the facial nerve is used by surgeons to denote the separation of the superficial parotid glands from the deep parotid gland; however, there is no anatomical correlation with this separation.

The submandibular, or submaxillary, glands are located between the digastric muscles and the mandible. Whereas the parotid glands are not palpable, the submandibular glands can be. The sublingual glands are a pair of small salivary glands located at the anterior floor of the mouth in the submental area. Multiple small accessory salivary glands—the labial, buccal, palatine, lingual, and incisive glands—are located in the tongue and the gingival and oropharyngeal mucosae [3].

Manuscript received November 14, 2004; accepted January 21, 2005.

Correspondence to: William Small, Jr., MD, Division of Radiation Oncology, Robert H. Lurie Comprehensive Cancer Center, Northwestern University, 675 N. St. Clair, Chicago, Illinois 60611; telephone: (312) 926-6810; fax: (312) 926-6374; e-mail: w-small@northwestern.edu

J Support Oncol 2005;3:191-200 © 2005 Elsevier Inc. All rights reserved.

Abstract Radiotherapeutic treatment of head and neck cancer patients often causes long-term dysfunction involving their salivary function, swallowing capabilities, and taste. Salivary gland dysfunction from radiation therapy is often the most unpleasant side effect of treatment. This article will review current knowledge concerning the anatomy and function of glands involved with salivation, measurement of salivary gland function, surgical and pharmacologic prevention and treatment of xerostomia, and methods to administer radiation while causing the least amount of damage to salivary glands.

PHYSIOLOGY

There are two primary types of salivary gland cells—serous and mucinous. The parotid gland is almost entirely composed of serous cells, whereas the submandibular comprises both the mucinous and serous types [4].

Resting saliva primarily is secreted by the submandibular glands. Unstimulated salivary flow rates are about 0.3 mL/min [5]; these rates decrease by 50% during sleep [6]. In contrast, stimulated flow primarily is from the parotid glands. Stimulation may result in a four fold increase in parotid salivary flow and a minor increase in submandibular flow.

The flow of saliva primarily is regulated by central nervous system pathways. There is little to no direct local stimulation of the salivary glands. Taste and mastication do not increase salivary flow in the absence of higher cortical connections.

Unstimulated salivary flow is affected by a variety of factors, as shown in Table 1 [5]. For example, a body weight loss of just 2% resulting from dehydration will decrease salivary flow by 60% [7], and a body water content loss of only 8% will stop all salivary flow [5]. However, standard metabolic markers for dehydration, such as urine osmolality and serum creatinine, do not correlate well with salivary flow rates [8].

Salivary flow rates vary during the day and are at their lowest during sleep. These flow rates also show seasonal variation, reaching their highest levels during the winter [6, 9, 10]. Smoking has

Dr. Berk is Medical Director of Newark Radiation Oncology, Newark, Ohio, and Vice Chair of the Radiation Therapy Oncology Group.

Dr. Shivnani is Chief Resident at Northwestern University, Radiation Oncology, Chicago, Illinois.

Dr. Small is Associate Professor of Clinical Radiology, Division of Radiation Oncology, Feinberg School of Medicine, and Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, Illinois.

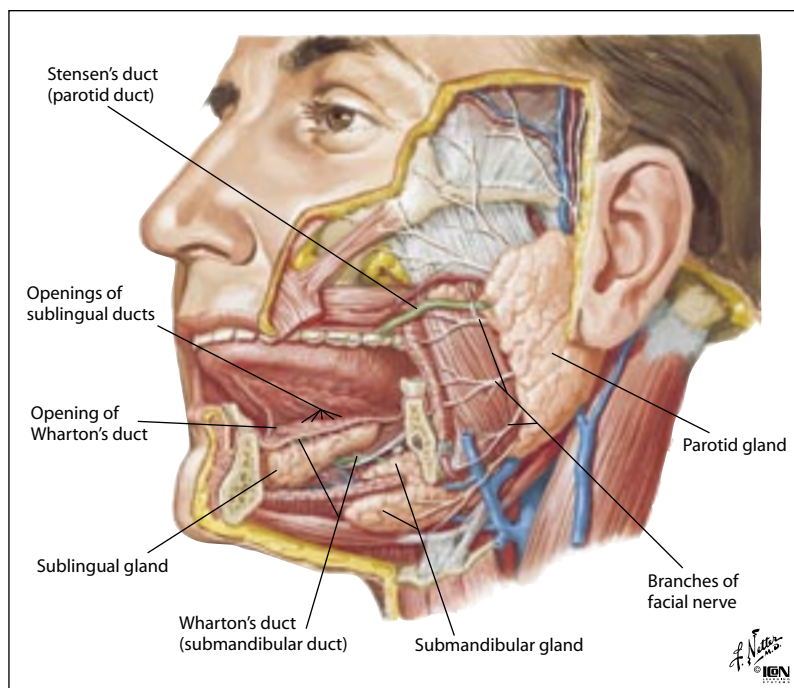


Figure 1 Anatomy of the Salivary Glands

The parotid glands are located in the space between the outer ear canal and the mandibular ramus, with some extension in front of the posterior portion of the mandible. Saliva exits the parotid into the mouth through Stensen's duct. The opening of Stensen's duct is at the level of the second upper molar. The facial nerve (cranial nerve VII) runs through the parotid gland. The submandibular glands (or submaxillary glands) are located between the digastric muscles and the mandible. The saliva from the submandibular gland exits into the floor of the mouth through Wharton's duct. The sublingual glands are a pair of small salivary glands located at the anterior floor of the mouth in the submental area. Multiple small ducts exit from the sublingual glands into the floor of the mouth. Netter medical illustration used with permission of Icon Learning Systems, LLC, a subsidiary of MediMedia, USA, Inc. All rights reserved.

Xerostomia

been found to increase [11], decrease [12], or not affect salivary flow [13, 14].

Factors that affect stimulated salivary flow are shown in Table 2 [5]. Chewing alone increases salivary flow, but the combination of taste and chewing provides greater stimulation. Of the four basic tastes—acid, salt, bitter, and sweet—acid is the strongest stimulant of salivary flow. In fact, citric acid commonly is used to induce salivary flow for measurement [11, 15, 16].

FUNCTIONS OF SALIVA

Bradley [17] described nine functions of saliva (Table 3). Salivary hypofunction, or xerostomia, may result in many subjective and objective oral problems. Importantly, a patient's subjective feeling of altered salivation and of dysfunction from salivation can differ from an objective measurement of salivary flow. Table 4 outlines objective

findings from patients with long-term xerostomia [18]. Bardow and colleagues [19] suggested that an unstimulated salivary flow of greater than 0.16 mL/min may be needed to prevent caries.

The interaction between salivary function and swallowing is complex. Saliva softens food both mechanically and enzymatically, allows formation of the food bolus to initiate swallowing, and lubricates the food bolus. Patients with a dry mouth after radiation therapy often complain of swallowing dysfunction; however, objective measurement of bolus transit time and swallowing function did not correlate with this perception [20, 21].

Wang et al [22] found that the sensation of mild xerostomia correlated with unstimulated salivary flow. However, Dawes [23] found that severe xerostomia reflected a change in both stimulated and unstimulated salivary flow, suggesting that an unstimulated flow rate of greater than 0.1–0.3 mL may be needed to avoid the sensation of xerostomia. He also postulated that the sensation of xerostomia is correlated to evaporation of the salivary coating on the oral mucosa and that the hard palate coating is lost most easily, causing the feeling of xerostomia.

Increased colonization with *Candida* is found among patients with xerostomia from radiation therapy [24]. Amifostine (Ethyol), a salivary gland function protectant, reduces the incidence of clinical oral candidiasis [25].

Burning tongue syndrome may be reported by patients with xerostomia after radiation therapy [26]. This effect often occurs in conjunction with xerostomia and dysgeusia, but the relationship between these symptoms is uncertain. It is possible that burning mouth syndrome is a neuropathic condition caused by salivary compositional changes and is not a direct reflection of mucositis from xerostomia [27].

MEASUREMENT OF SALIVARY GLAND FUNCTION

Objective measurement of salivary flow can be measured directly and indirectly. Direct measurement involves collection of either whole-mouth saliva or saliva from the individual glands. Whole-mouth saliva often is measured by having the patient collect saliva in the mouth without swallowing for a set period, such as 5 minutes, and then spitting out the saliva into a preweighed cup. However, more complicated measurement devices, such as the “three-channel photoelectric salivary flowmeter,” also have been used [28].

Salivary gland scintigraphy is an indirect measurement of salivary flow. It primarily measures the uptake of a radionuclide, such as technetium-99m pertechnetate, into the salivary glands [29, 30]. Another simple method of measuring stimulated salivary flow is to record the difference in the weight of hard candy before and after it sits under the dorsum of the tongue for 3 minutes [31].

One approach to the subjective measurement of salivary function is a visual analog scale developed by Pai et al [32]. Eight separate visual analog scores that evaluated issues such as “rate the dryness of your mouth” and “rate the level of your thirst” were measured for each patient. In this study, the team found a good correlation between measured salivation and a subjective feeling of xerostomia in normal subjects given an antisialagogue.

The University of Washington Quality of Life (QOL) Score for Head and Neck Cancer patients, versions 3 and 4, are the most common symptom scoring systems used in clinical research involving head and neck cancer patients [33]. The questionnaire used by these systems investigates multiple domains, including pain, appearance, and mood. It directly asks about saliva (“My saliva is of normal consistency”; “I have less saliva than normal, but it is enough”; “I have too little saliva”; “I have no saliva”). It also indirectly evaluates salivary function by asking questions about swallowing, chewing, and taste.

Radiation-induced Damage

MECHANISM OF SALIVARY GLAND DAMAGE

The exact mechanism of radiation-induced salivary gland damage is unknown. Actually, at least three mechanisms to explain the phenomenon have been hypothesized. One is direct damage to the DNA of the salivary gland cells by radiation-induced oxidative species. The second is cytotoxic damage to the cells initiated by the release of toxic materials from the cells themselves. The third is the induction by radiation of apoptosis by an intracellular mechanism [34, 35]. However, the majority of studies of radiation histopathology involved rodents and, therefore, may or may not directly relate to human response [36].

Studies of patients receiving definitive radiation therapy have shown a rapid diminution of salivary flow during the first 2 weeks of radiotherapy [37]. After 2 weeks of radiation therapy at doses of 20 Gy, the parotid and submandibular/sublingual sali-

Table 1

Factors Affecting Unstimulated Salivary Flow

FACTOR	EFFECT ON UNSTIMULATED SALIVARY FLOW
Dehydration	Decreases
Drugs	Primarily decreases
Posture (standing vs sitting)	Increases
Smoking	Varied

Adapted from Dawes⁵

Table 2

Factors Affecting Stimulated Salivary Flow

FACTOR	EFFECT ON STIMULATED SALIVARY FLOW
Mastication	Increases
Vomiting	Increases
Taste	Increases
Olfaction	Increases
Aging	None

Adapted from Dawes⁵

vary glands accomplished only 20% of their original salivary flow; the function did not recover after 6 weeks of radiation therapy. The parotid glands tended to lose more function than did the other salivary glands, with the former losing flow to nearly 0% and the latter stabilizing at 20%. However, no clinically significant difference in radiosensitivity between the parotid and submandibular/sublingual salivary glands was noted [38]. After high-dose radiation therapy, both serous and mucinous acini were almost completely obliterated [39–41].

Prevention

Much progress has been made in the past decade in preventing radiation-induced acute and long-term xerostomia. This section will review various methods of preventing xerostomia, including salivary gland transplantation, intensity-modulated radiotherapy (IMRT), and amifostine therapy.

SALIVARY GLAND TRANSPLANTATION

One approach to preserve salivary function is the surgical autotransplantation of a submandibular salivary gland outside of the radiation field. Although the parotid glands are larger than the submandibular glands, the parotid glands contribute just 20% of unstimulated saliva, whereas 65% of this flow arises from the submandibular glands and 8% from sublingual glands.

Peer viewpoints on this article by Drs. Avraham Eisbruch and Charles W. Scarantino appear on pages 201 and 207.

Table 3
Functions of Saliva

Lubrication
Digestion
Solvent action
Antibacterial action
Antifungal action
Buffering action
Remineralization
Temperature regulation
Production of growth factors and other regulatory peptides

Adapted from Bradley et al¹⁷

Table 4
Effects of Chronic Xerostomia

Increased caries formation
Increased rate of acute gingivitis
Dysarthria
Dysgeusia
Increased rate of candidal infection
Burning tongue

Adapted from Porter et al¹⁸

The parotid becomes the dominant gland at high flow rates (ie, stimulated, during eating). Jha and others [42] reported on a prospective series of patients who underwent transfer of the submandibular gland to the submental space before beginning radiation therapy. In their latest report, the team noted that salivary gland transfer was performed in 60 patients; 43 of these patients underwent postoperative radiation therapy with protection of the transferred salivary gland. The researchers measured whole salivary flow rates preoperatively, 2 weeks before surgery, at the end of radiation therapy, and at regular intervals up to 24 months after radiation therapy. In all, 19% of patients developed moderate to severe xerostomia immediately after radiation therapy; this effect was seen in 35% of patients at 6 months. This finding compared favorably with that of 16 patients who underwent submandibular gland transfer but who were not able to undergo shielding of the transferred submandibular gland due to tumor proximity: 48% of this group had moderate to severe xerostomia at the end of treatment, and this group grew to 71% at 6 months.

The prevention of xerostomia in this protocol was confirmed by measuring both salivary flow and QOL evaluations. The local recurrence rate was

6.6% at 14 months; no recurrences were seen in the submental space. Of 38 patients participating in this study and followed for at least 2 years, 26 had preservation of one submandibular gland, and 12 did not. Salivary flow was reported as normal in 83% of the group with preservation, compared with 0% in the non-preserved group [42].

The Radiation Therapy Oncology Group (RTOG) has activated a phase II protocol (RTOG 0244) to further investigate the role of submandibular gland transfer in a multi-institutional setting; the trial currently is open and is enrolling patients with biopsy-confirmed squamous cell carcinoma of the oropharynx, hypopharynx, or larynx or those having an unknown primary tumor with unilateral metastases to the neck nodes and at least 80% of parotids receiving ≥ 50 Gy. The choice of the side for submandibular salivary gland transfer depends on the side of the uninvolved neck and the side of the primary tumor. The transferred salivary gland is identified with the help of the computerized tomography (CT) scans taken in the treatment position. The shielding then is drawn to cover more than 70% of the transferred submandibular salivary gland and the major part of the sublingual salivary glands.

PAROTID-SPARING RADIATION THERAPY

With the advent of CT-based treatment planning and three-dimensional conformal radiation therapy (3DCRT), parotid-sparing techniques are advancing. Eisbruch et al [43] used beam's eye view displays to construct conformal beams to cover the tumor of 15 patients as they spared one parotid gland. Three months following radiation therapy, the spared parotid gland retained 50% of stimulated and unstimulated salivary flows; no saliva flow was seen in the unspared parotid gland in these patients. In all, 67% of these patients reported mild or absent xerostomia.

Maes and colleagues [44] used similar techniques to cover the primary tumor while maintaining the dose threshold to the contralateral parotid to 26 Gy. In 34 of 39 patients, the mean dose was ≤ 26 Gy. Using salivary gland scintigraphy, the mean loss of secretion function was 67% in the spared parotid and 100% in the unspared parotid. Normal excretion function was regained in 75% of spared parotids, and no recurrences were seen near these spared glands. Subsequent studies have confirmed that the benefit to using 3DCRT lies primarily in its ability to minimize radiation to the contralateral parotid [45].

The goal of xerostomia prevention has drawn closer with the more widespread use of IMRT, which uses complex treatment planning techniques to optimize radiation delivery to irregularly shaped volumes. Multileaf collimators available on many treatment machines allow for dynamic radiation delivery. The actual set of treatment beams and intensities is obtained using computer algorithms.

Reports have documented the benefits of IMRT using objective measures of salivary flow as well as oral-health QOL surveys. Munter and colleagues [46] reported on a series of 18 patients who received IMRT and required bilateral neck irradiation. Their goals were to spare the parotid glands without any increase in local failure rates and to analyze functional changes in the salivary glands as a function of dose using quantitative scintigraphy. The target mean dose for the parotid glands was 26 Gy, which was achieved in one gland in 11 of 18 patients and in both glands in 5 patients. The team made no attempts to spare the submandibular glands and used scintigraphy to measure salivary gland function. With maximal uptake as the primary measurement parameter, a dose threshold of 30 Gy was observed. However, this did not correlate with RTOG score, which measures subjective clinical symptoms. In this study of patients using IMRT techniques, the incidence of late RTOG grade 2 xerostomia was 17%.

Parliament et al [47] used a stricter criterion (goal mean dose to one parotid < 20 Gy) in a series of 23 patients. The actual combined mean dose to both parotids was 30 Gy. Oral-health QOL was measured using the University of Washington instrument [33]. Interestingly, patients with better-preserved unstimulated salivary flow rates in this study tended to report lower xerostomia scores.

Although the parotid gland sparing has been the focus of IMRT, some data have suggested that the sparing other major salivary glands and, perhaps, the minor salivary glands may be worthwhile objectives. Eisbruch et al [43] reported on a series of 84 patients who were given comprehensive bilateral neck radiation using IMRT. The team noted that salivary flow rates following radiation therapy from the parotid or submandibular glands failed to correlate with patient xerostomia questionnaire scores. The mean submandibular gland dose was a significant explanatory variable for xerostomia questionnaire score differences, whereas parotid dose was marginally significant ($P = 0.05$).

Additionally, the mean oral cavity dose, which represents radiation received by the minor salivary glands, also is a significant predictor of xerostomia severity. Although the minor salivary glands produce less than 10% of total saliva volume, they contribute more than 70% of the total mucins, which serve as mucosal lubricants and as selective permeability barriers of the mucosa. The importance of the nonparotid salivary glands is an active area of research; more data are needed to ensure that sparing these glands will not compromise tumor control.

In summary, available data suggest that using IMRT to keep the mean dose of the parotid glands to 26 Gy or less decreases the risk of long-term xerostomia. Furthermore, data suggest that sparing the submandibular and, perhaps, minor salivary glands can decrease this risk further. Therefore, in patients receiving IMRT, the parotid, submandibular, and submental glands should be contoured and preserved as much as possible.

AMIFOSTINE THERAPY

For decades, thiol-containing compounds such as amifostine have been known to have radioprotective properties [48–50]. The largest randomized trial of amifostine to date as a radioprotector for the salivary glands was conducted by Brizel and Wasserman, who reported their initial results in 2000 [51] and updated data at the 2004 American Society of Clinical Oncology annual meeting [52]. The study included patients with newly diagnosed squamous cell head and neck cancer who received radiation doses ≥ 40 Gy to at least 75% of both parotid glands. Both acute and chronic xerostomia were examined, and patients were stratified by treatment site, nodal status, institution, and definitive versus postoperative radiation therapy. Patients were randomized to receive 200 mg/m² of amifostine intravenously (IV) 15–30 minutes prior to radiation therapy on each day of treatment; because this was an open-label study, no placebo was given. The team randomized 315 patients and analyzed results for 303; 153 were given amifostine, and 150 patients were given radiation therapy alone.

The authors reported that 53% of patients receiving amifostine experienced at least one episode of nausea/vomiting, although it occurred with only 5% of all doses given. Despite the increase in nausea/vomiting, median weight loss was greater among patients treated with radiation therapy alone (5.6% vs 4.5% for those given amifostine).

Xerostomia

Further, 21% of patients discontinued amifostine before treatment was completed.

The efficacy of amifostine was statistically significant. The overall incidence of acute xerostomia was that of grade 2 or above was reduced (78% in the control group vs 51% in the amifostine group, $P < 0.0001$), as was chronic xerostomia of at least grade 2 (36% to 20%, respectively, at 24 months, $P = 0.002$). Saliva production was significantly higher in the group receiving amifostine, as were patient-benefit-questionnaire scores.

The 2004 update also included data on clinically meaningful (> 0.1 g) unstimulated salivary production, which was significantly higher in the treatment arm (76% vs 56% in the control arm at 24 months, $P = 0.01$). The incidence of mucositis was similar in both groups, and there was no significant difference in local control or overall survival (72% in the amifostine arm vs 67% in the control arm at 24 months, $P = 0.14$). Other studies have looked at higher doses (300 mg/m²) to further reduce symptoms [53].

Recently, subcutaneous (SQ) administration of amifostine has been explored as an alternative to use of the intravenous formulation. Cassatt et al [54] demonstrated equivalent tissue levels of the active metabolite of the drug, WR-1065, and oral mucositis protection using either the IV or the SQ formulation in an animal model.

Koukourakis et al [38] reported the results of a randomized trial comparing SQ amifostine with placebo in a group of 140 patients, 40 of whom had a head and neck carcinoma. Patients were treated with radiotherapy as definitive treatment or following incomplete resection, but no specific dose-volume requirements to the salivary glands were specified. Amifostine was administered daily at a dose of 500 mg and diluted in 2.5 mL of normal saline 20 minutes prior to radiotherapy. Grade 3/4 oral mucosal toxicities were reduced significantly with the addition of amifostine (30% in the radiation-only arm vs 0% in the amifostine arm, $P = 0.02$). A nonsignificant reduction in the number of days during which radiation was interrupted also was seen. Treatment breaks were given to patients who demonstrated grade 3/4 mucositis, and treatment was interrupted until mucositis returned to grade 1. Radiation-induced xerostomia (defined as severe mouth dryness and persistent use of water as a substitute for saliva) was noted in 75% of patients in the radiotherapy-only arm versus 58% of patients in the amifostine arm ($P = 0.32$).

However, no specific tests were performed to assess xerostomia.

Anne and Curran conducted a phase II trial [55] among head and neck cancer patients; in this study, at least 75% of patients would receive ≥ 40 Gy to both parotid glands. Prophylactic pilocarpine (Salagen) use was prohibited. Each day, 54 patients were treated with two 250-mg SQ injections of amifostine given in two locations 60 minutes before radiation therapy (50–70 Gy/2 Gy fractions). The team reported that 56% of patients developed acute xerostomia, which was similar to the 51% of patients reporting the effect after IV amifostine therapy in the Brizel study [52]. The median time to onset (40 days) and median cumulative radiation dose to onset (58 Gy) also were similar (45 days and 60 Gy, respectively, with IV amifostine). No grade 3 hypotension or nausea/vomiting was reported. Grade 3 cutaneous toxicity occurred in 13% of patients.

Bardet and colleagues [56] have published preliminary data from the phase III French Head and Neck Cancer Group (GORTEC) 2000-02 trial that compared IV and SQ administration of amifostine. Inclusion criteria in this study were similar to those of the Brizel study [52]. Administration of IV amifostine also was identical to that of the prior study; SQ amifostine was administered at a dose of 500 mg/day using two, slow, 1.25-mL injections delivered to two different sites 20–60 minutes before each radiotherapy session. Preliminary data on the first 54 patients of a target enrollment of 292 patients were published. No hypotension was noted in the group receiving SQ amifostine, and the rate of acute xerostomia of at least grade 2 was similar in both groups (23% IV vs 19% SQ amifostine). Compliance was 80% among patients receiving SQ amifostine as compared with 70% among those receiving IV amifostine.

In summary, available data show that amifostine significantly reduces the incidence of acute and long-term xerostomia. Short-term data suggest that SQ amifostine provides efficacy equal to that of IV amifostine, as it improves compliance and causes fewer side effects. However, long-term data are needed to confirm these results.

Treatment

Despite improvements in the prevention of xerostomia, this adverse reaction remains a significant morbidity for many head and neck radiotherapy patients. Therapeutic options for these patients currently are limited and include phar-

macologic agents, such as cholinergic agonists and complementary methods (eg, acupuncture).

CHOLINERGIC AGONISTS

One of the earliest agents studied to treat xerostomia was the muscarinic agonist pilocarpine. Pilocarpine has long been shown to stimulate salivary flow in normal volunteers as well as in patients with xerostomia secondary to radiation therapy [57]. The drug's pharmacokinetics and pharmacodynamics have been studied extensively in animal models [58, 59]. Studies based on varying levels of pilocarpine esterase activity in human serum samples by Aromdee and others [60–62] have shown variable responses to oral pilocarpine.

Early clinical studies involved the use of pilocarpine post radiation. Horiot and colleagues [63] reported on a 12-week, prospective study of 156 patients with severe radiation-induced xerostomia following radiation therapy who were treated with 15 mg of oral pilocarpine hydrochloride, followed by an optional 5-mg increase at 5 weeks and a second optional 5-mg increase at 9 weeks. In all, 75% of the patients complied with treatment, and 67% reported significant relief of xerostomia symptoms at 12 weeks. The group of patients having normal food intake increased from 13 to 24 patients with treatment; likewise, the number of patients unable to ingest solid foods declined from 47 to 29 patients. No correlation with dose/volume parameters was identified. The team concluded that pilocarpine's most important effect was on minor salivary glands.

Two prospective randomized clinical trials reported in the early 1990s confirmed the benefit of pilocarpine in the postradiation setting. LeVeque et al [64] performed a multicenter, double-blind, dose-titration study and concluded that optimal results were obtained with doses greater than 2.5 mg given three times daily for 8–12 weeks. Johnson et al [65], in a study of 207 patients, compared placebo with either 5 mg or 10 mg of oral pilocarpine given three times daily for 12 weeks. The pilocarpine group demonstrated significantly better subjective symptoms in every area assessed, with the best results coming at 12 weeks. Saliva production in the pilocarpine arm was improved significantly when compared with results in patients given placebo during the first 8 weeks of the study; however, the improvement in saliva production did not correlate with symptom relief. The most severe side effect was excessive sweating; however, no major adverse reactions were reported. In both of these

studies, pilocarpine was administered beginning at least 4 months after the end of radiotherapy.

Zimmerman et al [66] retrospectively compared concomitant pilocarpine use during head-and-neck irradiation with postradiation pilocarpine administration. Seventeen patients received concomitant pilocarpine (5 mg four times a day, continuing for 3 months following radiation therapy), and 18 patients received no pilocarpine. Results from patient questionnaires showed that the pilocarpine group had improved xerostomia scores when compared with the control group. An earlier study from the same group, presented only in abstract form, compared concomitant pilocarpine with postradiation pilocarpine and again documented improved xerostomia scores with the concomitant approach as compared with a salvage approach [67].

Warde et al [68] conducted a clinical trial of 130 patients randomized in a double-blind fashion between pilocarpine (5 mg three times daily during radiation therapy and 1 month afterward) versus placebo. They found no difference in xerostomia scores at 1, 3, or 6 months after treatment. Additionally, the team reported no improvement in acute side effects.

The largest study to date was conducted by Scarantino and colleagues [69] in the RTOG 97-09 trial. The team administered at least 50 Gy of radiation to 50% or more of the volume of major salivary glands of 249 patients; these subjects then were randomized to receive pilocarpine (5 mg four times a day) or placebo for 3 months starting 3 days prior to radiation. At 3 months following initiation of radiotherapy, the decline in unstimulated salivary flow due to radiation therapy was lower among the group receiving pilocarpine (–1.1 mL/min) than among the placebo group (–1.7 mL/min, $P < 0.047$). At 6 months, the difference in unstimulated flow was maintained, but it was not statistically significant ($P = 0.09$). However, by 6 months post radiotherapy, patients in both groups were allowed to take pilocarpine on an open-label basis. At 3 months, similar numbers of patients in each arm reported normal salivary flow (31% in the treatment arm vs 25% in the placebo arm) and impairment of eating and taste (78% and 90%, respectively). This trial is undergoing re-analysis prior to the publication of the final results.

Several investigators also have looked at the effectiveness of topical pilocarpine. Hamlar and colleagues at Ohio State University [70] have developed a pastille drug form that allows prolonged

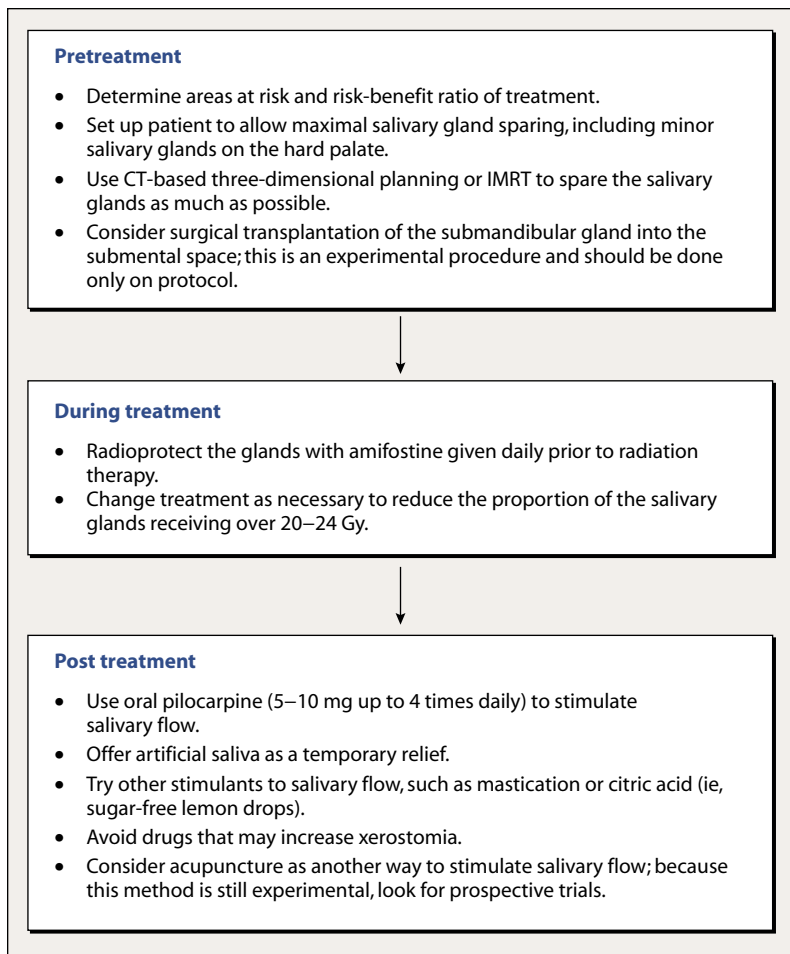


Figure 2 Xerostomia Prevention and Treatment

Xerostomia

and increased topical contact. During the pilot study, the time to complete dissolution of this pastille was 30 minutes—an extended dose when compared with systemic treatments.

The other hypothesized advantage of the pastille formulation is a decrease in systemic side effects. Thirty-four patients with clinically evaluable xerostomia at least 4 months following radiation therapy were enrolled in this double-blind, placebo-controlled trial in which dosages of 2.5–10.0 mg were used. The team noted nonsignificant improvement in subjective xerostomia; whole saliva production also was not affected significantly, and, although side effects were minor, sweating still was significantly higher than that seen among the placebo group.

A more recent study by Frydrych et al [71] tested a pilocarpine spray in a randomized, double-blind, placebo-controlled trial of 23 patients with radiation-induced xerostomia. No significant differences in dry mouth symptoms using this formulation were

seen between the groups, although the sample size was fairly small. Among patients whose baseline salivary flow rates were not zero, improvement in both stimulated and unstimulated salivary flow rates was noted among those using the pilocarpine spray.

Bernardi et al [72] reported on a placebo-controlled, randomized trial of various pilocarpine concentrations used as a mouthwash. Forty volunteers without xerostomia were randomized to hold 10 mL of 0.9% saline or of 0.5%, 1.0%, or 2.0% pilocarpine mouthwash for 1 minute and spit. Mouth rinsing with 1.0% or 2.0% pilocarpine induced significant objective and subjective increases in salivary flow.

A selective cholinergic agonist, cevimeline (Evoxac), also has been developed to treat radiation-induced xerostomia. Results from a phase III trial presented recently at the 2004 American Academy of Otolaryngology–Head and Neck Surgery annual meeting [73] reviewed findings among 284 patients with clinically significant salivary gland hypofunction who completed at least 40 Gy of radiotherapy at least 4 months before study entry; these patients were randomized to receive placebo or 30 mg of cevimeline three times daily for 6 weeks. If sufficient symptomatic improvement was not achieved, patients could increase the dosage to 45 mg three times daily for the remaining 6 weeks.

The researchers reported that cevimeline produced a statistically significant improvement in the global evaluation of dry mouth and in unstimulated whole salivary flow at 12 weeks when compared with placebo ($P < 0.05$). Sweating was the only adverse event that was significantly higher in the treatment arm.

ACUPUNCTURE

Investigators from Sweden examined the potential role of acupuncture in treating radiation-induced xerostomia [74–77]. Blom et al [74] reported results from randomizing 38 patients with xerostomia to receive acupuncture or placebo acupuncture following radiotherapy. Twenty patients in the experimental group and 18 patients in the control group received 12 acupuncture sessions, which lasted 20 minutes over 6 weeks; after a 2-week break, the patients received another 12 sessions. The control group underwent sham acupuncture involving superficial needle insertion about 1 cm away from the classic acupuncture points.

Both groups had improvements observed in salivary flow rates. Significant differences in salivary flow rates were noted in each group at differ-

ent intervals over the course of treatment, but no significant difference was observed. The authors concluded that superficial acupuncture was not a reliable placebo and should be considered to be a different type of acupuncture treatment.

Johnstone and colleagues [78] offered acupuncture to patients with pilocarpine-resistant xerostomia and reported the results in 18 patients treated with this approach. Their technique involved needling three points in the bilateral auricles and the second digit. Electrostimulation of the auricle also was used if no salivation was subjectively noted after 20 minutes. Patients received two sessions during the first week and three to four weekly sessions thereafter at approximately monthly intervals. All but two patients noted a subjective improvement; however, in all cases, relief was temporary and lasted up to 12 weeks.

Wong et al [79] reported on use of electronically stimulated acupuncture for radiation-induced xerostomia. The investigators found that although all of the patients in their analysis had statistically

significant improvements in salivary flow, no significant improvements showed in their QOL score.

Conclusion

Progress has been made in the prevention of xerostomia (Figure 2). Both treatment with amifostine and careful treatment planning, including that of IMRT, have demonstrated a proven benefit in reducing both acute and chronic xerostomia. Amifostine is available readily in the clinic today, and IMRT technology is available increasingly in both academic and community radiation oncology practices. Salivary gland transplantation also appears to be promising, but further data are needed to ensure that this technique can be performed reliably in a multi-institutional setting.

The use of cholinergic agonists in treating xerostomia has produced both objective and subjective symptomatic improvement following radiation therapy. Nonetheless, further research is needed to develop effective treatment strategies for radiation-induced xerostomia.

**Berk
Shivnani
Small**

*Peer viewpoints on
this article by Drs.
Avraham Eisbruch
and Charles W.
Scarantino appear on
pages 201 and 207.*

References

1. Pedersen AM, Bardow A, Jensen SB, Nauntofte B. Saliva and gastrointestinal functions of taste, mastication, swallowing and digestion. *Oral Dis* 2002;8:117-129.
2. Carlson GW. The salivary glands: embryology, anatomy, and surgical applications. *Surg Clin North Am* 2000;80:261-273.
3. Flatau AT, Mills PR. Anatomy and physiology: regional anatomy. In: Norman JD, McGurk M, eds. *Color Atlas and Text of the Salivary Glands: Diseases, Disorders and Surgery*. London: Mosby-Wolfe; 1995:13-39.
4. Cawson RA, Gleeson MJ, Eveson JW. *The Pathology and Surgery of the Salivary Glands*. Oxford, England: Isis Medical Media; 1997.
5. Dawes C. Factors influencing salivary flow rate and composition. In: Edgar M, Dawes C, O'Mullane DM, eds. *Saliva and Oral Health*. 3rd ed. London: British Dental Association; 2004:32-49.
6. Dawes C. Circadian rhythms in human salivary flow rate and composition. *J Physiol* 1972;220:529-545.
7. Walsh NP, Montague JC, Callow N, Rowlands AV. Saliva flow rate, total protein concentration and osmolality as potential markers of whole body hydration status during progressive acute dehydration in humans. *Arch Oral Biol* 2004;49:149-154.
8. Ship JA, Fischer DJ. Metabolic indicators of hydration status in the prediction of parotid salivary-gland function. *Arch Oral Biol* 1999;44:343-350.
9. Dawes C. Circadian rhythms in the flow rate and composition of unstimulated and stimulated human submandibular saliva. *J Physiol* 1975;244:535-548.
10. Dawes C. Rhythms in salivary flow rate and composition. *Int J Chronobiol* 1974;2:253-279.
11. Macgregor ID. Effects of smoking on oral ecology: a review of the literature. *Clin Prev Dent* 1989;11:3-7.
12. Maier H, Born IA, Mall G. Effect of chronic ethanol and nicotine consumption on the function and morphology of the salivary glands. *Klin Wochenschr* 1988;66(suppl 11):140-150.
13. Roesink JM, Terhaard CH. The influence of clinical factors on human stimulated parotid flow rate in cancer and other patients. *Oral Oncol* 2002;38:291-295.
14. Parvinen T. Stimulated salivary flow rate, pH and lactobacillus and yeast concentrations in non-smokers and smokers. *Scand J Dent Res* 1984;92:315-318.
15. Conduit R, Coleman G. Conditioned salivation and associated dreams from REM sleep. *Dreaming* 1998;8:243-262.
16. Fischer D, Ship JA. Effect of age on variability of parotid salivary gland flow rates over time. *Age Ageing* 1999;28:557-561.
17. Bradley RM. *Essentials of Oral Physiology*. St. Louis, Mo: Mosby-Year Book, Inc.; 1995.
18. Porter SR, Scully C, Hegarty AM. An update of the etiology and management of xerostomia. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2004;97:28-46.
19. Bardow A, Nyvad B, Nauntofte B. Relationships between medication intake, complaints of dry mouth, salivary flow rate and composition, and the rate of tooth demineralization in situ. *Arch Oral Biol* 2001;46:413-423.
20. Logemann JA, Smith CH, Pauloski BR, et al. Effects of xerostomia on perception and performance of swallow function. *Head Neck* 2001;23:317-321.
21. Hamlet S, Faull J, Klein B, et al. Mastication and swallowing in patients with postirradiation xerostomia. *Int J Radiat Oncol Biol Phys* 1997;37:789-796.
22. Wang SL, Zhao ZT, Li J, et al. Investigation of the clinical value of total saliva flow rates. *Arch Oral Biol* 1998;43:39-43.
23. Dawes C. How much saliva is enough for avoidance of xerostomia? *Caries Res* 2004;38:236-240.
24. Grotz KA, Genitsariotis S, Vehling D, Al-Nawas B. Long-term oral Candida colonization, mucositis and salivary function after head and neck radiotherapy. *Support Care Cancer* 2003;11:717-721.
25. Nicolatou-Galitis O, Sotiropoulou-Lontou A, Velegriki A, et al. Oral candidiasis in head and neck cancer patients receiving radiotherapy with amifostine cytoprotection. *Oral Oncol* 2003;39:397-401.
26. Johansson G, Andersson G, Attstrom R, Glantz PO, Larsson K. The effect of salinum on the symptoms of dry mouth: a pilot study. *Gerodontology* 1994;11:46-49.
27. Hershkovich O, Nagler RM. Biochemical analysis of saliva and taste acuity evaluation in patients with burning mouth syndrome, xerostomia and/or gustatory disturbances. *Arch Oral Biol* 2004;49:515-522.
28. Mason DK, Harden RM, Rowan D, Alexander WD. Recording the pattern of salivary flow. *J Dent Res* 1966;45:1458-1463.
29. Adams BK, Al Attia HM, Parkar S. Salivary gland scintigraphy in Sjögren's syndrome: are quantitative indices the answer? *Nucl Med Commun* 2003;24:1011-1016.
30. Aung W, Murata Y, Ishida R, et al. Study of quantitative oral radioactivity in salivary gland scintigraphy and determination of the clinical stage of Sjögren's syndrome. *J Nucl Med* 2001;42:38-43.
31. Wolff A, Herscovici D, Rosenberg M. A simple technique for the determination of salivary gland

hypofunction. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2002;94:175–178.

32. Pai S, Ghezzi EM, Ship JA. Development of a Visual Analogue Scale questionnaire for subjective assessment of salivary dysfunction. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2001;91:311–316.

33. University of Washington Surgical Outcomes and Research. Copies of the UW-QOL Scale. Available at http://depts.washington.edu/soar/projects/dxcat/hnca/qol_uw.htm. Accessed March 1, 2005.

34. Nagler RM. The enigmatic mechanism of irradiation-induced damage to the major salivary glands. *Oral Dis* 2002;8:141–146.

35. Fox PC. Acquired salivary dysfunction: drugs and radiation. *Ann N Y Acad Sci* 1998;842:132–137.

36. Ang KK, Stephens LC, Schultheis TE. Oral cavity and salivary glands. In: Scherer E, Streffer C, Trott K-R, eds. *Radiopathology of Organs and Tissues*. New York, NY: Springer-Verlag; 1991:283–311.

37. Burlage FR, Coppes R, Meertens H, Stokman MA, Vissink A. Parotid and submandibular/sublingual salivary flow during high dose radiotherapy. *Radiother Oncol* 2001;61:271–274.

38. Koukourakis MI, Kyrias G, Kakolyris S, et al. Subcutaneous administration of amifostine during fractionated radiotherapy: a randomized phase II study. *J Clin Oncol* 2000;18:2226–2233.

39. Valdez IH, Atkinson JC, Ship JA, Fox PC. Major salivary gland function in patients with radiation-induced xerostomia: flow rates and sialochemistry. *Int J Radiat Oncol Biol Phys* 1993;25:41–47.

40. Price RE, Ang KK, Stephens LC, Peters LJ. Effects of continuous hyperfractionated accelerated and conventionally fractionated radiotherapy on the parotid and submandibular salivary glands of rhesus monkeys. *Radiother Oncol* 1995;34:39–46.

41. Nagler RM. Effects of head and neck radiotherapy on major salivary glands—animal studies and human implications. *In Vivo* 2003;17:369–375.

42. Jha N, Seikaly H, Harris J, et al. Prevention of radiation induced xerostomia by surgical transfer of submandibular salivary gland into the submental space. *Radiother Oncol* 2003;66:283–289.

43. Eisbruch A, Ship JA, Martel MK, et al. Parotid gland sparing in patients undergoing bilateral head and neck irradiation: techniques and early results. *Int J Radiat Oncol Biol Phys* 1996;36:469–480.

44. Maes A, Weltens C, Flamen P, et al. Preservation of parotid function with uncomplicated conformal radiotherapy. *Radiother Oncol* 2002;63:203–211.

45. Malouf JG, Aragon C, Henson BS, Eisbruch A, Ship JA. Influence of parotid-sparing radiotherapy on xerostomia in head and neck cancer patients. *Cancer Detect Prev* 2003;27:305–310.

46. Munter MW, Karger CP, Hoffner SG, et al. Evaluation of salivary gland function after treatment of head-and-neck tumors with intensity-modulated radiotherapy by quantitative pertechnetate scintigraphy. *Int J Radiat Oncol Biol Phys* 2004;58:175–184.

47. Parliament MB, Scrimger RA, Anderson SG, et al. Preservation of oral health-related quality of life and salivary flow rates after inverse-planned intensity-modulated radiotherapy (IMRT) for head-and-neck cancer. *Int J Radiat Oncol Biol Phys* 2004;58:663–673.

48. Grdina DJ, Kataoka Y, Murley JS. Amifostine: mechanisms of action underlying cytoprotection and chemoprevention. *Drug Metabol Drug Interact*

2000;16:237–279.

49. Capizzi RL, Oster W. Chemoprotective and radioprotective effects of amifostine: an update of clinical trials. *Int J Hematol* 2000;72:425–435.

50. Dorr RT. Radioprotectants: pharmacology and clinical applications of amifostine. *Semin Radiat Oncol* 1998;8(4 suppl 1):10–13.

51. Brizel DM, Wasserman T. The influence of intravenous amifostine on xerostomia and survival during radiotherapy for head and neck cancer: two year follow-up of a prospective randomized trial. In: Program/Proceedings of the 40th Annual Meeting of the American Society of Clinical Oncology; June 5–8, 2004; New Orleans, La. Abstract 5536.

52. Brizel DM, Throuvalas N, Henke M, et al. Phase III randomized trial of amifostine as a radioprotector in head and neck cancer. *J Clin Oncol* 2000;18:3339–3345.

53. Antonadou D, Pepelassi M, Synodinou M, Puglisi M, Throuvalas N. Prophylactic use of amifostine to prevent radiochemotherapy-induced mucositis and xerostomia in head-and-neck cancer. *Int J Radiat Oncol Biol Phys* 2002;52:739–747.

54. Cassatt DR, Fazenbaker CA, Kifle G, Bachy CM. Subcutaneous administration of amifostine (Ethyol) is equivalent to intravenous administration in a rat mucositis model. *Int J Radiat Oncol Biol Phys* 2003;57:794–802.

55. Anne PR, Curran WJ Jr. A phase II trial of subcutaneous amifostine and radiation therapy in patients with head and neck cancer. *Semin Radiat Oncol* 2002;12(1 suppl 1):18–19.

56. Bardet E, Martin L, Calais G, et al. Preliminary data of the GORTEC 2000–02 phase III trial comparing intravenous and subcutaneous administration of amifostine for head and neck tumors treated by external radiotherapy. *Semin Oncol* 2002;29(6 suppl 19):57–60.

57. Greenspan D, Daniels TE. Effectiveness of pilocarpine in postradiation xerostomia. *Cancer* 1987;59:1123–1125.

58. Nagler RM, Laufer D. Protection against irradiation-induced damage to salivary glands by adrenergic agonist administration. *Int J Radiat Oncol Biol Phys* 1998;40:477–481.

59. Weaver ML, Tanzer JM, Kramer PA. Pilocarpine disposition and salivary flow responses following intravenous administration to dogs. *Pharm Res* 1992;9:1064–1069.

60. Aromdee C, Ferguson MM, Ledger R, Wall J. A pilot study of the disposition of pilocarpine in plasma, saliva and urine after a single oral dose. *Eur J Pharm Sci* 1999;8:81–83.

61. Aromdee C, Fawcett JP, Ferguson MM, Ledger R. Serum pilocarpine esterase activity and response to oral pilocarpine. *Biochem Mol Med* 1996;59:57–61.

62. Aromdee C, Fawcett JP, Ledger R. Sensitive high-performance liquid chromatographic assay for pilocarpine in biological fluids using fluorescence derivatization. *J Chromatogr B Biomed Appl* 1996;677:313–318.

63. Horiot JC, Lipinski F, Schraub S, et al. Post-radiation severe xerostomia relieved by pilocarpine: a prospective French cooperative study. *Radiother Oncol* 2000;55:233–239.

64. LeVeque FG, Montgomery M, Potter D, et al. 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.

65. Johnson JT, Ferretti GA, Nethery WJ, et al. Oral pilocarpine for postirradiation xerostomia in patients with head and neck cancer. *N Engl J Med* 1993;329:390–395.

66. Zimmerman RP, Mark RJ, Tran LM, Juillard CF. Concomitant pilocarpine during head and neck irradiation is associated with decreased post-treatment xerostomia. *Int J Radiat Oncol Biol Phys* 1997;37:571–575.

67. Zimmerman RP, Mark RJ, Juillard JF. Timing of pilocarpine treatment during head and neck radiotherapy: concomitant administration reduces xerostomia better than post-radiation pilocarpine. *Int J Radiat Oncol Biol Phys* 1996;36(suppl 1):236.

68. Warde P, O'Sullivan B, Aslanidis J, et al. 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.

69. Scarantino CW, LeVeque F, Scott C, et al. A phase III study on the concurrent use of oral pilocarpine to reduce hyposalivation and mucositis associated with radiation therapy in head and neck cancer patients: final results of RTOG 97-09. *Int J Radiat Oncol Biol Phys* 2001;51:85–86.

70. Hamlar DD, Schuller DE, Gahbauer RA, et al. Determination of the efficacy of topical oral pilocarpine for postirradiation xerostomia in patients with head and neck carcinoma. *Laryngoscope* 1996;106:972–976.

71. Frydrych AM, Davies GR, Slack-Smith LM, et al. An investigation into the use of pilocarpine as a sialagogue in patients with radiation induced xerostomia. *Aust Dent J* 2002;47:249–253.

72. Bernardi R, Perin C, Becker FL, et al. Effect of pilocarpine mouthwash on salivary flow. *Braz J Med Biol Res* 2002;35:105–110.

73. Weber RS, Chambers MS, Posner M, et al. Phase III study of cevimeline for radiation-induced xerostomia. In: Program/Proceedings of the 108th Annual Meeting of the American Academy of Otolaryngology/Head and Neck Surgery; September 19–22, 2004; New York, NY. Abstract P116.

74. Blom M, Dawidson I, Fernberg JO, et al. Acupuncture treatment of patients with radiation-induced xerostomia. *Eur J Cancer B Oral Oncol* 1996;32B:182–190.

75. Blom M, Lundeberg T. Long-term follow-up of patients treated with acupuncture for xerostomia and the influence of additional treatment. *Oral Dis* 2000;6:15–24.

76. Blom M, Kopp S, Lundeberg T. Prognostic value of the pilocarpine test to identify patients who may obtain long-term relief from xerostomia by acupuncture treatment. *Arch Otolaryngol Head Neck Surg* 1999;125:561–566.

77. Blom M, Dawidson I, Angmar-Mansson B. The effect of acupuncture on salivary flow rates in patients with xerostomia. *Oral Surg Oral Med Oral Pathol* 1992;73:293–298.

78. Johnstone PA, Peng YP, May BC, Inouye WS, Niemtzw RC. Acupuncture for pilocarpine-resistant xerostomia following radiotherapy for head and neck malignancies. *Int J Radiat Oncol Biol Phys* 2001;50:353–357.

79. Wong RK, Jones GW, Sagar SM, Babjak AF, Whelan T. A phase I-II study in the use of acupuncture-like transcutaneous nerve stimulation in the treatment of radiation-induced xerostomia in head-and-neck cancer patients treated with radical radiotherapy. *Int J Radiat Oncol Biol Phys* 2003;57:472–480.