Chapter 11

Xerostomia

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Introduction

Saliva is an essential body fluid. It is important in maintaining oral health, taste acuity, mastication, deglutition and digestion, regulation of oral flora, oral cleansing, voice acuity, and speech articulation. Saliva is composed largely of water but also contains minerals, electrolytes, buffers, enzymes, growth factors, cytokines, immunoglobulins, proteins, and metabolic waste products, with the concentrations and compositions of these components varying with the individual. Many systemic disorders, medications, and oncologic therapies can affect salivary function, greatly compromising oral health.

There are numerous minor salivary glands in the lining of the upper aerodigestive tract and the respiratory system. However, most of the saliva is produced by the three

pairs of major salivary glands: the parotid, the submandibular, and the sublingual glands. The paired major salivary glands have a basic anatomic structure that features acini with a specialized row of myoepithelial cells and a ductal system [1–3]. The acinar cells are the secretory end pieces and are responsible for the initial transport of fluid into the glandular ductal system [4]. The parotid glands consist mainly of serous acinar cells, which are highly radiosensitive, and secrete mainly under stimulation (e.g., gustatory, mastication). The submandibular glands consist of both mixed mucous and serous cells, whereas the sublingual glands consist mainly of mucinous cells, which are less radiosensitive. The ductal cells of each gland form a branching system that moves saliva into the respective glandular duct within the oral cavity [2–4].

The major glands combined produce up to 1.5 l of saliva a day [1]. This accounts for up to 90% of salivary secretions [5]. The parotid glands contribute between 52% and 70% of the salivary constituent upon stimulation (i.e., gustatory, masticatory) [2–4, 6]. The majority of the salivary flow from the parotid gland, however, is only induced during mastication and occurs for less than 1 h over the course of a day. The submandibular glands mainly provide resting saliva. More importantly, most of the protective function of the saliva is attributable to the effect of the submandibular glands. The submandibular glands contribute between 70% to 82% to the balance of resting whole saliva [2–4, 6].

The role of saliva in maintaining oral homeostasis is underappreciated and has not been fully elucidated. Saliva protects and lubricates the oral cavity and serves as an antibacterial, antiviral, and antifungal agent [1, 6]. Saliva is also an important facilitator of digestion, particularly the early breakdown of food, as well as taste acuity and articulation. Clinically, when the salivary glands are functionally deficient ("hypo" function), observable effects include difficulty speaking, difficulty chewing, difficulty swallowing, and impaired ability to taste. Other results of salivary gland hypofunction include an increased incidence of caries and periodontal disease with the presence of opportunistic organisms. The increased incidence of caries is caused by an increase in caries-forming organisms, which flourish in an acidic environment; therefore, even minimally functioning salivary glands can maintain an increase in the pH of the saliva and decrease the harmful effects of caries-forming organisms [2–4, 6–10]. Any increase in saliva, no matter how small, with concomitant increases in the production of salivary constituents may benefit patients with xerostomia [1].

The volume of salivary secretion may be decreased by a number of disease processes and other factors. Xerostomia is defined as the perception of dry mouth and is estimated to affect 22–26% of the general population [7]. It reportedly occurs more commonly in the elderly [10] and in patients with advanced cancer (29–77%) [7]. Xerostomia may also be associated with immunotherapy [9, 11], chemotherapy [6, 7], and radiation treatment involving the major salivary glands [12, 13].

Virtually all patients who undergo radiation therapy of the head and neck have some degree of xerostomia as a result of damage to the salivary glands [13–16]. Xerostomia may also be caused or exacerbated by the concomitant or sequential use of chemotherapy agents and other drugs [5]. Xerostomia is associated with oral discomfort and pain, increased rates of dental caries and oral infection, difficulty speaking and swallowing, and, ultimately, decreased nutritional intake and weight loss [13, 26] (Fig. 11.1). Thus, xerostomia significantly impairs the

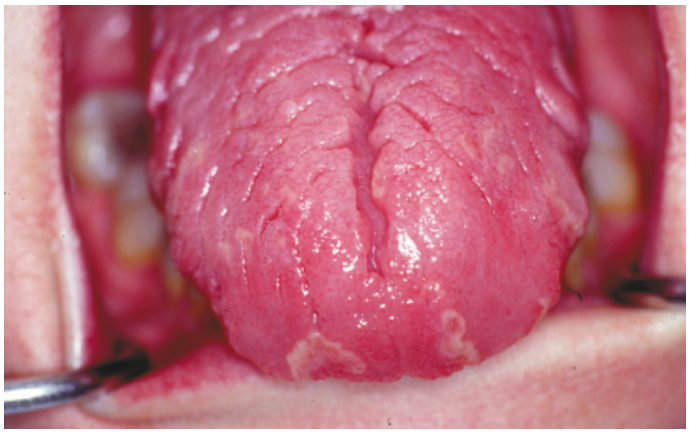

Fig. 11.1: Radiation-induced xerostomia of the oral tongue with fissuring of the dorsal anatomy, crenations, and leukoplakia

quality of life (QOL) and can compromise the continuity of cancer treatment.

The remainder of this chapter will be devoted to current knowledge of radiation-induced xerostomia and its sequelae.

Pathogenesis of Radiation-induced Xerostomia

A number of disease processes and other factors may decrease salivary secretion. Xerostomia has been reported in association with rheumatoid conditions, particularly Sjögren's syndrome [1, 17], human immunodeficiency virus infection [11], diabetes [12, 18], hypertension [12], and hematopoietic cell or bone marrow transplantation or graft-versus-host disease [19]. Medications also associated with xerostomia include many chemotherapy agents [20], antihypertensives [21], overactive-bladder agents [22], pain medications [21, 23], and psychiatric agents (Table 11.1) [21, 24]. Xerostomia has also been reported in association with some types of immunotherapy [25]. Radiation therapy, particularly directed at the oral mucosa and salivary glands can cause severe xerostomia [13, 26].

During therapy for head and neck cancer, the appropriate daily and total radiation doses are based on tumor size and individual clinical situations. Typically, daily radiation doses are 1.8–2 Gy, with subclinical microscopic cancer requiring at least 50 Gy over a 5-week period; smaller lesions (T1), 60–66 Gy; intermediate lesions (T2), 66–70 Gy; and large tumors (T3 and T4), more than 70 Gy [13, 14]. Radiation portals often include delivery of high doses to the parotid and submandibular glands bilaterally [27] and in some cases a large proportion of the minor salivary glands [28]. Clinically, xerostomia has been reported with as little as two or three doses of 2 Gy each, although many changes occurring with less than 60 Gy may be reversible [29, 30]. However, in some patients, doses greater than 30 Gy can cause permanent xerostomia [27].

Damage to the salivary glands results in reduced salivary flow, changes in the electrolyte and immunoglobulin composition of saliva, reduction of salivary pH, and repopulation of the mouth by cariogenic microflora [13]. When the major salivary glands are included in the radiation field, salivary function often decreases by 50–60% in the first week, with basal salivary flow reaching a measurable minimum 2–3 weeks after 23 Gy of fractionated radiation [13, 27, 30]. The extent of glandular change is generally directly related to the dose of radiation to the salivary glands, with the most severe and irreversible forms of salivary dysfunction resulting from damage to or loss of salivary acinar cells [13, 29].

Table 11.1. Drugs that may cause or exacerbate xerostomia [7, 13, 23]

Anorexiants
Antiacne agents
Antianxiety agents
Anticholinergic/antispasmodic agents
Anticonvulsants
Antidepressants
Antidiarrheal agents
Antihistamines
Antihypertensive agents
Anti-inflammatory analgesic agents
Antiemetic agents
Antiparkinsonian agents
Antipsychotic agents
Bronchodilators
Chemotherapy agents
Decongestants
Diuretics
Muscle relaxants
Narcotic analgesics
Sedatives

The pathogenesis of radiation-induced xerostomia involves more than damage to the salivary glands, however, a lack of lubrication reduces the ability of chemoreceptors on the tongue and palate to accept stimuli presented with foods or liquids, resulting in failure of the salivary response. The minimal volume and thickened mucinous saliva that is produced may form a barrier to dietary, thermal, and mechanical stimulation of the taste buds. This, in turn, affects the pathway of salivary gland stimulation and ultimate secretion. The mucosa of the tongue may be atrophied, with decreased surface area for taste buds. Significant loss of appetite may occur, along with mucositis. As dietary intake decreases, weight loss alone may become a significant factor in the continuity of cancer therapy [31]. Methods for assessing radiation-induced

xerostomia include clinical examination; subjective measures, such as patient self-report instruments and visual analog scales; and objective measures, such as assessment of stimulated and unstimulated salivary flow rates [32]. Metrics for describing xerostomia have been poor. The most recent version of the Common Terminology Criteria for Adverse Events v3.0 (CTCAE v3.0) has been developed and represents an important improvement as a comprehensive, multimodality grading system to include both acute and late effects [33, 34].

Quality of Life

Radiation-induced xerostomia can be an acute complication that improves with time but is often a permanent condition that seriously impairs the patient's well-being. Xerostomia predisposes patients to an altered oral microflora with increased virulent bacteria and fungal activity [35]. Loss of salivary function usually results in the appearance of an increased number of caries-forming bacteria (mutans Streptococci and Lactobacillus) in the oral cavity, with resultant "radiation caries" caused by a loss of buffering capacity, lowered salivary pH, elimination of mechanical flushing, and decreased production of salivary immunoglobulins (i.e., IgA, IgG, IgM), lysozymes, and peroxidases (Fig. 11.2) [6, 29, 35]. Xerostomia may result in mucositis; oral pain or discomfort; and difficulty with mastication, deglutition, and articulation; and it is associated with increased caries, dysgeusia, ageusia, soft tissue breakdown, bone loss, and chronic infection [15, 26]. When not monitored and controlled, xerostomia may lead to accumulation of plaque and other debris on teeth and periodontal tissues [6]. Cariogenic plaque buildup on teeth may lead to tooth decay, gingivitis, and periodontitis. According to Berger and Kilroy [31], elevated plaque matrix resulting from xerostomia may pose the greatest risk of osteoradionecrosis. Ill-fitting removable prostheses in patients with xerostomia, causing tissue irritation, can compound mucositis and result in fenestration of supporting mucosa and post-treatment osteoradionecrosis. In addition, recent evidence suggests a potential link between oral and dental disease and systemic illnesses, such as atherosclerosis, coronary artery disease, and cerebrovascular ischemia [36].

Saliva plays a significant role in taste acuity, although the interaction is not completely understood [37]. It is known that a diminished salivary flow can markedly affect this interaction [6]. Saliva has modulating effects on the basic taste modalities: sour, sweet, salty, and bitter. Saliva strongly influences salty taste threshold levels and provides the ionic environment necessary for signal transduction by taste cells. The type of taste stimuli can also influence salivary flow rate and composition. Sour taste induces the highest flow rate and sodium concentrations, whereas salt gives rise to high protein and calcium concentrations [37]. Chemoreceptors on the dorsal tongue anatomy are markedly affected by xerostomia with a diminished acuity, therefore decreasing the effect of taste and affecting the patient's QOL [6, 26, 37].

Patients with cancer of the head and neck must sometimes choose between treatment options that provide equivalent cure rates but potentially differing effects on QOL. Several recent studies have reported on the preva-

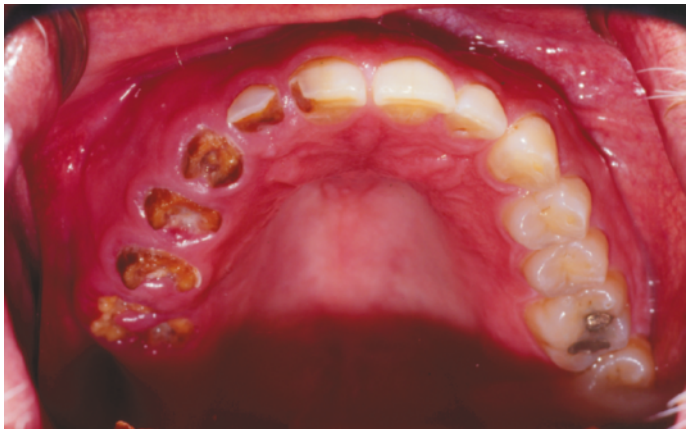

Fig. 11.2: Fifty-year-old male patient with history of adenocarcinoma of the parotid gland status post-parotidectomy and radiation therapy presenting with unilateral caries (1.5 years post-radiation therapy)

lence of xerostomia symptoms and their impact on QOL in persons treated for cancer of the head and neck [13].

Hughes et al. [38] investigated the prevalence of long-term dysphagia after radiation for carcinoma of the nasopharynx. These researchers assessed 50 patients, aged 26–75 years, who had received radiation 12–119 months earlier, and showed that 96% of patients had xerostomia and 76% had dysphagia. In another study, Logemann et al. [26] evaluated perception and performance of the swallow function in 36 patients, aged 40–76 years, who received radiation of at least 40 Gy to the oral cavity or oropharyngeal areas over a 6-week period, with or without concurrent chemotherapy. Each patient underwent pretherapy and post-therapy testing, including a questionnaire on the global perception of dry mouth, measurement of stimulated saliva production, and videofluorographic study of oropharyngeal swallow. After radiation therapy, significantly more patients reported swallowing difficulty, dry mouth, needing water while eating, food sticking to the mouth or throat, and change in taste. Mean saliva weight decreased from 5.1 g before treatment to 1.4 g after treatment ($p < .0001$) and generally was lower in patients who reported swallowing difficulty. The researchers concluded that chemoradiation therapy results in xerostomia and a significant increase in patient perception of swallowing difficulty.

Harrison et al. [39] treated 36 patients, aged 35–71 years, with primary radiation for squamous cell carcinoma of the base of the tongue; all received external beam radiation therapy (45–54 Gy) to the primary site and the neck, followed by an electron boost (up to 60 Gy) to involved neck nodes and an iridium-192 implant boost to the primary site (20–30 Gy). After a median follow-up of 5 years, 29 long-term survivors completed four surveys, including validated QOL instruments. From these results, the researchers concluded that most of the patients had excellent functional status and QOL and were able to maintain prediagnosis income and employment status. However, the results of the Memorial Symptom Assessment Scale indicated that xerostomia occurred in all patients and was rated as causing moderate to severe distress by 89%. Other commonly reported symptoms included difficulty swallowing (76%; moderate to severe distress in 90% of those affected) and decreased energy (48%; moderate to severe distress in 64%). Although only 34% of patients reported change in taste, 70% of these found this effect to cause moderate to severe distress.

Epstein et al. [40] used the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire, with an addendum to assess oral symptoms and function, to measure QOL of 65 patients, aged 21–79 years, who more than 6 months earlier had undergone radiation therapy with or without surgery for head and neck and oral cancers. Results showed that 91.8% of patients reported xerostomia; 75.4%, change in taste; 63.1%, dysphagia; 50.8%, altered speech; 48.5%, difficulty with dentures; 43%, difficulty chewing or eating; and 38.5%, increased tooth decay (in dentate patients). In addition, pain was common (58.4%), interfering with daily activities in 30.8%. The frequency of oral side effects was correlated with radiation treatment fields and dose. Most patients reported their overall QOL and overall physical condition to be less than excellent.

In a similar study, Epstein et al. [13, 40] found that xerostomia, change in taste, dysphagia, speech difficulties, and oral pain were commonly reported oral symptoms, and that oral QOL did not return to pretreatment levels by 6 months after treatment. Development of further general, disease-specific, and region-specific QOL studies are needed to help guide cancer treatment choices, assess QOL and function after treatment, and assess the management of oral complications after radiation for cancer of the head and neck [39, 40].

Treatment

Stringent Oral and Dental Care

To minimize the severity of xerostomia and oral complications, it is important to begin aggressive oral care prior to starting radiation therapy. Appropriate nutritional intake, effective oral hygiene, and early detection of oral lesions are important pretreatment practices. Evaluation by a dental team experienced in oral oncology, ideally weeks in advance of therapy, is essential to determine oral health status, perform necessary dental and oral interventions, and allow for healing from any invasive procedures that may be required. Greater attention will be required in identifying mucosal lesions, dental caries and endodontic disease, periodontal disease, ill-fitting dentures, orthodontic appliances, temporomandibular dysfunction, and salivary abnormalities. A stringent program of oral hygiene is crucial and should be performed before, during, and after therapy (Table 11.2) [6, 13, 15, 41].

Table 11.2. Management steps for patients with radiation-induced xerostomia [6, 13, 15, 41]

Function	Treatment options
Plaque removal	Tooth brushing (nontartar controlled)
	Flossing
	Other oral hygiene aids
Remineralization	Topical high-concentration prescription fluorides
	Children: topical and systemic
	Adults: topical
Prevention/treatment of infection	Antimicrobials, such as chlorhexidine rinses, povidone-iodine oral rinses, tetracycline oral rinses
Temporary relief of dryness	Salivary substitutes or rinses containing hydroxyethyl-, hydroxypropyl-, or carboxymethylcellulose
Stimulation of remaining salivary gland tissue	Sialogogic agents (cholinergic agonists)
	FDA-approved: pilocarpine
	Investigational: cevimeline, bethanechol chloride, others

Radiation Therapy Protectants

Agents have been developed to ameliorate or eliminate toxicities associated with chemotherapy and radiation [42]. Amifostine, an agent studied for its selective protection of normal tissue from damage induced by radiation and chemotherapy, was approved by the US Food and Drug Administration (FDA) as a cytoprotective agent with cisplatin-based chemotherapy for ovarian cancer and, later, for prevention of xerostomia in patients treated with radiation for head and neck cancer [43]. This recommendation was based on the results of a phase III multiinstitutional randomized study reported by Brizel et al. [44]. The incidence of grade 2 or higher chronic xerostomia was reduced from 57% in the control arm to 34% in patients receiving amifostine. There were no differences in survival or disease control, suggesting that amifostine protected salivary function without protecting the cancer. Clinical practice guidelines of the American Society of Clinical Oncology, published in 1999, indicate that amifostine may be considered for use in patients who undergo fractionated radiation in the head and neck region to decrease the incidence of acute and late xerostomia [42]. The recommended dose of amifostine is 200 mg/m² per day administered as a slow intravenous push over 3 min, 15–30 min before each fraction of radiation. Patients require close monitoring for side effects, including hypotension and nausea, and some patients may require antiemetics [42, 43]. Investigations with a subcutaneous administration of amifostine are ongoing, because this form of administration may be more practical and lower the toxicity of the drug.

Salivary Gland Transfer Techniques

Although the radiation ports used in treating cancer of the head and neck generally deliver 60–65 Gy to the major salivary glands, the submental region is regularly shielded, receiving only scatter radiation of 5% of the total dose [13, 16]. Several animal studies [45–47] have demonstrated the feasibility of microvascular autotransplantation of submandibular and parotid gland tissue. In a recent human study, Seikaly et al. [16] transferred the submandibular gland to the submental space in patients undergoing surgery and radiation for head and neck cancer. The glands survived transfer and continued to function after radiation with appropriate shielding. This continues to be an area of investigation in multicenter settings.

Table 11.3. Xerostomia: pharmacologic options [1]

	Product	Manufacturer
Saliva substitutes	Oral Balance	Laclede Research Labs, Gardena, CA
	Salivart	Gebauer Company, Cleveland, OH
	MouthKote	Parnell Pharmaceuticals, Larkspur, CA
	Saliva Substitute	Roxane Laboratories, Columbus, OH
	MoistPlus	Medical Warehouse, Stormville, NY
	MedOral spray	BHM Labs, Port Richey, FL
	Oasis	Glaxo Smith Kline, Philadelphia, PA
Fluoride	Gel Kam (0.4% SnF)	Colgate Oral Pharmaceuticals, Canton, MA
	Prevident Gel (1.1% NaF)	Colgate Oral Pharmaceuticals, Canton, MA
	NeutraCare (1.1% NaF)	Oral-B Laboratories, Belmont, CA
	Omni Gel (0.4% SnF)	Omni Gel, Gravette, AR
	Prevident 5000 plus dentifrice	Colgate Oral Pharmaceuticals, Canton, MA
Cholinergic agonists	Pilocarpine (Salagen)	MGI Pharma, Minnetonka, MN
	Cevimeline (Exovac)	Daiichi Sankyo, Montvale, NJ

Gene Therapy

Emerging research and medical technology are providing specificity and sensitivity methods to determine the roles of human salivary components. Gene transfer may be potentially useful for treating inherited single-gene deficiency disorders and malignancies refractory to other therapies, as well as restoring function to irradiated salivary glands [48, 49]. There are no published reports examining a prophylactic gene transfer approach to reducing or eliminating radiation damage of the salivary glands [48]. Translational studies involving plasmid-mediated gene transfer for reducing radiation-induced damage have been conducted, and results of in vivo animal studies in lung and esophageal tissue are quite promising [50, 51]. Research in nonviral gene-mediated therapeutics for restoring radiation-induced salivary gland dysfunction may prove beneficial [8].

Pharmacologic Options

Current therapies for the pharmacologic management of radiation-induced xerostomia include the use of prescription fluoride agents to maintain optimal oral hygiene, antimicrobials to prevent dental caries and oral infection, saliva substitutes to relieve dryness, and sialogogic agents, i.e., cholinergic agents, to stimulate saliva production from remaining intact salivary gland tissues (Table 11.3) [13, 15, 40].

Proper oral care before, during, and after radiation is essential, with the use of topical 0.4% stannous fluoride or 1.1% sodium fluoride gel once daily to minimize dental caries [6]. Oral antimicrobial agents may also be beneficial in preventing oral infection. Chlorhexidine gluconate, for example, provides broad-spectrum activity in vitro against gram-positive, gram-negative, and fungal pathogens and binds well to oral surfaces (minimizing gastrointestinal absorption). However, the desiccating effect of the alcohol in some chlorhexidine solutions may exacerbate xerostomia; therefore, an aqueous-based solution may be beneficial [6, 41].

Saliva substitutes containing hydroxyethyl-, hydroxypropyl-, or carboxymethylcellulose may be beneficial as palliative agents to relieve the discomfort of xerostomia by temporarily wetting the oral mucosa [52]. One recent study investigated the use of a xanthan gum-based saliva substitute [28]. Patient reports showed similar improvement with the xanthan gum-based saliva substitute and placebo (of similar composition, without xanthan gum),

but with a trend toward increased improvement in speech and sensory problems with the xanthan gum agent. The researchers concluded that this agent was not of greater benefit than other saliva substitutes for patients with radiation-induced xerostomia [28]. Other new saliva substitutes (moisturizing gels) with enzymatic and protein components (e.g., glucose oxidase and lactoperoxidase), which present prospective antibacterial effectiveness and increased oral moisture, are under study.

For patients with residual salivary gland function, cholinergic agonists may produce symptomatic improvement [18, 28]. Pilocarpine is currently the only sialogogic agent approved by the FDA for radiation-induced xerostomia. Pilocarpine functions primarily as a muscarinic-cholinergic agonist with mild β-adrenergic activity. Muscarinic agonists in sufficient dosage can increase secretion of exocrine glands, such as salivary and sweat glands, as well as the tone of smooth muscle in the gastrointestinal and urinary tracts. Studies have shown oral pilocarpine to have efficacy in patients with Sjögren's syndrome, radiation-induced xerostomia, and opioid-induced xerostomia, as well as increasing salivary flow and restoring salivary composition in those with graft-versus-host disease caused by allogeneic bone marrow transplantation [5, 25, 29, 53–56]. The role of pilocarpine during radiation to decrease xerostomia requires further investigation. Preliminary data from a randomized Radiation Therapy Oncology Group (RTOG) study suggest some improvement in objective saliva measurements in patients receiving pilocarpine during radiation compared with patients receiving placebo. However, there were no differences in patients' perception of their xerostomia when patients receiving active drug were compared with the placebo control arm [57]. Warde et al. [58] from Canada revealed in a smaller phase III trial that there was no beneficial effect of pilocarpine on radiation-induced xerostomia when administered during radiation for patients with cancer of the head and neck.

In October 2002, Hodson et al. [59] updated their Cancer Care Ontario Practice Guidelines (CCOPG) for the Symptomatic Treatment of Radiation-Induced Xerostomia in Head and Neck Cancer Patients. The group's recommendations were based largely on evidence from four randomized, placebo-controlled studies of oral pilocarpine [52, 60–62], one comparison trial of pilocarpine mouthwash versus artificial saliva [63], and one study of long-term efficacy [64]. In a crossover study by Greenspan and Daniels [61] including 12 patients who had severe xerostomia 6 months after radiation therapy, nine patients showed marked improvement after 3 months of treatment with 15–30 mg of pilocarpine daily, whereas none showed meaningful improvement while taking placebo. Schuller et al. [62] administered an oral solution containing 3 mg of pilocarpine or placebo to patients who had undergone surgery and postoperative radiation therapy an average of 21 months earlier; the pilocarpine solution produced no improvement in dry mouth, taste, or swallowing compared with placebo. LeVeque et al. conducted a randomized, placebo-controlled dose escalation study, and Johnson et al. conducted a three-arm randomized, placebo-controlled trial (placebo, pilocarpine 5 mg three times a day, and pilocarpine 10 mg three times a day) [52, 60]. In both studies, significantly more patients treated with pilocarpine than those subjects receiving placebo reported improvement in xerostomia. In addition, LeVeque et al. found that treatment with pilocarpine led to a significant decrease in the use of oral comfort agents such as artificial saliva, hard candies, and water [52].

In a randomized crossover study of pilocarpine mouthwash versus mucin-based artificial saliva, Davies and Singer [63] found a mean change in the xerostomia score after 3 months of 22.5% with pilocarpine and 15.2% with artificial saliva. For 36 months, Jacobs and van der Pas [64] followed patients with radiation-induced xerostomia who were treated with pilocarpine, 2.5–10 mg twice a day or three times a day (starting dose, 5 mg three times a day). They found improvements at the last visit in dryness of the mouth and tongue, oral comfort, ability to sleep, ease of speaking, and ability to eat. In these studies, no serious adverse events were associated with pilocarpine treatment. The most frequently reported adverse event was excessive sweating; others included chills, nausea, dizziness, rhinitis, and asthenia. Largely on the basis of these studies, the authors of the CCOPG [59] reached the following conclusions: (1) for patients with cancer of the head and neck with symptomatic xerostomia after radiation therapy using conventional fractionation schedules, pilocarpine 5 mg three times a day is recommended; (2) patients must have evidence of preexisting salivary function; (3) the ideal duration of treatment with pilocarpine is undefined, and the decision to extend treatment beyond 3 months can be made on the basis of clinical judgment only; (4) it is highly reasonable to use pilocarpine for patients with symptomatic xerostomia after hyperfractionated or accelerated-fractionation radiation [59]; and (5) pilocarpine is contraindicated in patients with uncontrolled asthma, acute iritis, or narrow-angle glaucoma. It should be used with caution in patients with controlled asthma, chronic bronchitis, chronic obstructive pulmonary disease, or cardiovascular disease [65].

Other cholinergic agents with sialogogic properties, such as cevimeline hydrochloride, may prove beneficial for cancer patients with xerostomia. Cevimeline is a newer muscarinic agonist that has been found to be safe and effective in treating xerostomia associated with Sjögren's syndrome and has received FDA approval for that use [66, 67]. In addition, cevimeline has shown efficacy in animal studies by increasing saliva secretions after X-ray exposure of the head and neck [68] and is currently under study for use in patients with cancer of the head and neck who have radiation-induced xerostomia. A randomized, double-blind, placebo-controlled study was conducted with cevimeline in patients with Sjögren's syndrome, and most of the subjects receiving active drug had a global improvement in their xerostomia. The effects of cevimeline at 15 mg three times a day (45 mg/day) and 30 mg three times a day (90 mg/day) were compared with those of placebo, and statistically significant global improvement in the symptoms of dry mouth ($p = .0004$) was seen for the 30 mg three times a day group than the placebo group. Salivary flow rates increased at both doses of cevimeline compared with placebo [69]. The incidence of serious adverse events was low in all treatment groups. The most common drug-related adverse events were excessive sweating, nausea, rhinitis, and diarrhea [70].

In addition to these currently available and emerging pharmacotherapies, the use of chewing gums made with noncariogenic sweeteners may help stimulate saliva secretion and reduce oral mucosal friction [71]. Humidification may also be helpful; in a recent study, however, hyperthermic supersaturated humidification by way of a nasal cannula in patients with radiation-induced xerostomia yielded little or no additional relief compared with a standard bedside humidifier [15].

Emerging Parotid Gland-sparing Techniques

Recent efforts have focused on the use of conformal radiation or other newer radiotherapy techniques to spare a portion of the major salivary glands [27]. Intensity-modulated radiotherapy (IMRT) is a form of conformal radiation that allows for sculpting dose distributions that conform specifically to a three-dimensional shape of the target. The clinical advantages to using IMRT are numerous and include improvement in radiation dose uniformity, creation of concave dose patterns conforming to the shape of the tumor, assignment of weightings to targets and critical structures, treatment of multiple targets simultaneously, and lowering of complication rates. The desire for conformal doses and the lack of internal organ motion make IMRT attractive for patients with cancer of the head and neck [72–74]. Several studies have demonstrated the significant benefit of IMRT over conventional treatment with respect to dosimetric superiority compared with more conventional approaches [75–77]. Recently, IMRT has been used for treatment of cancers of the head and neck and studied for improved tumor coverage with resultant increased rates in locoregional control and decreased short-term toxicity [76]. Longitudinal data on the therapeutic efficacy of IMRT are lacking with regard to long-term tumor outcome and late radiation toxicity [76]. However, a substantial number of studies have documented the reduction of radiation-induced xerostomia following IMRT for squamous cell carcinoma of the pharynx and larynx [13, 27, 72–77].

Conventional Parotid Doses and Sparing

Dreizen et al. [78] quantified saliva production in patients undergoing radiotherapy for cancer of the head and neck. In this study, after a dose of 10 Gy, patients had already developed a 50% reduction in salivary flow. After receiving 50 Gy, patients had less than 10% of their salivary flow remaining, and few patients regained salivary function. Emami et al. [79] defined the tolerance dose of the saliva glands to radiation, stating the minimum tolerance dose of 5/5 (tumor dose causing 5% complication rate at 5 years) as 30 Gy, and the tolerance dose 50/5 as 50 Gy. Leslie and Dische [80] described high rates of xerostomia in patients whose parotid glands were irradiated with 40 Gy but negligible rates in patients who received less than 14 Gy. Thus, the tolerance doses of the glands lie somewhere within this wide range.

Parotid-sparing Techniques

Reducing the radiation dose to the major salivary glands is achievable with IMRT [72, 77]. Reddy et al. investigated the use of parotid-sparing irradiation techniques in patients with cancer of the oral cavity. Thirty-one patients were treated with two-dimensional techniques sparing at least one parotid gland from radiation beams, whereas 83 patients were treated with bilateral opposed photon beams, including both parotid glands. Patients treated with the parotid-sparing technique were able to maintain nutritional intake and baseline body weight during and after radiation

therapy. In contrast, those treated with the bilateral technique had poor nutritional intake and lost more than 10% of body weight, which was not regained during the 2 years after treatment. When analyzed according to tumor stage, primary tumor control rates with the parotid-sparing and bilateral techniques were similar (93% and 87%, respectively, for early-stage tumors; 42% and 36%, respectively, for advanced-stage tumors); therefore, the authors noted that selection of patients who might benefit from this technique requires consideration of the risk of contralateral cervical lymph node metastases [30].

In another study, O'Sullivan et al. used an ipsilateral technique to restrict irradiation to the primary tumor and neck on the same side in patients with carcinoma of the tonsillar region. From 1970 to 1991, these researchers treated 228 of 642 patients with carcinoma of the tonsillar region (mainly T1 and T2, N0 and N1) with this technique. After a mean follow-up of 7 years, the 3-year actuarial local control rate was 77% and the cause-specific survival rate was 76%, with failure in the opposite side of the neck in eight patients. Difficulties with primary coverage early in the study resulted in higher rates of local failure. The researchers concluded that, in appropriately selected patients with carcinoma of the tonsil, the risk of failure in the opposite side of the neck is minimal with ipsilateral therapy, but CT planning is necessary to ensure adequate target coverage [81].

While the above suggest that a subset of patients requiring radiation therapy can be treated unilaterally, and avoid a high likelihood of developing xerostomia, most patients with mucosal cancer of the head and neck still require radiation to both sides of the neck. In order to diminish xerostomia in patients undergoing bilateral radiation therapy, conformal techniques and eventually IMRT were tested as methods to decrease the dose to the parotid glands [82–84]. Unfortunately, while it was recognized that the parotid glands are sensitive to radiation, the precise tolerance dose was unclear. To begin to answer the question of whether parotid gland sparing was feasible and efficacious, the dose, volume, and functional relationships in parotid salivary glands following conformal and multisegmental IMRT of the head and neck were studied by Eisbruch et al. [85]. Eighty-eight patients with cancer of the head and neck participated in the study. Unstimulated and stimulated saliva was measured from each parotid gland before radiotherapy and 1, 3, 6, and 12 months afterward. Glands receiving a mean dose below or equal to a threshold of less than 25% of the pretreatment level (24 Gy for unstimulated and 26 Gy for stimulated saliva) revealed preservation of the flow rates after radiotherapy. More importantly, and contrary to the belief that xerostomia was irreversible, these patients continued to improve over time [85]. The glands receiving doses below the threshold had functional recovery over time, whereas glands receiving higher doses did not recover [77, 85]. Age, sex, preradiotherapy surgery, chemotherapy, and specific intercurrent illnesses were not found to affect the salivary flow rates. Eisbruch et al. [82, 85, 86] concluded that a mean dose of less than 26 Gy to the parotid gland should be the planning goal for substantial sparing of gland function.

Besides objective measures of xerostomia (parotid flow rates) the University of Michigan team also performed subjective assessments. The group developed and validated the xerostomia questionnaire (XQ). This is an eight-item instrument in which subjects rate their own assessment of dryness with regards to talking, eating, sleeping, and the need for water for comfort in differing scenarios. Eisbruch et al. [27] then demonstrated that if the mean parotid dose was kept below 21 Gy, patients experienced lower scores (i.e., less subjective xerostomia). However, when compared to patients who were treated with unilateral techniques, despite improvement in xerostomia, patients treated to the bilateral neck still had more complaints of dry mouth. In addition, the oral cavity mean radiation dose was found to be significantly correlated with xerostomia scores, indicating that it may be beneficial to spare the uninvolved oral cavity to further reduce xerostomia [27].

These University of Michigan researchers also studied the parotid salivary function up to 12 months after radiotherapy in 20 patients undergoing bilateral neck parotid-sparing irradiation to determine if parotid preservation improves xerostomia-related QOL [84]. Salivary sampling and a 15-item xerostomia-related QOL scale were completed by each patient. The salivary flow from spared and treated glands significantly decreased at the completion of radiotherapy. After radiotherapy, unstimulated and stimulated function increased and was not significantly different from baseline figures; therefore, these authors concluded that, with the use of parotid-sparing radiotherapy, contralateral glands are preserved 12 months after treatment with parallel improvement in xerostomia-related QOL [84]. This same group of researchers [86, 87] also tested QOL and xerostomia in patients treated with IMRT compared to patients treated with conventional radiotherapy. Twelve months after parotid-sparing IMRT, statistical significance was found between patient-reported xerostomia and four domains of QOL: eating, communication, pain, and emotion [87].

Using mathematical modeling, Chao et al. [88] concluded that the functional outcome of salivary flow using inverse-planning IMRT could be modeled as a function of dose, and therefore the mean dose to each parotid gland is a reasonable indicator for the functional outcome of each gland. The entire parotid volume was used to compute dose-volume histograms in this trial evaluating 41 patients with head and neck cancer. Stimulated saliva production at 6 months reduced exponentially for each gland independently, at a rate of approximately 4% per Gy of mean parotid dose [88].

In another study by the same authors, acute toxicity, late toxicity, and tumor control were retrospectively compared in 430 patients with cancer of the oropharynx who underwent radiotherapy with a conventional beam arrangement or IMRT [89]. These investigators concluded that the dosimetric advantage of IMRT translated into significant reduction of late salivary toxicity, with no adverse impact on tumor control or disease-free survival [89, 90]. After IMRT, only 17–30% of patients had late grade 2 xerostomia. Although the majority had moderate to severe dry mouth during therapy, the spared salivary glands showed recovery over time. The dosimetric conformity of IMRT for normal tissue sparing in patients with oropharyngeal cancer was studied by Chao et al. [91] in assessing the therapeutic outcomes of IMRT as it relates to the impact on gross tumor volume (GTV) and nodal gross tumor volume (nGTV). A multivariate analysis revealed that GTV and nGTV were important independent risk factors predictive of therapeutic outcome for definitive treatment of oropharyngeal IMRT [91].

In delineating the target volume for radiation in parotid gland-sparing techniques, Eisbruch et al. [92] recently published results of a longitudinal clinical investigation assessing patients treated with parotid-sparing IMRT for non-nasopharyngeal squamous cell carcinomas of the head and neck; furthermore, patients were examined for locoregional failures near the base of the skull and their relationships to the target delineation in the upper neck. The results reported in this study confirmed that defining level II in the contralateral node-negative neck so that the targets included the subdigastric nodes, yet not to extend as cranial as in conventional radiotherapy, allowed substantial sparing of the contralateral parotid glands and, hence, reduced salivary dysfunction. Another study evaluating the radiotherapy target volume and organs at risk in oropharyngeal carcinoma defined the lowering of the cranial border of the level II lymph nodes from C1 to C2 in patients with bilateral cervical radiotherapy and found reduced toxic effects on major salivary gland tissue, as proposed by Astreinidou et al. [93]. The lowering of the cranial border to C2 with IMRT could be considered on the contralateral side if the risk of metastasis on that side is significantly low, thus reducing the average mean dose to the contralateral parotid gland. Astreinidou et al. [93] calculated that the reduction of the normal tissue complication probability for xerostomia 1 year after radiotherapy could be up to 68% (lowering the cranial border to C2), compared with conventional radiotherapy when treating C1.

Munter et al. [94] evaluated salivary gland function after IMRT for cancer of the head and neck using quantitative pertechnetate scintigraphy. The mean dose to the primary planning target volume was 61.5 Gy, and the median follow-up was 23 months. This study revealed that it was possible to protect the parotid glands and reduce the incidence of xerostomia in patients with cancer of the head and neck if mean parotid doses were less than 30 Gy.

Conclusions

Xerostomia has been reported as the most common late effect of radiation for cancer of the head and neck [13, 27]. Despite current preventive and treatment efforts, xerostomia remains a common complication of radiation, causing significant impairment of QOL. Several investigational interventions are promising. First, advanced radiation delivery techniques, such as IMRT, potentially deliver a higher dose to the tumor target without increasing the dose to normal tissues, such as salivary glands, thereby allowing a higher dose per fraction and improved physical and biologic therapeutic ratios. Emerging data indicate that IMRT and other new parotid-sparing techniques hold promise for the treatment of cancer of the head and neck, potentially offering reduced severity of xerostomia without compromised tumor control for appropriately selected patients [76, 95]. Second, early studies have demonstrated the feasibility of the transfer of the submandibular gland to the submental space in patients undergoing radiation, preserving salivary function and preventing xerostomia [16]. Third, sialogogic agents that have been effective in treating xerostomia associated with other disease processes, such as Sjögren's syndrome, hold promise of improved relief for patients radiated for cancer of the head and neck. Finally, the use of gene therapy and tissue engineering to restore salivary gland water pathways—or even the creation of an artificial salivary gland—may be on the horizon [13, 66]. Together with careful assessment, monitoring, and management of radiation-induced xerostomia, these emerging treatment strategies may signifi-

cantly improve the QOL for future patients undergoing radiation for cancer of the head and neck.

Take Home Messages

- Saliva is a complex bodily fluid that has multiple properties: protective, digestive, lubrication, remineralizing, and facilitating speech, eating, and swallowing.
- Damage to the salivary glands results in reduced salivary flow, changes in the electrolyte and immunoglobulin composition of saliva, reduction of salivary pH, and repopulation of the mouth by cariogenic microflora.
- Xerostomia is defined as the perception of dry mouth and is estimated to affect 22–26% of the general population.
- Xerostomia is associated with oral discomfort and pain, increased rates of dental caries and oral infection, difficulty speaking and swallowing, and, ultimately, decreased nutritional intake and weight loss.
- Current therapies for the pharmacologic management of radiation-induced xerostomia include the use of prescription fluoride agents to maintain optimal oral hygiene, antimicrobials to prevent dental caries and oral infection, saliva substitutes to relieve dryness, and sialogogic agents, i.e., cholinergic agents, to stimulate saliva production from remaining intact salivary gland tissues.
- Emerging data indicate that IMRT and other new parotid-sparing techniques hold promise for the treatment of cancer of the head and neck, potentially offering reduced severity of xerostomia without compromised tumor control for appropriately selected patients.
- Parotid gland mean dose of less than 26 Gy should be the planning goal for substantial sparing of gland function.

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