Radiation-induced xerostomia is a frequent and usually permanent side effect of radiation therapy for head and neck cancer. We summarize recent developments in the prevention and treatment of radiation-induced xerostomia.

Methods: The Medline database was searched for articles published within the past 10 years on the prevention and treatment of postirradiation xerostomia. Proceedings of recent important national meetings and government Web registries of clinical trials and therapeutic agents were also consulted. Priority was given to randomized controlled trials but, because of the scarcity of such trials, small open trials were included in this review. No other predetermined selection criteria were used, although articles exploring the effects of xerostomia and its treatment on quality of life were considered of special interest.

Results: A variety of preventive approaches for postirradiation xerostomia exist, involving more conformal radiation delivery technology, radioprotective agents, and even preirradiation surgical techniques. Therapeutic interventions include supportive care, saliva supplementation, and the use of procholinergic salivary secretagogues.

Conclusions: Radiation-induced xerostomia constitutes a significant morbidity after orofacial irradiation. Careful preventive techniques, meticulous supportive care, and new preventive and therapeutic agents may prove useful in combination.

The diagnosis of head and neck cancer is made every year in approximately 30,000 to 40,000 people in the United States. Many patients are treated with therapeutic irradiation delivered to the head and neck as sole treatment or in addition to surgery. Radiotherapy has also been combined with chemotherapy to sensitize locally advanced tumors to radiation or eradicate distant micrometastases. Xerostomia is a common, distressing side effect of radiotherapy for head and neck cancer, occurring to some degree in up to 100% of patients undergoing such treatment. Hyposalivation and the subjective perception of oral dryness occur predictably when the major salivary glands are included in the radiation field. The major salivary glands are responsible for 90% of saliva production, which in healthy individuals averages about 1000 to 1500 mL/day.

In patients with radiation-induced salivary gland injury, salivary flow typically decreases by 50% to 60% during the first week after 25 to 30 Gy of standard fractionated radiotherapy has been delivered, and basal flow reaches a nadir in 2 to
3 weeks. The magnitude of salivary flow reduction is primarily related to the radiation dosage and the amount of salivary gland tissue included in the irradiation fields. Although partial, usually early, symptomatic improvement of xerostomia may occur occasionally, reversion to preirradiation levels of salivation does not occur unless sufficiently large volumes of salivary gland tissue have been protected from exposure to more than a very limited radiation dose. Eisbruch et al demonstrated that with parotid mean doses exceeding 24 to 26 Gy, salivary recovery was very rare, yet patients whose doses were below those levels could experience significant recovery for up to 2 years.

Irradiation causes both quantitative and qualitative change in salivary gland function and saliva. Serous acini, found predominantly in the parotid glands, are the main contributors of stimulated salivary flow and appear to be particularly susceptible to radiation damage. As a result, saliva becomes more viscous and ropy and is diminished in quantity during key oral activities such as mastication.

Xerostomia results in difficulty in chewing and swallowing dry food, impaired phonation, a continuous parched feeling and burning sensation of the oral cavity, and dysgeusia. Patients describe a feeling of thickened saliva and often carry water bottles with them at all times. The chewing of dry foods such as crackers may be very painful for them, and physical examination may reveal a dry oral cavity mucosa, angular cheilitis, fissuring of the tongue and lips, accelerated dental caries, oropharyngeal candidiasis, or halitosis. The patient may experience loss of taste, mucosal sensitivity to acidic or spicy foods, or loss of appetite and weight loss.

Xerostomia is diagnosed through the patient’s report of dry mouth combined with the presence of the symptoms outlined above and is formally graded by the Common Terminology Criteria for Adverse Events v3.0 (Table 1). Because patients may not spontaneously report dry mouth symptoms and associated psychosocial problems, clinicians should ask patients who have undergone head and neck radiation therapy about oral function and associated quality-of-life (QOL) issues. The complications and morbidity associated with xerostomia, and the severity of their effect on patients’ QOL, are often misunderstood and underestimated. The prevalence of coronal and root caries was increased in patients with xerostomia compared with controls matched for number of teeth, age, sex, and alcohol and smoking habits. Hyposalivation increases the risk of oral infections, mainly dental caries, gingivitis, and candidiasis. The last can exacerbate xerostomia and may be difficult to eradicate, especially in patients wearing removable dentures. Patients’ nutritional status and their intake of fluids and nutrients essential for tissue healing can be compromised.

The impact of radiation-induced xerostomia and its complications on QOL is well documented; it has been suggested that the chronic aftereffects of radiation therapy may impair QOL more severely than cancer itself. In a recent study, oral complications after radiation treatment for orofacial cancer were assessed together with general QOL. Dry mouth was the most common complaint (95%) and was reported to be moderate or severe by 70% of patients. Altered taste was common (90%), and phonation was affected in 65% of patients. Dental decay rates were believed to be increased by 45% of patients, and 56% reported having problems with dentures. Oral QOL did not return to pretreatment levels by 6 months after irradiation.

**Preventive Strategies.** During the past decade, substantial effort has been devoted to strategies to prevent or mitigate xerostomia, using 2 approaches: improved targeting of the radiation beam and the development of radioprotective agents.

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<th>Grade Description</th>
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<tr>
<td>1: Mild AE Symptomatic (dry or thick saliva) without significant dietary alteration; unstimulated salivary flow &gt;0.2 mL/min.</td>
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<td>2: Moderate AE Symptomatic and significant oral intake alteration (eg, copious water, other lubricants, diet limited to purées and/or soft, moist foods); unstimulated salivary flow 0.1–0.2 mL/min.</td>
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<td>3: Severe AE Symptoms leading to inability to adequately aliment orally; intravenous fluids, tube feedings, or total parenteral nutrition indicated; unstimulated salivary flow &lt;0.1 mL/min.</td>
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<td>4: Life-threatening or disabling AE NA</td>
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<td>5: Death related to AE NA</td>
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**Abbreviations:** AE, adverse events; NA, not applicable.
Recent technological advances in therapeutic radiation delivery have allowed the sparing of a portion of the major salivary glands.\textsuperscript{6,17} Intensity-modulated radiation therapy (IMRT) involves the use of computer algorithms to adjust the dose delivered by segments (beamlets) of the radiation beam, so that the spatial distribution of the radiation dose conforms tightly to the target volume, whereas the dose to adjacent normal tissue is minimized.\textsuperscript{18} In a study comparing IMRT with conventional radiation therapy, IMRT reduced the incidence of late grade 2 xerostomia. In patients with oropharyngeal carcinoma, the dosimetric advantage of IMRT over conventional techniques resulted in a significant reduction of late salivary gland toxicity. Other reports of patients being treated for cancers in other head and neck sites, including the nasopharynx, have demonstrated significant salivary sparing.\textsuperscript{18,19} IMRT allows relative parotid salivary gland preservation, but the potential benefit may not be applicable to all patients; limitations in their use arise from the area anatomy and often from the extent of the tumors.\textsuperscript{17}

Amifostine is a cytoprotective organic thiophosphate that acts as a free radical scavenger.\textsuperscript{20} Preclinical studies using a rat parotid gland model demonstrated both short-term and long-term protection against radiation-induced injury of salivary glands, where amifostine accumulates preferentially. This finding led to early clinical trials in patients with head and neck cancer treated with radiation therapy, in which amifostine was reported to provide salivary gland protection.\textsuperscript{20} A more recent prospective phase III trial also showed that amifostine reduced both acute and chronic xerostomia in patients receiving radiation therapy for head and neck cancer.\textsuperscript{21} These findings led the Food and Drug Administration (FDA) to approve the use of amifostine to reduce the incidence and severity of radiation-induced xerostomia in patients with head and neck cancer receiving postoperative radiation therapy in which the radiation port includes a substantial portion of the parotid glands. Recent American Society of Clinical Oncology practice guidelines also recommend that amifostine be considered for these patients.\textsuperscript{22,23}

In the phase III study, amifostine was administered intravenously 15 to 30 minutes before each radiation treatment at a dose of 200 mg/m\textsuperscript{2}. Subcutaneous administration, although not FDA-approved, was found in a phase II randomized trial to be efficacious and well tolerated.\textsuperscript{24} Common side effects of intravenous amifostine include nausea, emesis, and hypotension. The rates of such high-grade symptoms are reduced significantly by subcutaneous administration, which has become the preferred route of administration at many institutions.\textsuperscript{6,9}

The potential to develop other protective agents that will prevent xerostomia instead of alleviating its symptoms continues to be a focus of research. This includes examining acinar cell proliferation stimulants, metal ion mobilizers or chelators, other free radical scavengers, and antioxidant molecules such as α-tocopherol and β-carotene.\textsuperscript{17}

**Management of Radiation-Induced Xerostomia.** For patients with radiation-induced xerostomia, treatments are nonspecific and are directed primarily toward alleviation of symptoms. Symptomatic relief can be achieved by behavioral modifications, replacement of missing saliva, and use of prosecretory drugs. Simple, helpful measures include the use of home humidifiers and a careful review of patients’ medications to exclude or replace those that exacerbate xerostomia. Patients may be encouraged to use sugar-free tart candy or sugar-free chewing gum to stimulate residual saliva production and should discontinue habits that exacerbate xerostomia, such as smoking and consuming dairy and sugar-containing products that thicken saliva, as well as alcohol.

Replacing saliva is important in the management of radiation-induced xerostomia, as it provides symptomatic relief, limits the damaging local effects of chronic xerostomia, and preserves QOL.\textsuperscript{6} Artificial saliva preparations act as substitutes for the lubricating, hydrating, and antimicrobial actions of natural saliva. Originally designed as aqueous ionic solutions, they have gradually become more complex with the addition of fluoride, carboxymethylcellulose, mucin, glycoproteins, and antimicrobial/antifungal peptides in various combinations. Unfortunately, the complex, multifunctional, and overlapping nature of saliva components has not been approached so far by any of the numerous existing saliva replacements/substitutes. Major limitations of saliva substitutes include short duration of action, undesirable taste, inconvenience, and cost. As a result, many patients prefer to carry water to drink and spray throughout the day.\textsuperscript{6} Nevertheless, artificial saliva can provide useful adjunctive therapy under special circumstances, for example, at bedtime and during air travel.\textsuperscript{9}
Patients often resort to complementary and alternative medicine for primary or adjunct therapies. In particular, acupuncture has gained significant momentum in current research, after reports of successful palliation of xerostomia appeared in the West as early as 1981. A regimen of 3 or 4 weekly sessions followed by monthly maintenance sessions was recommended in a open-label study of 50 patients, although some patients achieved lasting remission without further therapy. This approach has yet to be tested in a prospective randomized trial.

Promising preliminary data were reported from a group of patients with strictly defined pilocarpine-resistant radiation-induced xerostomia. While the precise mechanism of action of acupuncture is still unknown, autonomic stimulation by the acupuncture needles is presumed to be at least partially responsible for the effect, although different acupuncture points and techniques have been used. Other investigators have reported equally promising results using noninvasive transcutaneous electrical nerve stimulation (TENS) of acupuncture points with either traditional TENS or the newer proprietary Codetron technique.

Surgical relocation of the submandibular gland to the submental space, before radiation therapy, was recently proposed as a novel way to preserve salivary function and prevent xerostomia. Approximately 200 to 300 mL/day of saliva, or about 15% to 30% of normal daily output, is produced by the submandibular salivary glands. A Canadian group has suggested that surgically transferring the submandibular gland, before irradiation, to the submental space, which is shielded from all but 5% of the total radiation dose, can preserve its function. They performed the procedure in 24 eligible patients who maintained a salivary flow rate, ranging from −29% to +12% of the preoperative rate, and good subjective patient-benefit scores. This report represents proof of the principle that the physical sparing of the submandibular gland can lead to reduction of xerostomia rates. However, the reproducibility and safety of this procedure remain to be confirmed, as there is a potential risk of co-transferring tumor cells to the submental “safe haven,” as occurred in 1 patient in the study. The Radiation Therapy Oncology Group is currently investigating this technique.

The current treatment of choice for patients with remaining functional acinar tissue involves the use of parasympathomimetic secretagogues. These agents stimulate the M3 muscarinic receptors found in salivary glands, leading to increased saliva secretion, and thus offer a more physiologic treatment for the symptoms of xerostomia than saliva substitutes. Pilocarpine is currently the only secretagogue approved by the FDA for the symptomatic treatment of postirradiation xerostomia and is also approved for the treatment of dry mouth symptoms associated with Sjögren syndrome. In a randomized controlled trial involving 207 patients with radiation-induced xerostomia, pilocarpine 5 mg 3 times per day (tid) improved oral dryness in 44% of treated patients compared with 25% of placebo recipients (p = .027). Similar improvement was seen with a dose of 10 mg tid (46, p = .020). Furthermore, patients in both treatment groups experienced improvement in the overall condition of xerostomia (p = .010) and mouth and tongue comfort (p = .001). Another study has shown that pilocarpine can also be efficacious when dissolved in artificial saliva and administered in a mouth spray, provided there is residual salivary function.

Pilocarpine mouthwash, when compared in a crossover randomized study with a mucin-based saliva substitute, was found to be efficacious after 3 months of treatment, leading to a mean change in the xerostomia score in 22.5% of patients compared with 15.2% of patients using artificial saliva alone. Preliminary animal data suggested that administration of pilocarpine before or during irradiation could provide protection against the development of xerostomia. Subsequently, human studies were conducted to verify this observation; whereas the protective effect seemed to be reproduced in a few small trials, others failed to demonstrate either a symptomatic improvement accompanying the maintained salivary flow rate or any preventive action at all. The use of pilocarpine may be limited in some patients by side effects and contraindications that stem from its fundamental mechanism of action, muscarinic-cholinergic agonism with mild β-cholinergic activity. The secretory activity of exocrine glands other than the salivary glands and the smooth muscle tone of the gastrointestinal and genitourinary tracts are increased. As a result, the use of pilocarpine is contraindicated in patients with uncontrolled asthma, acute iritis, and narrow-angle glaucoma. Pilocarpine should also be prescribed cautiously for patients with a history of severe cardiovascular disease or with biliary disease, gastric ulcer, nephrolithiasis, or diarrhea. The most frequent adverse effects...
associated with pilocarpine use are sweating, nausea, and rhinitis. Less frequent are chills, diarrhea, urinary frequency, blurred vision, dizziness, abdominal cramps, palpitations, lacrimation, and headaches. Side effects are often dose-related: in clinical trials. Excessive sweating occurred in 68% of patients receiving 10 mg tid vs 29% of patients receiving 5 mg tid and 9% receiving placebo. Cevimeline hydrochloride is a newer muscarinic agonist that was found safe and effective in treating xerostomia associated with Sjögren syndrome and has been FDA approved for this use. Cevimeline has a selective affinity for M3 muscarinic receptors, which are the major receptors associated with stimulation of salivary flow. In 3 clinical trials, cevimeline improved symptoms of dry mouth in patients with Sjögren syndrome. In the first 2 trials (involving 75 and 197 patients, respectively), a significantly higher percentage of patients receiving cevimeline 30 mg tid reported improvement in the overall condition of dry mouth compared with patients receiving placebo (p = .0043 and .0004). Patients receiving cevimeline 30 mg tid in the third trial were more likely than placebo recipients to have increased postdose salivary flow (p = .0017). Of 1777 patients with Sjögren syndrome or other conditions treated with cevimeline in clinical trials, 11.1% discontinued treatment because of adverse events. Excessive sweating, nausea, rhinitis, and diarrhea occurred in 18.7%, 13.8%, 11.2%, and 10.3%, respectively, of patients receiving cevimeline 30 mg tid compared with 2.4%, 7.9%, 5.4%, and 10.3% of placebo recipients. Recently, cevimeline was shown in animal studies to increase salivation after head and neck irradiation. Two phase III trials including a total of 570 patients with radiation-induced xerostomia evaluated the efficacy and safety of cevimeline in this population. Patients were randomized to cevimeline 30 to 45 mg tid or placebo for 12 weeks. In 1 study, global improvement in dry mouth symptoms was reported by significantly more patients in the cevimeline-treated group than in the placebo group (47.4% vs 33.3%, p = .0162). In both studies, cevimeline-treated patients had significantly greater increases in unstimulated salivary flow than placebo recipients at the final evaluation. Increased sweating was the significant adverse event reported more frequently in the cevimeline groups than in the placebo groups. The longitudinal safety evaluation phase of the studies is currently in progress.

CONCLUSION
Radiation-induced xerostomia causes significant morbidity after irradiation for head and neck cancers. Other patients affected are those receiving iodine 131 therapy for thyroid cancer or total body irradiation for allogeneic stem cell transplant.

Current options for prevention and treatment are limited. New, more selective radiation-delivery techniques (eg, IMRT) allow some degree of salivary gland preservation. A proposed surgical preventive strategy, submandibular gland transfer, may help preserve gland function after irradiation but is still investigational. There is increased interest in the combined use of IMRT and radioprotective agents: acinar cell proliferation stimulants, metal ion mobilizers or chelators, free radical scavengers, and other antioxidant molecules. The FDA approved amifostine to prevent radiation-induced xerostomia in patients receiving postoperative radiation therapy for head and neck cancers. Patients whose symptoms of dryness are not optimally controlled by moisture replacement should be considered for treatment with secretory stimulants (secretagogues) to stimulate the M3 muscarinic receptors found in salivary glands, leading to enhanced secretion. These agents include pilocarpine and cevimeline. Furthermore, intensive ongoing research in gene therapy, aiming to repair salivary glands damaged by irradiation or autoimmune processes, has produced encouraging results, establishing the foundation of a promising future. Key to the management of postirradiation xerostomia is symptomatic relief with saliva supplementation/stimulation and a multidisciplinary approach that includes physicians of various specialties, dentists, and even complementary and alternative medicine modalities (eg, acupuncture or Codetron treatments). The authors thank Daiichi Pharmaceutical Corporation for funding this publication and IMPRINT Publication Science, New York, for their editorial support in the preparation and styling of this manuscript.

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