The Role of Saliva in Oral Health: Strategies for Prevention and Management of Xerostomia

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Abstract Oral complications are the most frequent and debilitating sequelae of radiation treatment for patients with head and neck cancer. Impaired salivary function and consequent xerostomia can persist for years after radiation treatment, significantly increasing the risk of oral and dental disease and negatively affecting patients' quality of life. Current evidence indicates that many patients undergoing radiation treatment do not receive adequate oral and dental care and follow-up and that patients' compliance with oral care recommendations is frequently poor. Topical lubricants, coating agents, and saliva substitutes or lozenges may provide transient relief from xerostomia. Cholinergic stimulants such as pilocarpine improve salivary flow but have had mixed results in improving patients' assessments of symptoms or other quality-of-life measures. Advances in radiotherapy techniques, such as intensity-modulated radiation therapy, have enabled increased delivery of therapeutic doses of radiation to tumors while limiting exposure to normal tissues, thereby reducing the incidence, duration, and severity of xerostomia in some patients with head and neck cancers. Additionally, radioprotective agents such as amifostine have been shown to reduce radiation-induced toxicity to normal tissues within the radiation field. Studies are ongoing to determine the optimal approaches for these techniques and agents to maximize clinical response while improving the overall quality of life for patients with head and neck cancer.

Each year, an estimated half million people worldwide are diagnosed with head and neck cancer, a broad diagnostic category that includes oral, laryngeal, and nasopharyngeal cancers.[1] Because patients who are diagnosed early and/or receive effective antitumor therapy can expect to live for many years after treatment, preservation of normal tissue function during anticancer treatment is crucial to ensuring long-term quality of life.[2]

Although radiation therapy (RT) following surgery is the primary treatment for patients with localized head and neck cancer,[3] combined-modality treatment with RT and chemotherapy (CT) is the current standard of care for the 60% of patients with locally advanced disease at diagnosis.[4] Oral complications affect 100% of patients who receive RT to fields involving the oral cavity,[5] and combined-modality treatment with chemoradiotherapy (CRT) may compound these effects. Acute adverse events such as mucositis can lead to dose reductions and treatment interruptions that compromise treatment efficacy. Complications such as xerostomia (dry mouth), dental caries, trismus, and osteonecrosis may persist long after treatment is complete, significantly impairing patients' oral health and functioning.

Xerostomia disrupts the normal homeostasis of the oral cavity, leading to a range of oral and dental disorders (Figure 1). Xerostomia-related dental caries and changes in taste, speech, and the ability to eat have a significant negative impact on patients' health and overall quality of life.

Parotid-sparing RT techniques have been used widely in recent years with varying results. Existing treatments for xerostomia offer some relief from the symptoms of dry mouth but are of limited efficacy in restoring the oral environment and alleviating the symptoms and sequelae of xerostomia. Therefore, there is a significant need for effective techniques to protect salivary glands and preserve salivary function in patients undergoing treatment for head and neck cancer.

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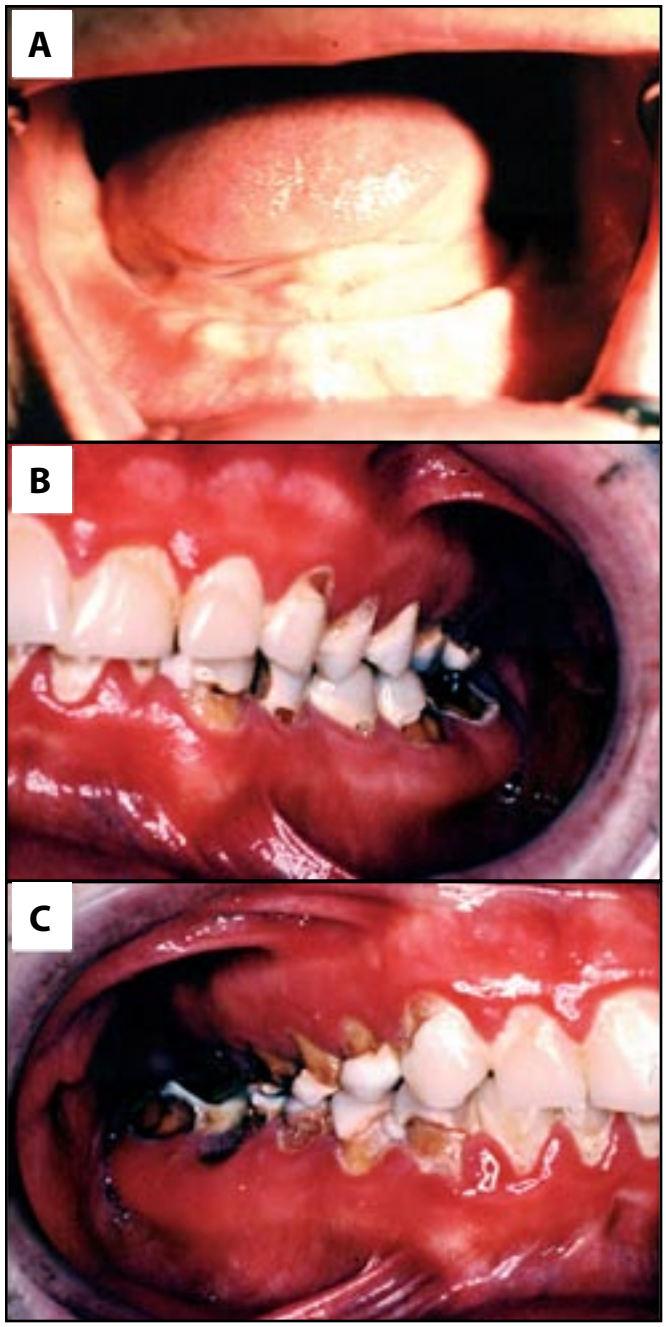

Figure 1 Radiation-Induced Oral and Dental Toxicities

(**A**) Xerostomia; (**B** & **C**) Tartar, plaque, and dental caries. Courtesy of Mary Elizabeth Brosky, DMD. Used with permission.

This article discusses the role of saliva in oral health and reviews the impact of RT-induced xerostomia on the oral health and quality of life of patients with head and neck cancer. Strategies for effective prevention and management of xerostomia are also discussed.

The Role of Saliva in Oral Health

Saliva plays a critical role in the maintenance of oral and dental health. Saliva is a complex fluid composed of secretions from the salivary glands and gingival crevicular fluid.[6,7] Ninety percent of saliva is produced by the major salivary glands: the parotid, submandibular, and sublingual glands (Figure 2).[8] Approximately 10% is produced by minor salivary glands clustered in the oral mucosa (lingual, labial, buccal, palatine, glossopalatine).[6–8]

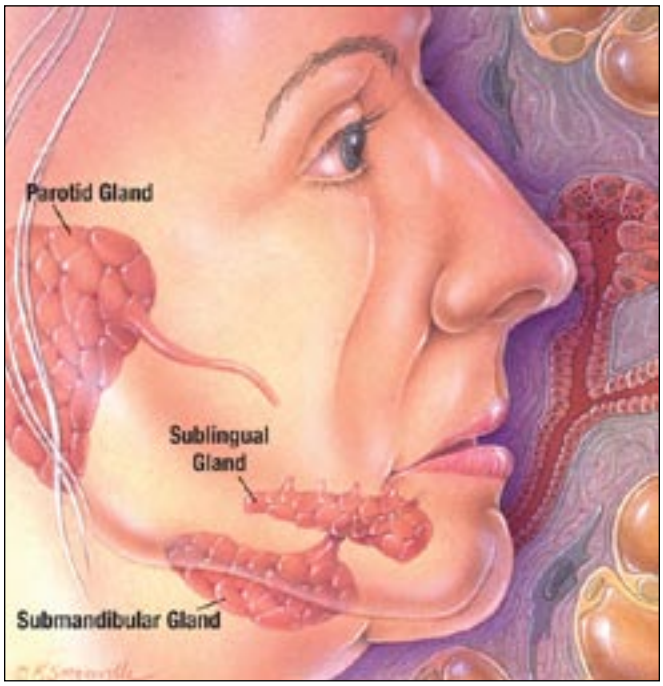

Figure 2 Salivary Glands

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Salivary secretions are classified as serous (primarily from the parotid glands), mucous (from the minor salivary glands), or mixed (from the submandibular and sublingual glands). As their names imply, serous secretions contain more water than the viscous saliva produced by mucous glands.[3,6] In a healthy mouth, the mean volume of saliva ranges from approximately 1.07 mL before swallowing to approximately 0.77 mL after swallowing[9], total daily flow of saliva ranges from 500 mL to 1.5 L.[3,7]

Salivary flow varies in the stimulated (eg, chewing) and unstimulated state.[7] Stimulated flow contributes up to 90% of average daily saliva production, at a rate of between 0.2 and 7 mL/min. In the stimulated state, the parotid glands contribute > 50% of total salivary flow. In contrast, normal flow in the unstimulated state is > 0.1 mL/min, with the submandibular glands contributing approximately 65% of total flow; the parotid glands, 20%; and the sublingual glands, 7%–8%.

Although the fluid component of saliva accounts for 99% of the total volume, both the fluid and solute components play important roles in maintaining oral and dental health (Table 1; Figure 3).[6,7] In addition to solubilizing food and physically cleansing the oral cavity of detritus, saliva exerts a range of protective functions on oral tissues and teeth, including facilitating the demineralization and remineralization of teeth, modulating the adhesion of microorganisms to teeth and other oral surfaces, and buffering dietary acids.[7]

Table 1

Functions of the Fluid and Solute Components of Saliva

Fluid
Cleansing of oral cavity
Solubilization of food
Dilution of detritus
Lubrication of oral surfaces
Bolus formation
Facilitation of: • Taste perception • Mastication • Swallowing • Speech
Solutes
Protection of teeth and mucosa
Buffering (acid neutralization)
Protection of oral mucosa
Antimicrobial defense
Digestion

Adapted with permission[3]

Both the composition and the functions of saliva are strongly affected by flow rate. Salivary concentrations of total protein, sodium, total calcium, chloride, and bicarbonate tend to be higher during high flow rates, which are also associated with more effective buffering action.[6,7]

The Impact of Radiation Therapy and Chemoradiotherapy on Salivary Function and Oral Health

Radiation therapy for the treatment of head and neck cancers typically consists of a total dose of 50–70 Gy administered in fractionated doses (2.0 Gy/d × 5 d) over 5–7 weeks.[3] Salivary glands are highly sensitive to ionizing radiation[3]: a single dose of 20 Gy can permanently stop salivary flow, and cumulative doses above 52 Gy are associated with severe salivary dysfunction.[10]

Dose-response modeling of saliva as a function of parotid dose distribution indicates that stimulated saliva flow 6 months post treatment is reduced by approximately 4%–5% per gland with each gray of mean parotid dose.[11,12] The total reduction varies depending on the radiation field: bilateral RT can result in reductions of up to 80%, whereas unilateral RT results in a 50%–60% reduction, and mantle therapy reduces salivary flow by 30%–40%.[10]

The impact of RT on salivary flow was documented in a comparison of 25 healthy control patients and 22 patients with head and neck cancer treated with RT.[13] At baseline, there was no between-group difference in unstimulated saliva flow. In RT-treated patients, however, salivary flow decreased significantly during RT and remained low at the end of the treatment period. After RT was completed, 32% of the treated patients were diagnosed with xerostomia.

Ohrn and colleagues[14] evaluated the correlation between changes in salivary function and the incidence of oral complications in 18 patients treated with RT for head and neck cancer. Salivary flow decreased significantly during treatment, whereas oral symptoms increased (Figure 4). Notably, reports of mouth dryness, salivary viscosity, and lip dryness remained at approximately the same level 1 month after treatment as at the end of RT.

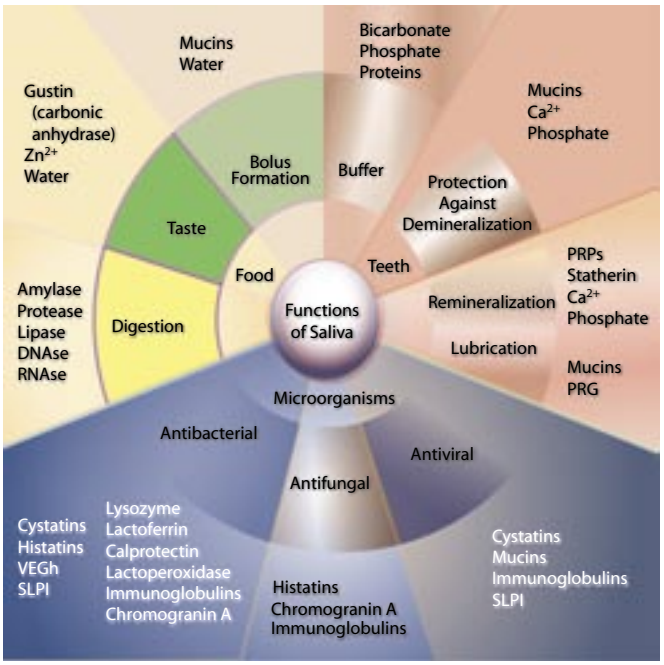

Figure 3 The Functions of Saliva and Its Constituents

Abbreviations: Ca^{2+} = calcium; PRG = proline-rich glycoprotein; PRPs = proline-rich proteins; SLPI = secretory leukocyte protease inhibitor; VEGh = Von Ebner glands protein; Zn^{2+} = zinc

Adapted with permission from Nieuw Amerongen et al[102]

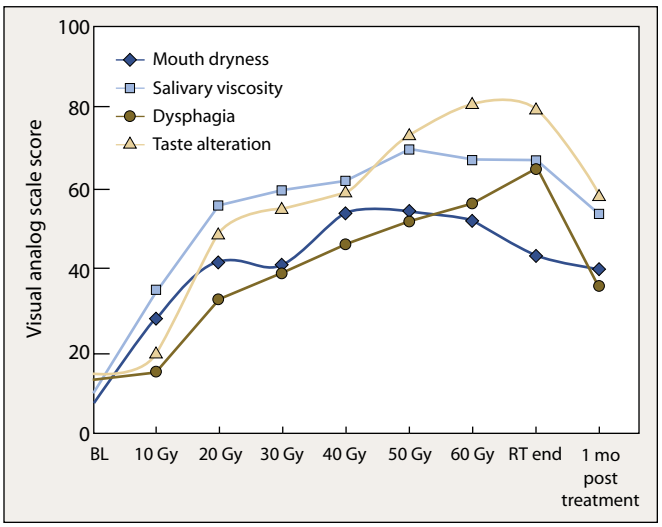

Figure 4 Reports of Oral Symptoms During and Following Radiation Therapy (n = 12)

Adapted with permission from Ohrn et al[14]

Abbreviations: BL = baseline; RT = radiotherapy

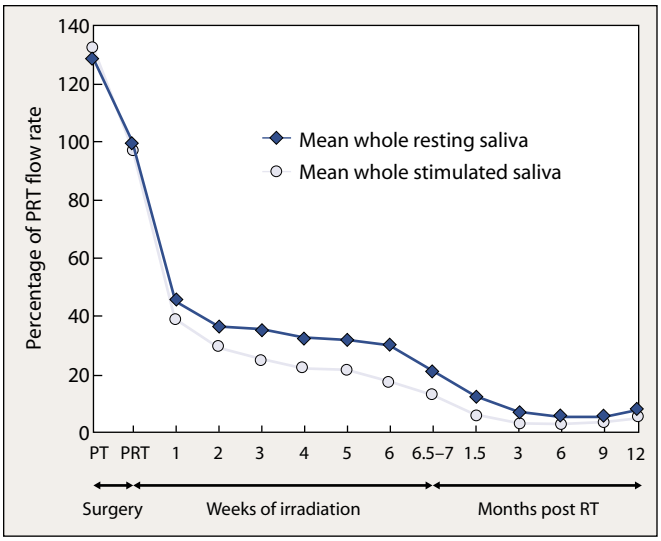

Figure 5 Impact of Radiation Therapy on Resting and Stimulated Saliva

Mean whole resting saliva and mean whole stimulated saliva flow rates expressed as percentage of PRT values before, during, and after RT.

Abbreviation: PRT = preradiation therapy; PT=pretreatment; RT = radiation therapy

Adapted with permission from Moller et al[15]

Because many of the radiation-induced changes in salivary glands may be irreversible, symptoms may persist for months or years after treatment. A prospective study[15] in 54 patients with locally advanced squamous cell carcinoma also documented significantly decreased resting and stimulated salivary flow rates during and after RT (Figure 5). In addition, RT was associated with a persistent shift in pH; at 12-month follow-up, mean pH for whole resting saliva was higher than at baseline, whereas pH for whole stimulated saliva was slightly acidic and below the baseline level. These changes were accompanied by statistically significant decreases in salivary buffering capacity ($P < 0.0001$). In another study of patients receiving RT (50–70 Gy) for head and neck cancer, 36% of patients continued to experience moderate to severe xerostomia and 43% of patients had unstimulated saliva flow rates ≤ 0.1 g 2 years after completion of therapy.[16]

Fewer data are available on the impact of CRT on salivary function, but induction and concurrent CT with RT have been linked to xerostomia in head and neck cancer patients,[17,18] most likely through alterations of salivary buffering capacity and an increase in salivary viscosity.[8]

In addition to impairing or eradicating salivary flow, RT leads to acute and late histopathologic changes in salivary glands that affect the composition of saliva (Table 2). RT has been shown to cause an increase in the viscosity and acidity of saliva, with a concomitant decrease in buffering capacity and secretion of protective proteins such as salivary epidermal growth factor.[3]

In addition to acute and long-term xerostomia, patients receiving RT for head and neck cancer may experience mucositis,[3] fissured tongue with atrophy of filiform papillae,[19] cervical caries,[19] trismus,[20,21] swallowing difficulties,[22–26] alterations in taste sensation,[27] reduced dietary intake,[28] disturbed sleep,[29] speech difficulties,[27,30] and psychologic difficulties.[29]

Radiation generates reactive oxygen species that directly injure mucosal cells and trigger a cascade of biologic events that impair the integrity of oral mucosa and pave the way for acute mucositis and secondary infections such as candidiasis.[31,32] Radiation-induced damage to blood vessels and alterations in collagen synthesis can also lead to progressive fibrosis and trismus that impair patients' ability to maintain proper oral hygiene and dentists' ability to provide dental care.[20,33,34]

Impact of Xerostomia on Oral Health and Quality of Life

Xerostomia can have a significant impact on patients' health, well-being, and overall quality of life. Studies have documented speech difficulties,[30] changes in taste sensation,[27] swallowing dif-

Table 2

Acute and Late Radiation-Induced Histopathologic Changes in Salivary Glands

GLAND	ACUTE CHANGES	LATE CHANGES
Parotid	Inflammatory cell infiltration Degeneration Loss of serous cells Necrosis Duct dilatation Serous cell degranulation Nuclear pyknosis Cytoplasmic vacuolization	Lymphocytic infiltration Degeneration Loss of serous cells Duct dilatation Atrophy Fibrosis
Submandibular	Inflammatory cell infiltration Degeneration Loss of serous cells Necrosis Duct dilatation Serous cell degranulation Little or no change in mucous acinar cells	Plasma cell infiltration Degeneration Duct dilatation Atrophy Fibrosis Adiposis Mucous cells relatively unaffected

Adapted with permission[3]

ficulties,[22,23,26] and decreased dietary intake[28] in head and neck cancer patients with xerostomia. In a survey of 33 head and neck cancer patients who had undergone RT with or without CT, 14% of patients cited dry mouth as the most troublesome or debilitating side effect.[27]

Although chronic xerostomia is a common complication in patients treated with RT for head and neck cancer, it is frequently overlooked by clinicians. In a survey of 99 patients with advanced cancer (34 of whom had received RT to the head, neck, or chest), 88% reported a dry mouth, with a mean severity of 6.2 on a 0-to-10 visual analog scale.[35] More than half of these patients had been experiencing dry mouth for ≥ 1 month, and 17% had been experiencing it for more than 1 year. Despite the high prevalence, dry mouth was documented in the charts of only five patients. Similarly, an evaluation of oral function and quality of life in 20 patients with head and neck cancer who received a mean total radiation dose of 52.1 Gy found that 70% of patients reported moderate to severe dry mouth 6 months post therapy, with more than 45% reporting taste changes and difficulty in swallowing and 25% reporting difficulties with speech.[36] In a study of patients with laryngeal cancer, dry mouth was present 5 years after treatment in 42% of patients who received conventional RT and in 25% of those who received hyperfractionated RT.[37]

Managing Oral Health in Patients Undergoing Radiation Therapy for Head and Neck Cancer

Few studies have evaluated the frequency of oral and dental healthcare before, during, and after RT in patients with head and neck cancer; however, available evidence indicates that many patients do not receive adequate care or instruction in oral hygiene. There is considerable variation in the approach to management of oral/dental complications as well as a lack of established and well-accepted clinical guidelines.[38–42] The rate of pre-irradiation dental consultation in patients with head and neck cancer is low (12.1%–44%).[41] Between 50% and 76% of patients are noncompliant, even when routine dental care is available, and about half (51%) of patients are lost to dental follow-up.[43–46] In addition, a retrospective comparison of dental consultation rates in 104 patients with head and neck cancer at 3 US teaching hospitals found that the majority of patients did not receive an oral evaluation and dental care before or during RT, despite the presence of dental and/or oral maxillofacial clinics in these hospitals.[41]

The lack of appropriate oral assessment in patients with head and neck cancer is particularly worrying, given that many of these patients have less-than-optimal dental health before they begin RT. Lockhart and Clark[43] documented a low rate of routine dental care in 131 patients with head and neck cancer, as well as high rates of plaque, calculus, caries, and generalized bone loss around existing teeth; 95% of dentulous patients required oral prophylaxis with scaling before starting RT.

Even when oral hygiene education and/or routine dental care are provided, a significant proportion of patients fail to comply with recommended oral hygiene measures and follow-up care. Lockhart and Clark[43] reported that only 19% of patients complied with the oncology team's "strong advice" regarding prophylactic dental treatment. At one oncology dental support clinic, 29% of patients referred for long-term dental follow-up failed to return to their private dentists after completing RT.[46] A 1995 survey of 78 patients who had been treated with RT for oral cancer found that 57% failed to continue daily use of fluoride gel after treatment completion.[45] Similarly, in a retrospective chart review of 334 patients who received preradiation dental consultation, only 28% of patients complied with routine dental follow-up examinations, and 51% were lost to dental follow-up within 7.5 months of receiving RT.[44]

Table 3

Oral Care in Patients With Xerostomia

Oral hygiene
Plaque control
Chlorhexidine, fluoride mouthwash, or fluoride gel daily
Oral hygiene instruction
High fluoride toothpaste
Dentures
Ensure proper fit
Oral hygiene instruction
Antifungals
Nystatin pastilles
Amphotericin lozenges
Miconazole gel

Data from Cassolato et al[8] and Porter et al[10]

PREVENTIVE DENTAL CARE

Strategies for minimizing oral complications of RT focus on preventive care. Before starting RT, it is recommended that patients undergo a full dental assessment with prophylactic interventions to address potential sources of irritation and infection (such as ill-fitting dentures or defective restorations) as well as preexisting oral and dental disease.[39,47,48] Meticulous oral care is a major component of xerostomia management during and after RT treatment, because alterations in salivary buffering capacity and decreased levels of protective salivary proteins increase patients' risk of dental caries, plaque, and gingivitis (Table 3).[8] Because radiation-induced changes in the oral milieu can persist for years after therapy is completed, ongoing dental care is crucial.[49] Following RT, it is recommended that patients be reviewed quarterly to monitor dental health status. Physical therapy, including heat packs and range-of-motion exercises, may help prevent the development of trismus in patients showing signs of radiation-induced fibrosis.[20,33]

Oral health can be optimized through a combination of rigorous oral hygiene, regular assessment of dental and mucosal health, and timely interventions to alleviate oral symptoms. Patients should receive information on the potential oral adverse effects of RT and information on daily oral hygiene mea-

sures, including brushing with a fluoride toothpaste, flossing (when possible), applying topical fluoride gel or mouthwash, and using oral lubricants and coating agents.

Xerostomia Prevention and Management

Current strategies for the management of xerostomia focus on palliative measures and can be local or systemic. Treatment essentially relies on the residual secretory capacity of the salivary glands.[21] Several factors other than the radiation dose, including dehydration and concomitant medications, influence salivary flow rates.[50] In addition, correlations between salivary flow measurements, physicians' assessments of a patient's condition, and a patient's own assessment of how he feels and his quality of life have varied with the methods used to make the assessment.[51–56] Importantly, clinicians' evaluations frequently do not agree with patients' assessments.[57] Ultimately, the goal of intervention should be relief of symptoms that adversely affect a patient's quality of life. Thus, the most effective intervention for reduced salivary function is its prevention.[21]

PAROTID- AND SUBMANDIBULAR-SPARING RADIATION THERAPY

Significant, often permanent reductions in unstimulated and stimulated salivary flow can occur with cumulative RT doses as low as 26 Gy to the parotid glands.[58] The advent of parotid-sparing RT techniques such as 3-dimensional conformal RT and intensity-modulated RT (IMRT) has enhanced cytocidal efficiency while reducing damage to healthy tissues. This is accomplished through planned delivery such that the radiation dose to adjacent healthy tissues is reduced while permitting increased doses to tumor tissues, thereby increasing the therapeutic ratio.

The use of parotid-sparing RT has been associated with preserved salivary function in spared salivary glands, with a gradual increase in flow post treatment[52,59,60] and a lower incidence of weight loss during and after treatment.[61] Parotid-sparing IMRT techniques can allow damaged glands to recover over time. One study evaluated xerostomia in patients treated with IMRT for oropharyngeal cancer.[62] A reduction in the incidence of grade 2 xerostomia from 60% immediately after RT to 33% at last visit was seen in 30 patients with at least 9 months of follow-up.

Recently, Saarilahti and colleagues[63] described the first attempt to spare submandibular gland function in patients with head and neck cancer receiving parotid-sparing IMRT, the rationale being that submandibular glands produce up to 90% of unstimulated salivary output. The procedure is more demanding than parotid-sparing techniques and involves excluding the contralateral submandibular gland from the planning target volume with the risk of also excluding lymph nodes that may contain cancer cells. Unstimulated salivary flow rates 12 months after RT were 60% of baseline values in patients with one submandibular gland spared and 25% in those with none. Stimulated flow rates were not significantly different.

Improvements in xerostomia symptoms often lag behind objective improvements in salivary function following gland-sparing RT.[52,59,64] Possible reasons for these inconsistencies include discrepancies between salivary output and actual hydration of mucosal tissues[52] and alterations in salivary composition secondary to histopathologic changes in salivary tissues.[65] Findings from several small studies[66,67] and the trial experience from one institution[62,68] report improvements in late xerostomia with parotid- and submandibular-sparing IMRT. However, residual late xerostomia and the high incidence of acute xerostomia remain a problem in patients treated for head and neck cancer. This situation is complicated by the finding that xerostomia associated with IMRT may be underestimated by physicians. Meirovitz and coworkers[57] recently reported that, in a cohort of 38 patients who received IMRT for head and neck cancer, there was a poor correlation between xerostomia severity assessed using a physician rating scale compared with patient self-reported questionnaires. Physicians tended to underestimate the severity of xerostomia and hence the likely impact on quality of life. The fact that acute xerostomia is still a problem in patients treated with IMRT for head and neck cancer and that physicians frequently fail to appreciate xerostomia's impact underscores the need for additional measures that can protect salivary tissues and preserve the normal balance of salivary function.

CYTOPROTECTION

Amifostine (Ethyol) is an aminothiol prodrug approved to reduce the incidence of moderate to severe xerostomia in patients undergoing postoperative RT for head and neck cancer, where the radiation port includes a substantial portion of the parotid glands.[69] The recommended dose for amifostine in head and neck cancer patients is 200 mg/m^2 administered once daily as a 3-minute intravenous (IV) infusion 15 to 30 minutes before RT.[70]

Amifostine is converted by membrane-bound alkaline phosphatase to the active metabolite WR-1065.[71] Uptake of WR-1065 is up to 100 times greater in normal cells than in tumor cells because tumor cells are deficient in membrane-bound alkaline phosphatase, and activation is slower in the hypoxic-acidic environment of neoplastic tissues.[71] As a result, there is more rapid generation of WR-1065 in normal cells, as well as a higher rate of uptake.[71] In normal cells, WR-1065 protects against CT- and RT-induced damage by scavenging free radicals, depleting oxygen, donating hydrogen ions to free radicals, and directly binding and inactivating cytotoxic drugs.[71] Although theoretical concerns have been raised that amifostine may interfere with the antitumor efficacy of CT or RT, there is no clinical evidence that amifostine has a protective effect in tumor cells.[72] In *every* clinical trial of amifostine to date, survival rates and treatment responses have not been affected by the addition of amifostine to CT or RT.[73]

The radioprotective effect of amifostine on salivary glands was first demonstrated in a pilot study of salivary flow in 8 patients treated with RT (≥ 45 Gy 5 times per wk) plus amifostine (100 mg/m^2, 6-min IV infusion, 10–15 min pre-RT).[74] During RT, the mean flow rate of the stimulated parotid gland decreased to 1.4% of the baseline level, but by 18 months the

Table 4

Clinical Trials of Amifostine Therapy During Radiation Therapy or Chemoradiotherapy for Head and Neck Cancer

STUDY	TREATMENTS	KEY FINDINGS
Radiotherapy (RT)		
Wagner 1998[75]	RT + IV amifostine (n = 14)	IV amifostine ↓ oral symptoms and ↓ duration of mucositis compared with historic controls
Bourhis 2000[76]	RT + IV amifostine 150 mg/m² (n = 13) vs RT alone (n = 13)	IV amifostine ↓ duration of acute mucositis and ↓ duration of feeding tube
Brizel 2000[51]	RT + IV amifostine (n = 150) vs RT alone (n = 153)	IV amifostine ↓ acute xerostomia, ↓ chronic xerostomia, and ↑ saliva production
Koukourakis 2000[78]	RT + SC amifostine 500 mg (n = 20) vs RT alone (n = 20)	SC amifostine ↓ severity of oral mucositis
Anné 2002[79]	RT + SC amifostine 500 mg (n = 54)	SC amifostine ↓ acute xerostomia comparable to IV amifostine (historic comparison to Brizel 2000[51])
Chemoradiotherapy (CRT)		
Büntzel 1998[80]	CRT + IV amifostine 500 mg (n = 25) vs CRT alone (n = 14)	IV amifostine (chemotherapy days only) ↓ mucositis and ↓ xerostomia
Peters 1999[82]	CRT + IV amifostine (n = 14) vs CRT alone (n = 14)	IV amifostine (chemotherapy days only) had no significant effect on mucositis or xerostomia
Antonadou 2002[81]	CRT + IV amifostine 300 mg/m² (n = 22) vs CRT alone (n = 23)	IV amifostine (before each fraction of RT) ↓ mucositis and ↓ xerostomia
Vacha 2003[83]	CRT + IV amifostine 250 mg (n = 26) vs CRT alone (n = 26)	IV amifostine (before each fraction of RT) ↓ xerostomia; reduction of mucositis was not statistically significant
Buentzel 2006[84]	CRT + IV amifostine 300* mg/m² (n = 67) vs CRT + placebo (n = 65)	IV amifostine (before CRT) had no significant effect on mucositis or xerostomia

*200 mg/m² on RT-only days.

Abbreviation: IV = intravenous; SC = subcutaneous

flow rate had recovered to 54% of pretreatment levels.

These preliminary findings are supported by data from several clinical trials (Table 4).[16,51,75–84] In a multicenter, randomized phase III clinical trial, 315 patients with head and neck cancer received standard fractionated RT with or without amifostine.[51] The incidence of grade ≥ 2 acute xerostomia was significantly lower in the amifostine plus RT group compared with patients receiving RT alone (51% vs 78%; $P < 0.001$; Figure 6). In addition, the radiation dose necessary to cause grade ≥ 2 acute xerostomia in 50% of patients was 40% higher in the amifostine-treated patients. Furthermore, the positive effects on salivary gland function were maintained over time. At 1 year, significantly more patients in the amifostine group were able to produce a clinically meaningful amount of whole saliva (> 0.1 mL/min) than those treated with RT alone. At 2 years, amifostine-treated patients continued to show a higher rate of meaningful unstimulated saliva production and a lower incidence of grade ≥ 2 xerostomia (20% vs 36%; $P = 0.002$).[16]

A subset analysis from three German sites in the phase III clinical trial indicated that amifostine may also benefit patients' long-term dental health.[77] Of 90 patients enrolled, 35 patients had at least four teeth at the beginning of RT and were available for assessment 1 year post treatment. Notably, only 5 patients performed dental care according to the instructions provided by investigators (one in the amifostine group vs four in the control group). Of these 5 patients, only 1 showed a deterioration in dental status 1 year after RT, versus 9 of 19 patients who did not comply with the instructions (12 patients in the amifostine group vs 7 in the control group). In the amifostine group, significantly fewer teeth developed caries or were extracted than in the control group ($P = 0.01$). Amifostine-treated patients were also more likely to have unchanged dental health than control patients ($P = 0.015$). Other studies with amifostine used before each RT dose have also showed a reduction in acute xerostomia in patients treated with IV amifostine before each RT dose.[83]

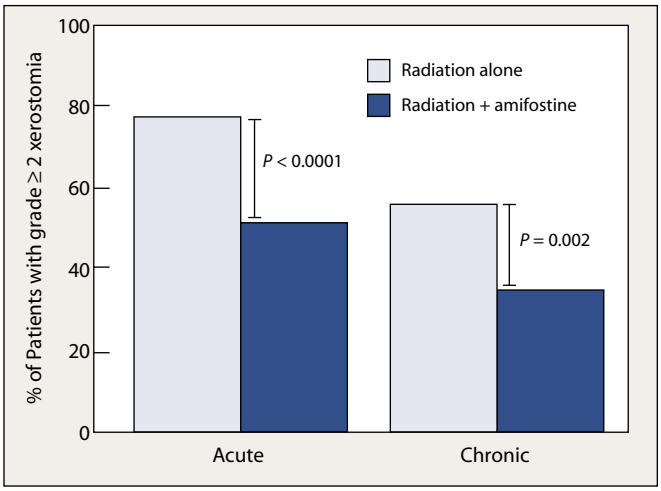

Figure 6 Reduction of Xerostomia With Addition of Amifostine to Radiation Therapy in Patients With Head and Neck Cancer

Data from Brizel et al[51]

Table 5

Topical Therapies for Xerostomia

Lubricants
Oral Balance (gel), Biotene (mouthwash, toothpaste, gum)
Mucin spray
Lozenges
Humidifiers
Coating agents
"Magic mouthwash" (viscous lidocaine/Maalox/diphenhydramine)
Gelclair
Saliva stimulants
Gums and candies (sugar free)
Pastilles
Lozenges

Data from Cassolato et al[8]

The findings from the pivotal phase III trial are supported by a recent meta-analysis of randomized trials, which reported a significant 76% reduction ($P < 0.001$) in acute grade 2/3 xerostomia and a 67% reduction in grade 2/3 late xerostomia ($P < 0.001$) in patients receiving RT with amifostine compared with patients receiving RT alone.[73]

Clinical trials that have investigated the role of amifostine in head and neck cancer patients undergoing treatment with CRT have reported mixed results. Büntzel et al[85] reported that 500 mg of IV amifostine administered at the same time as CRT in patients with head and neck cancer significantly decreased the incidence of xerostomia and mucositis compared with CRT alone. Subsequently, Antonadou and colleagues[81] reported the results of a study in which 45 patients received conventional RT plus carboplatin with or without IV amifostine for 6 to 7.5 weeks. The incidence and severity of xerostomia were significantly reduced with amifostine at 3, 6, 9, 12, and 18 months of follow-up compared with control patients.

More recently, a phase III randomized, double-blind, placebo-controlled, multicenter trial reported the efficacy and safety of combined CRT (RT plus carboplatin) with or without IV amifostine (300 mg/m^2 before carboplatin; 200 mg/m^2 on RT-only days) in 132 patients receiving treatment for advanced head and neck cancer.[84] There was no significant difference in the incidence of grade ≥ 2 acute or chronic xerostomia or grade ≥ 3 oral mucositis between treatment groups. The rates of acute and late xerostomia in patients treated with amifostine (39%) were similar to those reported in the pivotal phase III trial.[51] However, the rates of acute xerostomia (34% vs 78%) or acute mucositis (22% vs 39%–52%) reported in control patients in previous studies were relatively low compared with other trials.[51,81,85] This study was powered to detect a reduction in xerostomia or mucositis based on the assumption that at least 80% of patients treated with placebo would exhibit xerostomia and at least 50% of patients would exhibit acute mucositis. However, the observed rates of only 34% for grade ≥ 2 xerostomia and 22% for grade ≥ 3 acute mucositis were unexpectedly low, which impaired the ability of the study to demonstrate significant benefit with amifostine. These low rates, together with variations in the timing and dose of amifostine during CT days in relation to RT, may have influenced the drug's efficacy.

To improve the simplicity of drug administration, Koukourakis et al[78] administered amifostine subcutaneously (SC) in 140 patients, including 40 patients with head and neck cancer, and reported that SC amifostine reduced mucositis compared with no pretreatment. Anné[79] administered SC amifostine to 54 patients with head and neck cancer in a single-arm study and found that acute xerostomia was reduced by SC amifostine to an extent comparable to that reported by the phase III study of IV amifostine. The preliminary results from a phase III trial conducted by the French Group of Radiation Oncology for Head and Neck Cancer that compared the two routes of administration (IV vs SC) indicated similar incidences of acute xerostomia with both routes (39% for IV; 40% for SC).[86]

The most commonly reported adverse events associated with amifostine include hypotension and nausea/vomiting, which can generally be minimized or averted with proper administration techniques.[51] Careful monitoring of patients' blood pressure before, during, and after administration of the drug; use of adequate hydration; and timely administration of antiemetic medication (90 to 120 min before and in conjunction with amifostine treatment) are recommended strategies to improve tolerability.[70] Studies with SC dosing have reported fewer adverse events than those with IV dosing,[78,79] although IV is the approved route of administration.

LOCAL TREATMENT STRATEGIES

Numerous saliva substitutes and topical agents that increase salivary output (eg, sugar-free gums and lozenges) are currently available and have been shown to provide transient relief of xerostomia (Table 5).[8,10] Saliva-stimulating lozenges provide subjective relief of dry mouth and improve quality of life in patients with radiation-induced xerostomia,[87] and small studies of over-the-counter oral moisturizers (eg, Optimoist, Biotene, Oral Balance) indicate that these agents can significantly relieve oral discomfort.[88–91] These agents attempt to replace essential salivary components with ingredients such as animal mucins, carboxymethylcellulose or derivatives, polyglycerylmethacrylate, lactoperoxidase, glucose oxidase, lactoferrin, and lysozyme. However, viscosity, surface tension, and adsorption/desorption of saliva substitutes differ markedly from those of whole saliva and may limit the duration and extent of their effects.[92]

The cholinergic stimulant pilocarpine stimulates salivary flow though local and direct cellular stimulation and is currently approved for treatment of radiation-induced xerostomia. Because it can take several weeks for pilocarpine to produce symptomatic improvement, it is recommended that patients be treated for a minimum of 90 days to produce maximum therapeutic benefit.[8]

Trials of pilocarpine as a radioprotective agent in head and neck cancer patients have yielded mixed results (Table 6).[93–100] In a randomized study of 69 patients, pilocarpine treatment

Table 6

Clinical Trials of Pilocarpine Therapy During Radiation Therapy for Head and Neck Cancer

STUDY	TREATMENTS	KEY FINDINGS
Rode 1999[93]	Pilocarpine 5 mg TID during and 6 wk after radiotherapy (n = 9) vs Biperiden during and pilocarpine 6 wk after radiotherapy (n = 30) vs No treatment (n = 30)	Pilocarpine resulted in a significantly greater decrease in saliva production compared with the control group
Sangthawan 2001[94]	Pilocarpine 5 mg TID during and after radiotherapy (n = 30) vs Placebo (n = 30)	No significant differences in oral dryness; oral discomfort; or ability to chew, swallow, speak, and sleep between pilocarpine and placebo
Mateos 2001[95]	Pilocarpine 5 mg TID (n = 26) vs No treatment (n = 23)	No differences in salivary gland scintigraphy or subjective assessment of mouth dryness between pilocarpine and no treatment
Haddad 2002[97]	Pilocarpine 5 mg TID for 3 mo (n = 18) vs Placebo (n = 21)	Pilocarpine significantly reduced subjective and objective xerostomia scores compared with placebo 6 months after completing radiotherapy
Warde 2002[98]	Pilocarpine 5 mg TID during and up to 1 mo after radiotherapy (n = 65) vs Placebo (n = 65)	No significant differences in xerostomia severity or quality of life between treatment groups
Fisher 2003[99]	Pilocarpine 5 mg QID (n = 121) vs Placebo (n = 125)	Pilocarpine increased unstimulated salivary flow at the end of radiotherapy, but no difference in patient reports of xerostomia symptoms was observed
Gornitsky 2004[100]	Pilocarpine 5 mg 5 × d during radiotherapy, then QID for 5 months (n = 29) vs Placebo (n = 29)	Pilocarpine improved oral pain and quality-of-life scores but did not change oral symptoms, xerostomia, or saliva production
Nyarady 2006[96]	Pilocarpine 5 mg TID, wks 1–12 (n = 33) vs Pilocarpine 5 mg TID, wks 7-12 (n = 33)	Significant improvement of salivary flow, patient comfort, and symptoms in the prevention + treatment group (wks 1–12) as compared with the treatment-only group (wks 7–12)

during and after RT resulted in a greater decrease in saliva production than was seen in untreated controls.[93] In a double-blind, placebo-controlled trial of pilocarpine therapy during RT in 60 patients with head and neck cancer, there was no statistically significant difference in xerostomia symptoms between treatment groups.[94] Similar findings were seen in an open-label, randomized study of 49 patients with head and neck cancer treated with pilocarpine during RT.[95]

However, a randomized placebo-controlled trial of RT plus pilocarpine found that mean subjective and objective xerostomia scores in 39 evaluable patients were significantly lower in the pilocarpine group 6 months after completing RT.[97] In the largest reported clinical trial to date (n = 130), Warde and colleagues found no difference in oral dryness or quality-of-life scores between patients treated with pilocarpine and those treated with placebo.[98] Radiation Therapy Oncology Group trial 97-09 evaluated the impact of concurrent pilocarpine (5 mg four times daily) and RT versus RT plus matched placebo. Despite a statistically significant increase in unstimulated salivary flow in pilocarpine-treated patients at the end of RT, there was no difference in patient reports of xerostomia symptoms or other quality-of-life measures.[99,101] More recently, a small placebo-controlled trial found that patients who received pilocarpine during RT (5 mg, five times daily) reported significantly higher quality-of-life scores and less oral pain than control patients, although there were no significant differences in oral symptoms, xerostomia, or saliva production.[100]

Conclusion

Radiation-induced xerostomia significantly increases the risk of oral and dental disease in patients with head and neck cancer. Palliative agents, such as topical fluoride gel, oral lubricants, coating agents, and saliva substitutes, or pharmacologic stimulation of salivary flow with agents such as pilocarpine may improve symptoms in some patients. The incidence and severity of xerostomia may be decreased with the use of radiologic techniques that minimize radiation doses to normal tissues or by using radioprotective agents during RT. The ultimate goal of management of head and neck cancer should be curative treatment while preserving the overall quality of life for patients.

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