27 Xerostomia and Hyposalivation in Patients with Cancer

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Core Messages

- Hyposalivation has a major effect on patients with head and neck cancer during and after therapy.
- Hyposalivation affects quality of life and all aspects of oral function.
- Multiple factors in addition to radiotherapy may affect salivary gland function; these include chemotherapy, chronic comorbidities, such as diabetes, and commonly prescribed medications such as opioid analgesics, antihypertensives, anxiolytics, and antidepressants.
- Prevention and early intervention of hyposalivation and related complications are critical.
- The integrated multidisciplinary team has a critical role before, during, and after cancer treatment in promoting prevention, early detection of complications of hyposalivation, and management of saliva as well as complications that may follow for oral and dental health and oropharyngeal function.

Saliva is essential to oral health, and low salivary flow rates (hyposalivation) cause lack of mucosal wetting and oral lubrication, which affect many functions, and may predispose to infections as a consequence of reduced oral defenses. Hyposalivation is the objective measure of reduced saliva secretion.

Dry mouth (xerostomia) is a common symptomatic salivary complaint—not a disease, but a symptom arising from a wide range of triggering factors.

Definitions

Xerostomia is not synonymous with hyposalivation.

- Xerostomia: subjective complaint of oral dryness.
- Hyposalivation (hyposialia): reduction in saliva production.

Physiology of Saliva

Salivary tissue consists of the following:

- Acinar tissue: It contains serous or mucous cells or a combination and produces the initial secretion of fluid, with an electrolyte composition similar to that of plasma. Secretion appears to be dependent on several modulatory influences that act via either a cyclic adenosine monophospate or a calcium-dependent pathway.
- Duct cells: They specialize both in function and in structure. Striated duct cells selectively reabsorb certain electrolytes and contain numerous peptides such as epidermal growth factor (EGF) and nerve growth factor.
- Myoepithelial cells: They are around acini and extend down the ducts, have contractile properties, and assist in saliva secretion.

Salivary Glands

Salivary glands are classified as follows:

- Major glands:
  - Parotid glands: They are principally serous with a "watery" secretion, primarily producing saliva upon physical or taste stimulation.
  - Submandibular and sublingual glands: They are largely mucous, secrete mucins that give saliva a more viscous, sticky nature, and provide much of the resting/basal saliva volume.
- Minor glands: They are scattered across the oral mucosa but are especially common in lips, soft palate, and the ventrum of the tongue; they are mainly mucous in type.

Control of Salivary Gland Secretion

Salivary gland secretion is controlled via neurotransmitters under the influence of the autonomic nervous system, although various hormones may also modulate salivary composition. In general, parasympathetic stimulation

increases fluid secretion as a result of the activation of M3 muscarinic receptors on acinar cells; sympathetic stimulation via alpha-1-adrenergic receptors also produces more saliva, though much less than that occurs after muscarinic stimulation; and stimulation via beta-adrenergic receptors stimulates salivary protein release from acinar cells via fusion of zymogen granules. Neuropeptides (substance P and vasoactive intestinal peptide) and autacoids (histamine and bradykinin) may also influence salivary secretion. Water-specific channels or aquaporins facilitate water movement across acinar cell plasma membranes and provide the only source of fluid secretion in salivary glands.

Composition and Functions of Saliva

The most obvious function of saliva water, mucins, and proline-rich glycoproteins is to lubricate food and mucosa and help taste perception and swallowing, but other functions include the following (**Table 27.1**):

- Digestive: Salivary amylase has a very minor role in humans in the conversion of starch to maltose. Salivary lipase may assist fat digestion.
- Excretory: Some drugs, such as alcohol, are excreted in saliva. Secreted cancer chemotherapy agents may lead to mucosal toxicity, and some may result in altered taste.
- Maintenance of tooth integrity: The buffering capacity and supersaturated calcium and phosphate are important in maintaining tooth integrity.
- Hormonal: EGF (urogastrone), a polypeptide from submandibular glands (SMGs), may play a role in wound healing. Homeostatic proteases, such as kallikrein, renin, and tonin, may control local vascularity and water/electrolyte transport.
- Protective: The lubricative and mechanical washing effects of saliva as well as nonspecific and specific immune-protective mechanisms protect the host. Saliva is inhibitory to various microbial agents, including human immunodeficiency virus (HIV).

These mechanisms include the following:

- Mucins that aid lubrication, aggregate bacteria, are antiviral, and limit mucosal permeability to various toxins.
- Inhibitors of proteolytic enzymes, such as cysteine-containing phosphoproteins and antileukoproteases that are, with mucins, protective against proteolytic enzymes from bacteria and leukocytes.
- Bacterial aggregators that can aggregate bacteria and prevent their attachment to oral surfaces, such as mucins, some glycoproteins, and lysozyme.
- Direct nonimmune antimicrobial mechanisms, such as defensins,
  - Lysozyme interacts with anions such as thiocyanate to lyse gram-positive bacteria.
  - Defensins and histidine-rich peptides in parotid saliva also suppress oral bacteria and fungi.
  - Lactoferrin chelates iron and deprives bacteria of an essential factor.
  - Peroxidase with thiocyanate and hydrogen peroxidase acts against some gram-positive and gram-negative bacteria and yeasts.
  - Amylase may, for example, protect against *Neisseria gonorrhoeae*.
- Immune protection—principally via secretory immunoglobulin A antibodies.

Table 27.1 Functions of Saliva

Maintaining mucosal barrier
Lubrication, speech, and deglutition
Allowing tastants to contact taste receptors
Regulating pH; hypotonic environment
Mineralization: supersaturated $CaPO_4$
Antimicrobial: lysozyme, lactoferrin, sIgA
Digestion: amylase

Etiology of Hyposalivation

Treatment of head and neck cancer (HNC) and bone marrow (hematopoietic stem cell) transplants may especially be associated with xerostomia[1,2]; in patients with cancer, xerostomia has independent negative influences on the quality of life (QoL).[3,4] This also applies to children with malignant disease[5] and in patients who receive chemotherapy for solid tumors.[6] Furthermore, patients with advanced cancer frequently have xerostomia and dry mouth, which is commonly associated with oral discomfort and dysphagia.[7] This chapter summarizes the area and highlight recent advances and future directions: several recent reviews have covered this field comprehensively.[8]

The other main causes of hyposalivation are drugs (those with anticholinergic or sympathomimetic activity), irradiation of the major salivary glands, Sjögren syndrome, diabetes, HIV infection, sarcoidosis, and dehydration (**Table 27.2**).

Cancer Therapy Effects on Salivation

While the direct effects of some cancer therapies on salivary function frequently cause hyposalivation, 18 to 19% of both hospitalized patients with cancer and patients without cancer may suffer from dry mouth,[9] suggesting a strong role of medications and anxiety and/or depression in hospitalized patients.

Effects of Cancer Therapy

In addition to saliva production, the quality of saliva is frequently affected. Increased viscosity produces symptoms

during cancer therapy, which may become a chronic complaint. The mucous acini of salivary glands have a reduced sensitivity to toxicity, and as serous secretions decline, they may retain function for some time. The production of excessively thickened secretions affects the flow of the secretion and may lead to nausea and vomiting, particularly in patients receiving chemotherapy that places them at increased risk for nausea.

Irradiation of the major salivary glands is common in the treatment of cancers of the head and neck (H&N), thyroid, and lymphomas. In HNC, when the salivary glands and bilateral neck irradiation is required, hyposalivation occurs. Hematopoietic stem cell transplantation also involves damage to salivary function,[10] particularly when total body irradiation is part of the conditioning protocol and if graft-versus-host disease develops and involves the salivary glands.[11]

Radiotherapy (RT) causes acinar cell apoptosis, leading to a change in saliva quantity and quality in approximately 1 to 2 weeks of beginning RT at a cumulative dose of approximately 10 Gy; salivary function falls as the RT dose increases, and at a total dose of more than 50 Gy, virtually complete hyposalivation can follow when all glands are in the RT field.[12,13] Salivary flow rates fall dramatically during the first 2 weeks of RT, and both the parotid and submandibular/sublingual glands can be similarly affected.[14]

Patients with HNC treated with RT either alone or in combination with chemotherapy or surgery report xerostomia as one of the most frequent complaints, and this has a significant effect on the more general dimensions of health-related QoL.[15] In HNC, xerostomia increases from 19% pretreatment to 62.6% during RT and 53.2% after RT.[16] In patients treated for nasopharyngeal carcinoma, xerostomia persisted at the last follow-up (24 months).[17]

Salivary function recovery may occur within 1 year after RT[18]; however, little improvement can be expected after 1 year following cancer treatment, and dry mouth is the most common chronic complaint of patients after HNC therapy that includes radiation therapy.

Diffusion-weighted magnetic resonance imaging allows noninvasive evaluation of functional changes in the major salivary glands after RT and is a promising tool for investigating RT-induced xerostomia.[19]

Table 27.2 Causes of Xerostomia

- Interference with neural transmission
  - Medications/drugs
    - Drugs with anticholinergic or sympathomimetic effects
    - Drugs that directly damage salivary glands: antineoplastic agents
    - Drugs with anticholinergic activity: atropine, scopolamine
    - Antireflux agents: proton-pump inhibitors
    - Antidepressants
  - Tricyclic antidepressants
  - Selective serotonin reuptake inhibitors
    - Phenothiazines
    - Benzodiazepines
    - Opioids
    - Antihistamines
    - Drugs acting on sympathetic system: ephedrine
    - Antihypertensives
- Autonomic dysfunction
- Conditions affecting the central nervous system
- Dehydration
  - Diabetes mellitus
  - Diabetes insipidus
  - Diarrhea and vomiting
  - Hypercalcemia
  - Renal disease
  - Severe hemorrhage
- Starvation
- Cancer therapy
  - Irradiation (radiotherapy or radioactive iodine)
  - Chemotherapy
- Targeted therapy
  - Chemoradiotherapy
  - Hematopoietic stem cell transplantation/bone marrow transplantation/chronic graft- versus-host disease
- Salivary gland aplasia
- Systemic conditions affecting salivary glands
  - Autoimmune conditions
  - Sarcoidosis
  - Cystic fibrosis
  - Ectodermal dysplasia
  - Viral infections
  - Deposits

Effects on Quality of Life

The assessment of QoL in HNC includes the Head and Neck Symptom Scale of the University of Washington Quality of Life (UW-QoL) questionnaire, which includes items related to saliva amount and consistency (**Table 27.3**).[20]

The University of Michigan Xerostomia-Related Quality of Life Scale[21] is a 15-question survey, with each

Table 27.3 Scoring Salivary Function

Saliva Amount	Saliva Consistency
10: I have a normal amount of saliva.	10: My saliva has normal consistency.
20: I have a mild loss of saliva.	20: My saliva is slightly thicker.
30: I have a moderate loss of saliva.	30: My saliva is moderately thicker.
40: I have a severe loss of saliva.	40: My saliva is extremely thicker.
50: I have no saliva.	50: I have saliva that dries in my mouth and/or on my lips.

response based on a 5-point severity response. Others have used broad QoL questionnaires with modifications or additional sections. Dry mouth has a significant effect on overall QoL.[22] Two hundred and eighty eight patients with all stages of HNC were assessed by using the European Organization for Research and Treatment Core QoL Questionnaire (EORTC QLQ-C30) and Radiation Therapy Oncology Group (RTOG) toxicity criteria up to 24 months after cancer therapy.

Xerostomia was found to have a significant effect on overall QoL ($p < 0.001$) and the effect on QoL increased over time.[22] One hundred and forty nine patients with stage III or IV HNC were assessed pretreatment and at 1 year after treatment by using EORTC QLQ-C30 and EORTC H&N35. The primary complaints were dysphagia, dry mouth, and thick saliva ($p < 0.05$), and patients with oral cancer had limited improvement at the last follow-up.[23]

A study of 65 patients with HNC who had completed RT more than 6 months earlier showed the most common chronic symptoms—dry mouth (92%), change in taste (75%), difficulty in swallowing (63%), moderate to severe difficulty in chewing (43%), and sore mouth when eating (40%).[24] A prospective study of 357 patients with HNC identified chronic oral symptoms—dental problems, trismus, xerostomia, and sticky saliva that persisted or increased over time after 1 year and persisted for 5 years.[25]

EORTC QLQ-C30 has been used for the assessment of QoL, and specific addenda addressing oral symptoms and effect on QoL have been used in several studies.[26]

Other tools have been assessed, including a visual analogue scale (VAS) for subjective assessment of saliva and a reliability of seven of eight VAS responses, which were found to predict changes in saliva flow induced by xerostomic medications.[27]

A prospective, multicenter study of QoL conducted in 122 patients with oral cancer (62% man, mean age 61 years) with patient reported outcomes completed pretreatment, and at 1 and 5 years after treatment,[28] it found oral complaints to include dry mouth, sticky saliva, speech changes, dental problems, and sleep disturbance. Symptom burden remained significant at 5 years after treatment in patients who were treated with RT, and these complaints were associated with decreased QoL ($p < 0.01$). In another study, 107 patients completed QoL surveys before and 6, 12, 24, and 36 months after HNC treatment.[29] Most short-term morbidity resolved in 1 year of cancer treatment. At the end of follow-up, physical functioning, taste/smell, dry mouth, and sticky saliva were significantly worse compared with those at baseline.

Several studies assessing chronic symptoms more than 6 months to 5 years following Tradiotherapy for HNC have shown that dry mouth, thick saliva, and dysphagia are the most common and troubling persisting complaints.[28,30,31] Most short-term morbidity resolved in 1 year of cancer treatment. At the end of follow-up physical functioning, taste/smell, dry mouth and sticky saliva were significantly worse compared with baseline.

Minimizing Radiation-Induced Xerostomia

Several strategies are available to minimize radiation damage to salivary glands (**Table 27.4**).

Table 27.4 Strategies to Minimize Radiation-Induced Xerostomia

Minimizing radiation field/volume
Using positioning devices, shielding, and conformational field planning
Using intensity-modulated radiation therapy, image-guided radiation therapy, or tomotherapy
Minimizing the exposure doses
Using radiation-protective agents
Repositioning of surgical salivary gland

Minimizing Radiation Exposure Doses

Minimizing salivary gland radiation exposure is one effective strategy to minimize radiation-induced xerostomia. For example, in selected patients with early and moderate stages, well-lateralized oral and oropharyngeal carcinomas, ipsilateral irradiation treatment of the primary site, and ipsilateral neck spares salivary gland function on the uninvolved side, without compromising locoregional control.[32]

In conventional RT, reducing the mean dose to the contralateral SMG below 40 Gy is possible with a reasonable dose coverage.[33] Limiting the mean parotid dose to 31 Gy or less and mean minor salivary gland dose to 11 Gy or less in patients with lymphoma having RT to the H&N reduces the risk of xerostomia.[34]

Using Positioning Devices, Shielding, and Conformational Field Planning

Positioning devices, shielding, and conformational field planning may also minimize salivary damage. The use of computed tomography (CT)-based delineation guidelines for organs at risk in the H&N should reduce inter- and intraobserver variability and therefore unambiguous reporting of possible dose-volume-effect relationships.[35]

Intensity-modulated radiotherapy (IMRT) reduces doses when compared with standard three-dimensional conformal radiotherapy (CRT)[36,37] and reduces xerostomia.[38]

Parotid gland sparing IMRT for patients with HNC improves xerostomia-related QoL compared with CRT both at rest and during meals: patients with laryngeal cancer had fewer complaints but benefited equally from IMRT compared with patients with oropharyngeal cancer.[39] IMRT in the treatment of nasopharyngeal carcinoma produced significant reductions in the occurrence rates and severity of acute skin reaction, neck fibrosis, trismus, and xerostomia.[40]

SMG dose reduction to less than 39 Gy and without target underdosing is feasible in some patients at the expense of modestly higher doses to some other organs.[41] Stimulated SMG flow rates decrease exponentially by 1.2% as mean doses increased up to 39 Gy threshold and then plateau near zero. At mean doses of 39 Gy or less, but not higher, flow rates recover over time at 2.2% a month. Similarly, the unstimulated salivary flow rates (USFRs) decrease exponentially by 3% as the mean dose increases and recovers over time if the mean dose was less than 39 Gy. IMRT replanning reduces mean contralateral SMG dose by an average of 12 Gy, achieving 39 Gy or less in five of eight patients, without target underdosing, and increasing the mean doses to the parotid glands and swallowing structures by an average of 2 to 3 Gy.

However, others have found that by 1 year after RT, normal tissue complication probability curves for IMRT and CRT were comparable with a median toxic dose (uniform dose leading to a 50% complication probability) of 38 and 40 Gy, respectively.[42] Helical tomotherapy (TomoTherapy Hi-Art System; Accuracy, Sunnyvale, California, United States) of the parotid gland seems to largely preserve the function.[43]

Using Radiation-Protective Agents

Radiation-protective agents can protect salivary glands in animal models, but translation of agents from animal testing to be used as prophylactic adjuncts or postexposure treatments in RT has been slow. Agents approved for the purpose by the U.S. Food and Drug Administration include amifostine (Ethyol, Ethiofos, WR-2721), an organic thiophosphate prodrug for alleviating xerostomia associated with RT. Amifostine is a free-radical scavenger, and it also accelerates DNA repair.[44] The selective protection of certain tissues of the body by amifostine is believed to be due to higher alkaline phosphatase activity, higher pH, and vascular permeation of normal tissues.

Acute xerostomia was significantly lessened in intravenous (IV) amifostine-treated patients with HNC (51%) compared with controls (78%).[45] Salivary output was significantly raised above that that for untreated controls 1 year after RT,[45] and xerostomia was reduced at 2-year follow-up.[46] Xerostomia after RT in a study by another group was similarly lower in amifostine-treated patients (57.5%) with HNC compared with controls (70%).[47] Amifostine was initially administered intravenously before chemotherapy or RT, but because of adverse effects and the cost of delivery, it is now provided through the subcutaneous (SC) route.[48] A study of 20 patients with HNC having RT-CT examined SC amifostine versus historical data of IV amifostine found outcomes from SC similar to those from IV but with reduced nausea/vomiting and hypotension after SC administration and showed xerostomia with SC drug as 42% (12 months) and 29% (18 months).[49] The Groupe d'Oncologie Radiothérapie Tête Et Cou study compared IV (200 mg/m^2) versus SC (500 mg/d) amifostine in HNC and found less hypotension with SC amifostine,[50] which is virtually identical with other results.[51]

Both amifostine and IMRT are able to partially preserve parotid function after RT, although the effect of IMRT appears greater.[52]

However, amifostine has not been shown to provide significant radioprotective effects on salivary glands in high-dose radioactive iodine–treated patients with differentiated thyroid cancer.[53]

Pilocarpine (Salagen) is a slowly hydrolyzed muscarinic agonist with no nicotinic effects, which can increase secretion by the exocrine glands. The salivary, sweat, lacrimal, gastric, pancreatic, and intestinal glands and the mucous cells of the respiratory tract may be stimulated. In animal models, preirradiation treatment with pilocarpine induces a compensatory response at lower doses in the irradiated gland and at higher doses in the nonirradiated gland, reducing late damage, because of stimulation of unirradiated or surviving cells to divide.[54,55] A prospective, double-blind, placebo-controlled, randomized trial by the same authors in patients with HNC having RT showed that the concomitant administration of pilocarpine have no effect on parotid flow rate complications; however, patient-rated xerostomia scores showed trends toward less dryness-related complaints and there was reduced loss of parotid flow 1 year after RT in those patients who received pilocarpine and a mean parotid dose of more than 40 Gy.[56]

In patients with HNC treated with bilateral RT in a double-blind, placebo-controlled, randomized trial using 5 mg of pilocarpine five times a day during RT, there was an improved overall QoL and less oral discomfort.[57] Others have also found some improvements,[58] although the clinical impact of the effect on salivation is not well defined.

The use of pilocarpine both during and after RT is also beneficial.[59]

Repositioning of Surgical Salivary Gland

Surgical repositioning of the SMG out of the planned RT field to the submental space can protect the gland.[60] One study suggested that SMG transfer procedure is superior to pilocarpine in the management of RT-induced xerostomia.[61]

However, as RT is now delivered to the H&N with conformal fields/IMRT and tomotherapy, the reduction in the volume of high-dose radiation allows sparing of high-dose exposure to all salivary glands in many cases, with the increased potential for residual gland function and stimulation with sialogogues.

Management of the Patient with Cancer Liable to Hyposalivation

Recent recommendations for the management of patients with cancer liable to hyposalivation are as follows[62]:

- Patients with cancer should be regularly assessed for salivary gland dysfunction (SGD);

- The management of SGD should be individualized;
- Consideration should be given to strategies to prevent the development of RT-induced SGD;
- Consideration should be given to the treatment of the cause(s) of SGD;
- The treatment of choice for the symptomatic management of SGD is use of an appropriate saliva stimulant;
- Strategies to prevent the complications of SGD should be in place;
- Early diagnosis and treatment of the complications of SGD should be conducted; and
- Patients with SGD should be regularly reassessed.

Treatment is largely palliative and preventative in nature. Because oral dryness is a subjective complaint, it is not surprising that there is a great variation in the patient's threshold of discomfort or other symptoms and it is also affected by tolerance and adaptation over time.[63–65]

Clinical Features

Oral complaints (often the presenting features) can include

- Xerostomia;
- Oral soreness or burning sensation;
- Difficulty in eating dry foods;
- Difficulty in speaking for long periods of time, the development of hoarseness, or there may be a clicking quality of the speech as the tongue tends to stick to the palate;
- Difficulty in swallowing;
- Difficulty in controlling dentures;
- Need of putting up a glass of water at night (and, sometimes, resulting nocturia); and
- Complications such as unpleasant taste or loss of sense of taste, oral malodor, caries, candidosis, and sialadenitis.

Common Terminology Criteria for Adverse Events (CTCAE v3.0) are as in **Table 27.5**.[67]

A positive response to the questions in **Table 27.6** is significantly associated with reduced salivary output.[68]

Table 27.5 Common Terminology Criteria for Adverse Events

Symptomatic (dry or thick saliva) without significant dietary alteration; unstimulated saliva more than 0.2 mL/min.
Symptomatic and significant change in oral intake (e.g., copious water, other lubricants, diet limited to soft, moist foods); unstimulated saliva 0.1 to 0.2 mL/min.
Symptoms leading to inability to take oral nutrition; use of intravenous fluids, tube feedings, or total parenteral nutrition indicated; unstimulated saliva less than 0.1 mL/min.

Table 27.6 Features of Hyposalivation: Questions and Responses

Do you have difficulty in swallowing any food? Yes/No
Does your mouth feel dry while eating a meal? Yes/No
Do you sip liquids to aid swallowing dry food? Yes/No
Does the amount of saliva in your mouth seems to be too little, too much, or never noticed it?

Chronic Complications

Chronic complications of hyposalivation may include the following (**Table 27.7**):

- Shift in the oral microflora and risk of oral infection (caries, candidosis, bacterial sialadenitis) (**Figs. 27.1** to **27.4**);
- Oral malodor;
- Altered/reduced taste;
- Mucosal dryness and sensitivity;
- Impaired chewing: patients with reduced or increased salivary flow, however, may not present measurable alterations in masticatory efficiency[69];
- Difficulty in swallowing;
- Difficulty in denture use and function, but there are few clinical research studies on the effect of hyposalivation on denture retention and mucosal trauma[70];
- Nutritional defects; and
- Altered speech.

Table 27.7 Clinical Symptoms of Xerostomia

Dryness
Discomfort
Taste reduction
Speech and deglutition affected
Denture use and function affected
Compromised diet/nutrition

Quality of Life Scales Focused on Xerostomia

Scales focused on xerostomia are shown in **Table 27.8**. The UW-QoL saliva domain seems to be a suitable means of screening for dry mouth in head-and-neck clinics and can be used to trigger interventions.[71]

Patient self-reported, rather than physician-assessed, scores should be the main end points in evaluating xerostomia because correlations between RTOG/EORTC grades and salivary flow rates are poor; in contrast, significant correlations are found between the patient self-reported scores and nonstimulated or stimulated salivary flow rates. No significant correlation was found between the

Table 27.8 Quality of Life Scales

Xerostomia-Related Quality of Life Scale
The University of Washington Quality of Life questionnaire (Version 4; dry mouth item)
Vanderbilt Head and Neck Symptom Surgery ECOG QLQC30; HN35.

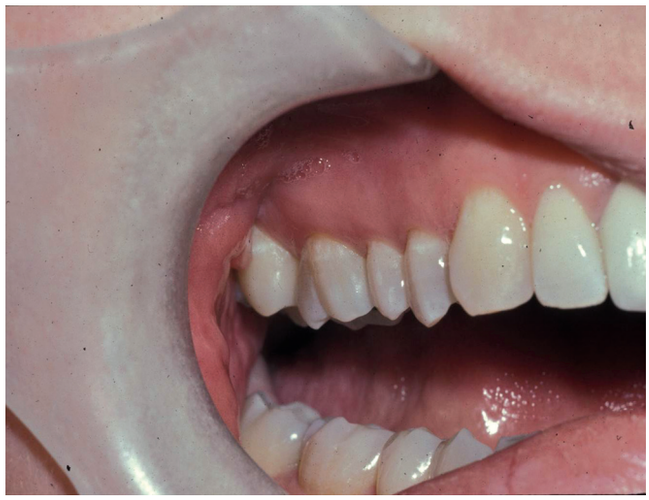

Figure 27.1 Early decalcification of teeth.

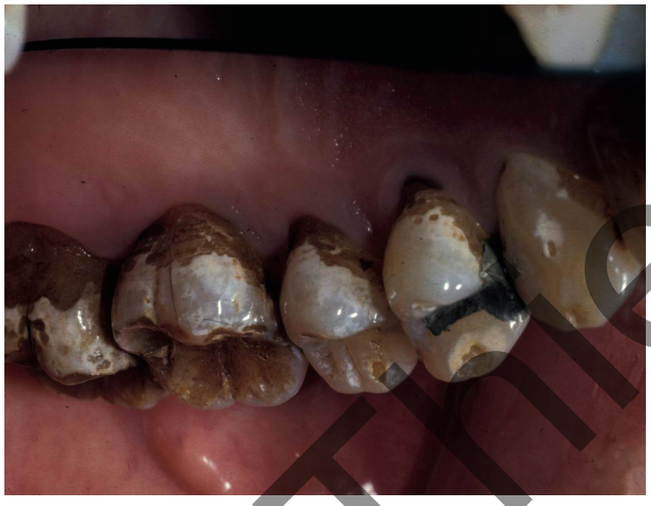

Figure 27.2 Dental caries (radiation caries).

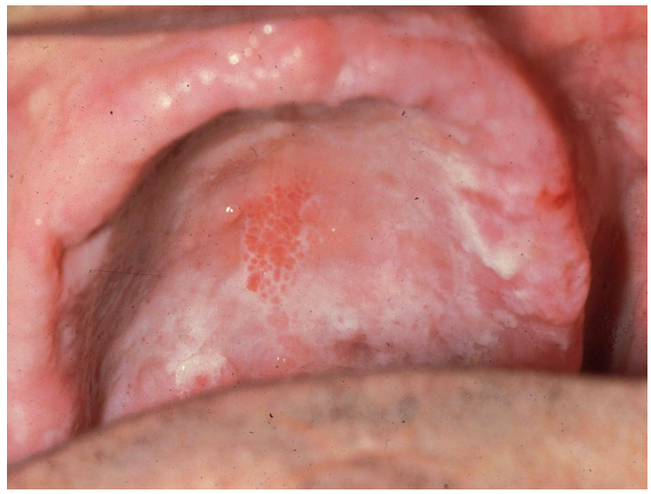

Figure 27.3 Mucositis.

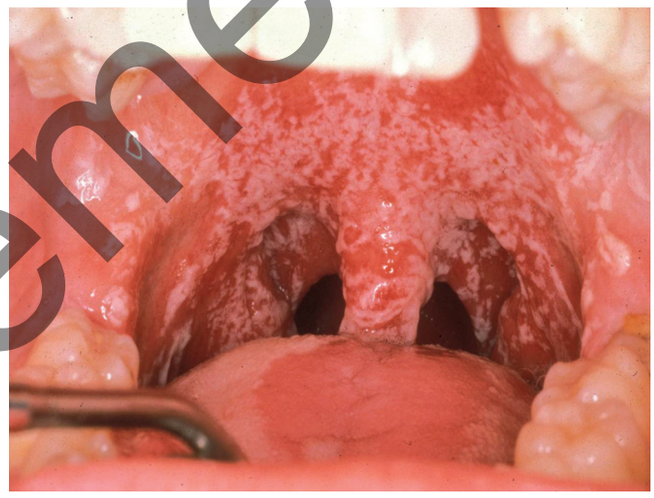

Figure 27.4 Candidosis.

RTOG/EORTC grades and the Xerostomia-Related Quality of Life Scale scores.[72–74]

Clinical Signs of Hyposalivation

The dry mucosa may become tacky and mucosal surfaces, including the lips, can adhere one to another. There may be saliva flowing poorly, if at all, from the ducts of the major glands on stimulation or palpation. The following signs may also be present:

- Tendency of the mucosa to stick to a dental mirror or tongue spatula.
- Food residues in the mouth after eating.
- Lack of sublingual salivary pooling.
- Frothiness of saliva, particularly in the lower sulcular reflection, and absence of frank salivation from major gland duct orifices.
- A change in tongue appearance—lobulated, usually red, surface with partial or complete depapillation.
- In advanced cases, clinically dry and glazed oral mucosae can be observed.

Examination

The patient should be examined

- Through inspecting.
- Through facial symmetry.
- For evidence of enlarged glands.
- Through salivary ducts for evidence of salivary or pus flow.
- Through saliva.
- By palpating the glands.
- Through parotids.
- By using fingers placed over the glands in front of the ears to detect pain or swelling.
- Through submandibulars.
- Through bimanual palpation between fingers inside the mouth and extraorally.

- Through the mucosa; note particularly mucositis, angular cheilitis, dryness, and lingual depapillation or erythema and masses in the immovable soft palate and posterior aspect of the hard palate.

Objective Determination of Hyposalivation

Because baseline salivary flow rates for individual patients with cancer are generally unknown, unless this is assessed before beginning cancer therapy, it is rarely possible to determine whether there has been a reduction in salivary flow. The normal salivary flow rate also varies by the time of day (diurnal variation) and varies widely from person to person.

The USFR of whole saliva is generally determined. The USFR uses a simple draining test for 5 minutes at rest: If USFR is less than or equal to 0.1 mL/min, the patient has hyposalivation. Stimulated saliva flow can be assessed by collecting saliva while chewing unflavored chewing gum base or wax for 5 minutes.

Normal and reference values for salivary flow are given in **Table 27.9**.

Volume of saliva can be measured, or the saliva collected can be weighed. The Saxon test is a simple, reproducible, and low-cost test for xerostomia, which involves chewing on a folded sterile sponge for 2 minutes. Saliva production is quantified by weighing the sponge before and after chewing. Normal control subjects produced 2.75 g or less of saliva in 2 minutes.[75]

Instruments to measure moisture include Moisture Checker (MucusIII; MCM; Life Co., Ltd., Saitama, Japan), a device for measuring moisture of the oral submucosa,[76] and the capacitance method Moisture Checker for Mucus (Life Co., Ltd., Saitama, Japan).[77]

Therapy

As noted, there may be little correlation between patient symptoms and objective tests of salivary flow. Clinical management may be based on the symptoms; however, as the effect on oral health depends on salivation, this should be considered in all patients as some may have symptomatically accommodated to their dry mouth.

Management is multidisciplinary and multimodal, and treatment essentially involves use of salivary stimulants and/or salivary substitutes and begins with simple measures such as the following:

Table 27.9 Whole Saliva Flow Rates

	Flow rate (mL/min)	
	Normal	**Hyposalivation**
Unstimulated (resting)	0.3–0.4	< 0.1
Stimulated	1–2	< 0.5

Note: Whole saliva is the total output from the major and minor salivary glands.

- Sipping water or other fluids throughout the day, protecting the lips with nonpetroleum-based lip applications, and modifying the eating behavior (e.g., small bites of food, eating slowly) and diet (moist, creamy foods [casseroles, soups] or cool foods with a high liquid content [melon, ice cream]) as well as moistening foods with water, gravies, sauces, extra oil, dressings, sour cream, mayonnaise, or yoghurt are advantageous.
- Avoiding mouth breathing, drugs that may produce xerostomia (e.g., tricyclic antidepressants), alcohol (including in mouthwashes), smoking, caffeine (coffee, some soft drinks), dry foods such as biscuits (or moisten in liquid first), spicy foods, and oral health care products containing sodium lauryl sulfate, which may irritate the mucosa. There is good evidence to support that xerostomia is commonly associated with anticholinergic and opioid drugs, and altering such agents, when possible, can be important in the management after RT.[78,79]

In patients with residual salivary gland function, salivary stimulants (**Table 27.10**) appear to be more beneficial than the simple use of salivary substitutes and should be considered before palliation of symptoms.[80]

Table 27.10 Stimulation of Salivation

Local/topical
• Taste stimulation
• Masticatory stimulation
• Oral rinses, gels, mouthwashes
• Acupuncture
Systemic sialogogues

Sialogogues

Salivation may be stimulated by using chewing gums (containing xylitol or sorbitol, not sucrose), sugar-free (diabetic) candies, or other topical agents that stimulate salivation (sialogogues) (**Table 27.11**).

Table 27.11 Gustatory/Mechanical Stimulation of Salivation

United States	**United Kingdom**
Sugar-free gum/candy	Sugar-free gum/candy
Salese Lozenge (Nuvora Inc.)	Salivix (KoGEN) Pastilles
Oramoist Lozenge (Quantum Inc.)	SST (Medac) tablets

If these fail to give satisfactory benefit, cholinergic sialogogues, such as pilocarpine, cevimeline, or bethanechol (Urecholine) may help, as may other agents (**Table 27.12**). Salivary stimulant medication may be needed indefinitely for maintenance of saliva flow.

Pilocarpine

Pilocarpine used after RT can increase salivation by 64.5%.[81] In controlled trials, pilocarpine used after RT increased

Table 27.12 Systemic Sialogogues

Cholinergic Agents[a]	Other Agents
Pilocarpine (Salagen)	Anetholetrithione (Sialor)[b]
Cevimeline (Evoxac)	
Bethanechol (Urecholine)	
Physostigmine	

See text for newer agents.

[a]May require several months to determine effectiveness; avoid in patients with narrow-angle glaucoma and uncontrolled asthma; caution in hypertensive patients using beta-blocker.

[b]Not available worldwide.

whole resting saliva (69 vs. 43% in controls), unstimulated parotid saliva (30 vs. 3%), and stimulated parotid saliva (45 vs. 28%).[82] A double-blind, placebo-controlled trial of pilocarpine (3 or 5 mg) versus placebo in patients with HNC after RT showed a significant increase in the unstimulated whole saliva flow rate.[83] Pilocarpine may also ameliorate xerostomia induced by opioid drugs[84] and likely other medications.

Adverse effects of pilocarpine include sweating, nausea, palpitation, and tearing, with sweating as the most common side effect.[85]

Pilocarpine is contraindicated in patients with uncontrolled asthma, narrow-angle glaucoma, and acute iritis and should be used with caution in patients with cardiovascular disease.[86] Pilocarpine produces maximum saliva stimulation after 1 hour, and the effect continues for 2 to 3 hours. Five milligrams of pilocarpine three times a day may cause a high incidence of unacceptable adverse effects in Japanese patients for whom a lower dose of pilocarpine should be considered.[87]

Cevimeline

Cevimeline is a parasympathomimetic agent with the pharmacologic profile similar to that of pilocarpine, a cholinergic agonist with the effect on M3 receptors located in smooth muscles and glands and endothelium.[88] In patients with HNC having xerostomia after RT, 30 mg of cevimeline (Evoxac) three times a day improved oral dryness and significantly increased unstimulated saliva flow.[89,90]

Bethanechol

Bethanechol used during RT may result in increased unstimulated whole salivary flow.[91]

Physostigmine

Application of physostigmine to the oromucosal surface produced long-lasting (120 minutes) relief in the feeling of dryness, which was six times greater than that to placebo. The volume of saliva collected in response to physostigmine was also five times higher over 180 minutes than that collected in response to placebo.[92]

Comparative Studies of Sialogogues

Forty-two patients with HNC having xerostomia after RT were randomized to pilocarpine or bethanechol. All subjects reported improved symptoms, but only minimal measurable increase in saliva volume. In 27 patients who completed the crossover, the possible increase in saliva suggested that an increased duration of sialogogues may improve the outcome.[93] Another study assessed 20 patients in a crossover design by using pilocarpine, cevimeline, or bethanechol, and all sialogogues increased saliva, but bethanechol increased saliva more than did pilocarpine ($p = 0.0272$); pilocarpine was more associated with increased sweating compared with both bethanechol ($p = 0.0588$) and cevimeline ($p = 0.0143$).[94]

Mouth-Wetting Agents (Saliva Substitutes)

Mouth-wetting agents may help symptomatically relieve xerostomia after RT.[95] Many of these agents are available (**Table 27.13**) with differences in their performance and patient acceptance. These topically applied products can be assessed in individual patients and the preferred agent determined.

Table 27.13 Mouth-Wetting Agents and Local Stimulants

United States	United Kingdom
Entertainer's Secret (KLI Corp) spray	AS Saliva Orthana (AS Pharma) spray
Glandosane (Fresenius Kabi) spray available unflavored, lemon, mint	Biotene Oralbalance (Anglican) gel
Moi-Stir (Kingswood Laboratories)	BioXtra (RIS products) gel
Mouth-Kote[a] (Parnell Pharmaceuticals)	Glandosane Frenius Kabl) spray
Oasis Mouthwash and Mouth Spray (GlaxoSmithKline) and liquid	Luborant (Goldshield) spray
Oral Balance (Laclede Professional Products) gel	Salinum (Crawford) liquid
Oramoist Lozenge (Quantum, Inc.) lozenges	Saliveze (Wyvern) spray
Salese Lozenge (Nuvora, Inc.) lozenges	Xerotin (SpePharm) spray
Saliva Substitute (Roxane Laboratories) liquid	
Salivart (Xenex Laboratories, Inc.)	
SalivaSure (Scandinavian Natural Health & Beauty) tablets	

[a]Contains citric acid.

Apart from water, various saliva substitutes are available, including those based on carboxymethylcellulose (CMC) (some are particularly useful because they contain fluoride and are thus caries protective). CMC-based saliva replacements have moderate effects on reducing dry mouth–related symptoms and behaviors, with more significant effects on patients whose residual secretory potency was severely compromised.[96]

In a sample of older adults with dry mouth, a mouthwash and oral gel containing the antimicrobial proteins lactoperoxidase, lactoferrin, and lysozyme improved some subjective and clinical aspects, though a placebo effect cannot be discarded.[97,98] Oral care using such a moisturizing gel might also have other benefits because it may contribute to preventing respiratory tract infections from oral contamination in patients with cerebrovascular disease.[99]

Other wetting agents are based on animal mucin, but there may be religious or cultural objections to the use of mucin.

Quality and Control of Saliva

Viscosity of oral secretions may be a considerable problem for patients with cancer during therapy and thereafter it may be a chronic problem. There has been limited study of approaches to management. Possible interventions include trials of systemic sialogogues that may increase residual serous saliva production; however, if serous function cannot be stimulated, they may serve to increase mucous secretions that increase patient symptoms. Mucolytic agents such as *N*-acetylcysteine (Acetadote) and guaifenesin (Duratuss G) have been considered, but no significant benefits have been demonstrated.

Management of oral secretions can be affected by diminished lip competence and tongue mobility, dysphagia, and fistulae.[100]

Management may include physical therapies (suction, frequent changes of dressing, pressure dressings, fibrin glue, aspiration of sialoceles), pharmacologic therapy (anticholinergics, xerogenergic medications, botulinum toxoid),[101] or surgical approaches (gland removal, duct ligation, duct repositioning, chorda tympanectomy, tympanic neuroectomy).[102]

Management of Complications of Hyposalivation

Complications of hyposalivation should be managed by

- Avoiding sucrose-sweetened foods;
- Maintaining good oral hygiene and plaque control;
- Using fluorides and remineralizing products; and
- Using mouthwashes with chlorhexidine.

Dental Caries

Dental caries may be prevented as shown in **Table 27.14**.

Dietary control of sucrose intake, the daily use of fluoride toothpastes, and other fluoride applications are essential.

Table 27.14 Caries Prevention and Control after Radiotherapy

Caries risk assessment/diet assessment
Early detection of caries and prevention of demineralization
Remineralization • Sodium fluoride: 1.1% neutral gel, lozenges, 0.05% rinse, 5% varnish • Fluoride varnish: 1% difluorosilane varnish • Calcium/phosphate: calcium and phosphate are essential components of the enamel and dentine and form highly insoluble complexes, but, in the presence of casein phosphopeptide (CPP), they remain soluble and biologically available as amorphous calcium phosphate (ACP). The CPP-ACP complex can be applied to teeth by means of chewing gum, toothpaste, lozenges, mouth rinses, sprays, and so on.
Recaldent-containing chewing gum
Artificial saliva (Caphosol)

Management of Cariogenic Flora

Cariogenic flora can be managed through

- Oral hygiene;
- Chlorhexidine; and
- Xylitol-containing products.

ACP can aid remineralization of white spot lesions in a similar effect to self-applied fluorides, which also reduces the appearance of new caries lesions.[103] One therapeutic approach is the daily use of a supersaturated calcium phosphate rinse in conjunction with 1.1% NaF.[104]

Candidosis

Candidosis may cause soreness or burning and thus should be treated with antifungals until symptoms and signs resolve. Risk factors must be addressed or infection will recur and prophylaxis should then be considered (**Table 27.15**).

Topical antifungal drugs in liquid form, such as nystatin, are effective and most acceptable because the mouth is

Table 27.15 Prevention and Management of Candidosis after Radiotherapy

Topical antifungal drug with lowest risk for dental caries
Nystatin (Mycostatin and Nystan) vaginal tablets three times a day
Clotrimazole (FungiCURE Pump Spray) five times a day
Compounded fluconazole (Diflucan) rinse
Sips of water as necessary to dissolve antifungal tablets
Dentures and mucosa require antifungal treatment
Topical antifungal creams applied to denture surface
Systemic antifungals are more effective with salivary stimulation
Continue antifungal drug until signs and symptoms resolve (4 to 10 weeks)
Consider maintenance dose of the antifungal drug

dry. However, the sucrose content of the product must be considered because of the effect of sucrose on dental caries, the risk of which is already increased in patients with dry mouth. Nystatin suspension has a high sucrose content (and a small level of alcohol). Fluconazole suspension also has a high sucrose content. Other preparations such as miconazole (Monistat; cream, adhesive tablet, or gel may be available), clotrimazole (not available in the United Kingdom), or amphotericin suspension (not available in the United States) are also effective.

Acrylic surfaces of prostheses are frequently infected, and so dentures and other removable appliances should be left out of the mouth at night and stored in antifungals such as sodium hypochlorite solution, chlorhexidine, or benzalkonium chloride to disinfect. An antifungal such as miconazole (cream or gel) or amphotericin or nystatin (cream or ointment) should be spread on the prosthesis fitting surface before reinserting it in the mouth.

Bacterial Sialadenitis

Mouth-wetting agents such as lactoperoxidase gel may reduce both periodontal-associated bacterial pathogens and *Candida* species.[105] Stimulation of salivation and antibacterial agents such as 0.12 or 0.2% chlorhexidine gluconate mouthrinse and xylitol (in sugar-free gums and mints) may also have utility. Bacterial sialadenitis may best be treated with a penicillinase-resistant antibiotic such as flucloxacillin.

Therapeutic Modalities in Trial Stages

Several therapeutic modalities for hyposalivation in trial stages are shown in **Table 27.16**.

Key Web Sites

Listed below are Web sites that provide information related to xerostomia and hyposalivation (accessed December 19, 2011).

- http://cancer.gov/cancertopics/pdq
- http://www.drymouth.info/practitioner/sources.asp
- http://mascc.org

Table 27.16 Therapeutic Modalities in Trial Stages

Modalities
• *Capparis masaikai Levl*
• Nizatidine
• Rebamipide
• Xialine
• Salivary irrigation
• Acupuncture
• Hypnosis
• Electrostimulation
• Stem cell therapy
• Gene therapy

Dilemmas

- Limited approaches to manage viscous/mucous secretions.
- Limited oral medications that are sucrose-free.
- Limited contact time of topical products in the oropharynx.
- Limited information on the pH of mouth-wetting agents.
- Limited data on remineralizing products.

Clinical Pearls

- To avoid tooth demineralization and caries, minimize or avoid refined carbohydrates or topical agents sweetened with sucrose.
- Topically applied mouth-wetting agents can be assessed in individual patients and the preferred agent determined.
- Where systemic sialogogues are considered, measure saliva production at rest and upon stimulation: if saliva is produced, anticipate beneficial effects. Challenge the patient with 5 mg of pilocarpine and assess salivary flow; if it increases, prescribe sialogogue. Re-evaluate the patient after three consecutive months of treatment with 5 mg of pilocarpine three or four times per day.
- Dental providers should be involved as part of the multidisciplinary health care team.

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