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This series aims to enhance the healthcare team's awareness of the importance of early detection by recognizing signs and symptoms of orofacial cancers and their management , and of prevention. It discusses treatment complications from surgery, radiotherapy (RT) and chemotherapy (CTX), summarizing the outcomes of a meeting on 'Oral Healthcare in People Living with Cancer' held in 2010, attended by 300 delegates from 33 countries – dentists, specialists, and Dental Care Professionals (DCPs), and the cancer support team. There is a considerable body of literature on oral cancer but very little is written on healthcare aspects of people living with cancer and a particular focus of this meeting was caring for survivors. The Faculty included European leaders in the field who have authored the series. The full peer-reviewed papers from the meeting are published in Oral Oncology 2010; ***46****; 485–570.*

Oral Cancer: Comprehending the Condition, Causes, Controversies, Control and Consequences

15. Salivary and Taste Complications

Salivary dysfunction

Saliva is essential to oral health. Low salivary flow (hyposalivation) causes lack of mucosal wetting, lubrication and defences, which affects many functions, and can predispose to infections.

Hyposalivation is not synonymous with Xerostomia.

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

Salivary 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 secretion as a result of activation of acinar cell M3 muscarinic receptors; sympathetic stimulation also produces more saliva – via alpha 1 adrenergic receptors, though much less than occurs following muscarinic stimulation. Water-specific channels, or aquaporins (AQPs) facilitate water movement across acinar cell plasma membranes, and provide the fluid secretion in salivary glands. Stimulation via beta adrenergic receptors stimulates protein release from acinar cells. The neuropeptides substance p and vasoactive intestinal peptide (VIP), as well as autocoids (histamine and bradykinin) may also influence salivary secretion.

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Causes of hyposalivation

Radiotherapy (RT) involving the salivary glands readily causes hypofunction. The main other causes of hyposalivation are drugs (cytotoxics and those with anticholinergic or sympathomimetic activity), Sjögren's syndrome, diabetes, HIV disease, sarcoidosis, and dehydration.

RT-induced salivary gland damage can affect over 60% of patients, often giving rise to problems in chewing, swallowing, speech and taste (Table 1) and affecting quality of life.

Hyposalivation and xerostomia arise in the first week of conventional RT and salivary flow may fall by 50–60% in the first week and can fall to 20% after a further 5 to 6 weeks of RT. Whole saliva becomes thick and tenacious, the pH falls, and the amount of salivary sediment rises. There may be some recovery over the next 12 to 60 months but there is rarely ever a return to normality. Fractionated two-dimensional RT and ipsilateral RT may cause less salivary gland dysfunction.The advent of various 3D techniques, including 3D conformal RT, helical tomotherapy and IMRT, provided the opportunity to target radiation dose better and restrict involvement of adjacent structures – particularly the salivary glands. Several studies confirm that IMRT reduces the frequency and/or severity of RT-associated xerostomia without any loss of effectiveness against cancer, significantly lessening the xerostomia both at rest, and with meals, and reducing the effects upon quality of life. This benefit from IMRT may also remain significant at three or more years post-RT.

- Dysphagia
- Dysarthria
- Dysgeusia
- Mucosal dryness and soreness
- Susceptibility to infection (caries, gingivitis, candidosis, sialadenitis)

Table 1. Manifestations of radiation-associated hyposalivation.

Prevention of radiotherapy-associated xerostomia

Amifostine, an intracellular scavenger of free radicals, acts as a radioprotectant, reducing the risk of RT-associated salivary damage, although the benefits may not be seen until after 3 to 12 months. IMRT alone, however, may be more effective than amifostine in reducing long-term salivary dysfunction.

Pilocarpine administration before or during the RT may also reduce the severity of xerostomia. Salivary gland transfer may be more effective than pilocarpine, although clearly requires surgical treatment before starting RT.

Management of radiotherapy-associated xerostomia

Xerotomia can be managed either by:

- Substituting lost saliva with another fluid (using mouth-wetting agents) or
- Stimulating salivation from remaining viable glands (using sialogogues).

Oral
- Radiotherapy
- Hyposalivation
- Infection
- Ulceration
- Malignancy

Systemic disease
- Respiratory (infection, malignancy)
- CNS (temporal lobe tumours and epilepsy)
- Gastrointestinal – reflux disorders
- Endocrine – diabetes mellitus
- Renal – chronic kidney disease
- Hepatic – liver failure
- Deficiency states (eg zinc)
- Psychiatric (including hypochondriasis)
- Drugs (Table 3)

Table 2. Causes of dysgeusia.

Any of the wide range of mouth-wetting agents (salivary substitutes) available may reduce symptoms and improve oral function and quality of life, but no one agent seems substantially better than another.

Sialogogues such as confectionery or chewing gum (sugar-free), ascorbic acid tablets, or malic acid-containing agents may reduce xerostomia after RT, and they are inexpensive and readily available, often over-the-counter (OTC). However, they can provide only transient relief and some may give rise to local (eg caries, dental erosion) or gastrointestinal adverse-effects.

Cholinergic sialogogues can be used for the treatment of RT-associated xerostomia. Pilocarpine, cevimeline, bethanechol, carbecholine and anetholetrithione are available. Oral pilocarpine can reduce the frequency and severity of RT-induced hyposalivation and associated symptoms, usually with only relatively mild adverse effects, such as sweating, but there is a need for appropriate randomized controlled trials comparing the various agents.

Other treatment options suggested helpful for objective and subjective aspects of RT-associated salivary dysfunction include:
- Acupuncture;
- Hypnosis;
- Hyperbaric oxygen.

Future management strategies, currently experimental, may include:
- Gene therapy;
- Stem cells and tissue regeneration;
- Neuroelectrostimulation.

Taste

Taste (gustation) sensation is essential to the acceptability and enjoyment of food and drink, and helps prevent ingestion of toxins. The sense of smell is intimately linked, and it can be difficult to differentiate anomalies of these two senses.

There are five taste senses:
1. Bitter (detects minute levels of noxious compounds);
2. Sweet (identifies energy-rich nutrients);
3. Salt (ensures adequate intake of electrolytes);
4. Sour (also warns of noxious/poisonous agents); and
5. Umami (recognizes amino acids).

Taste buds on tongue, soft palate, pharynx, larynx and upper third of oesophagus register tastes. Each bud consists of up to 100 taste-receptor cells which have a short lifespan of about 10 days.

Taste-related nerve impulses are transmitted via the trigeminal, facial, glossopharyngeal and vagus nerves to the nucleus of the solitary tract and thereafter via the thalamus to the brain post-central gyrus-facial area and olfactory cortex.

Disorders affecting salivation, taste buds/mucosa, or peripheral or central nerve pathways may lead to taste abnormalities.

Taste abnormalities

The sense of taste can be distorted (dysgeusia), reduced (hypogeusia), and/or lost (ageusia). A wide spectrum of disorders can give rise to altered taste, although diseases of the mouth and upper respiratory tract are the most common (Table 2).

Taste in patients with head and neck cancer

Taste dysfunction is common in patients with head and neck cancer either as hypogeusia, dysgeusia and/or ageusia, and as a consequence of the tumour or RT. Taste disturbance may arise prior to RT suggesting that tissue necrosis, infection and/or invasion associated with oral malignancy can be causative. Altered

Antibiotics	**Anti-inflammatory agents**	**Cardiovascular agents**
Ampicillin	Auranofin	Acetazolamide
Azithromycin	Colchicine	Amiloride
Ciprofloxacin	Dexamethasone	Betaxolol
Clarithromycin	Gold	Captopril
Griseofulvin	Hydrocortisone	Diltiazem
Metronidazole	Penicillamine	Enalapril
Ofloxacin	**Antimania drug**	Hydrochlorothiazide
Tetracycline	Lithium	Nifedipine
Anticonvulsants	**Antineoplastics**	Nitroglycerin
Carbamazepine	Cisplatin	Propranolol
Phenytoin	Doxorubicin	Spironolactone
Antidepressants	Methotrexate	**Decongestants**
Amitriptyline	Vincristine	Pseudoephedrine
Clomipramine	**Antiparkinsonian agents**	**Lipid-lowering agents**
Desipramine	Levodopa	Fluvastatin
Doxepin	**Antipsychotics**	Lovastatin
Imipramine	Clozapine	Pravastatin
Nortriptyline	Trifluoperazine	**Muscle relaxants**
Antihistamines	**Antithyroid agents**	Baclofen
Chlorphenamine	Methimazole	Dantrolene
Loratadine	Propylthiouracil	

Table 3. Drugs that may alter senses of taste and smell.

taste affects up to 100% of patients with cancer in the head and neck, particularly those who have received RT, usually arising within days of starting RT and becoming exponentially worse beyond RT doses of 20Gy, such that 90% of patients who have received 60Gy are likely to have significant taste disturbance. In general, taste disturbance is maximal within the first 2 months of RT, but normal taste sensation usually returns within 6 to 24 months. No one taste sense is consistently lost.

It is probable that post-RT taste dysfunction reflects mainly the loss of taste receptor cells (as part of mucositis). Synaptic uncoupling may also be of some relevance. Mucositis may itself give rise to altered taste. There may be correlation between the volume of tongue irradiated and the likelihood and/or severity of taste disturbance. Perhaps surprisingly, post-RT taste disturbance is *not* strongly influenced by the degree of hyposalivation and certainly the general improvement in post-RT taste dysfunction contrasts with the lack of resolution of RT-induced xerostomia.

Patients who have received RT often describe food as tasting 'soapy', 'burning', 'oily', 'powdery', 'chemical' and/or 'awful'. Patients receiving chemotherapy can also experience taste dysfunction. Any disturbance in taste sensation is likely ultimately to affect the nature and constituents of a patient's diet, resulting in anorexia, reduced food intake, weight loss, and potentially poorer treatment outcomes. This can lead to reduced calorie intake, a change to a more sugary cariogenic diet, and/or reduced quality of life.

Prevention and management of taste disturbances

Amifostine has been suggested to reduce RT-associated taste disturbance. IMRT and image guided radiotherapy (IGRT) might also be expected to lessen the risk of taste dysfunction.

The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE 3.0) and the Subjective Total Taste Acuity (STTA) scales provide patient-reported scoring of perceived taste dysfunction. Subjective assessments include gustometry and electrogustometry, although only the former permits examination of all five taste cues. Objective assessments include testing with tasty substances such as sugar, salt, lemon and vinegar; gustatory evoked potentials; functional Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET).

Management of taste disturbances is variably effective. Dietary counselling and modification by the addition of seasoning, avoidance of unpleasant foods and extending dietary choice may be of potential benefit. It was suggested that zinc sulphate could reduce the severity and duration of post-RT taste dysfunction but a randomized controlled trial failed to confirm reliable benefit.

There thus remains no proven effective means of preventing or treating taste disturbances which, fortunately, are usually temporary only.