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Review

Taste disorders in cancer patients: Pathogenesis, and approach to assessment and management

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SUMMARY

Taste dysfunction in cancer patients impacts quality of life and impairs oral intake, which may have broader implications consisting of weight loss and nutritional compromise. These consequences may in turn affect broad symptom clusters including tissue healing, energy levels and mood. Patient evaluation and management should include a complete patient history and examination, and may require special tests. Patient-reported outcomes together with taste and smell testing are often necessary for diagnosis and management of taste disorders. Understanding, prevention and management of taste disorders in cancer patients requires continuing study. Current practice and recommendations are based on limited evidence. Due to its potentially significant impact on quality of life during and following cytotoxic therapy, and considering the increase in cancer survivorship, further research on this topic is imperative.

Introduction

Taste is an important sensation that serves to evaluate the nutritious content of food, support oral intake and prevent ingestion of potentially toxic substances. It is commonly used to describe pleasure associated with food consumption and is related to several sensations including tactile (texture), temperature, and smell that are perceived when placing a substance in the mouth. Taste is comprised of five basic qualities: sweet, bitter, salty, sour and umami.[1] This latter quality is associated with desirable flavor associated with interest or pleasure. There is redundancy in taste as a basic sensation that protects the host from ingestion of toxins, which are often associated with a bitter or sour flavor.

Taste disorders are common in cancer patients who may experience taste loss (ageusia), alteration (dysgeusia), or heightened sensitivity (hypergeusia). The potential impact in this population includes reduced interest in food resulting in decreased oral intake that may lead to nutritional compromise and weight loss. Taste disorders may also affect use of topical oral products as well as impair quality of life. In this article, we review the literature that addresses taste changes in cancer patients and review guidelines for prevention, diagnosis and treatment of taste disorders in this population.

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Taste function

Taste is mediated by specialised epithelial cells distributed throughout the oral cavity, oropharynx, larynx and upper third of the esophagus. On the tongue, taste buds are located on the foliate and circumvallate papillae, each comprised of 50–100 taste-receptors that have a lifespan of approximately ten days. Greater taste sensitivity is present near the tip and the posterior aspect of the tongue. While prior animal models have shown taste mapping on the tongue, no segregation of taste qualities has been mapped in humans where taste-receptors appear to be pluripotent[2–4] (Table 1).

Stimulation occurs when a ligand binds to the extracellular domain of a taste receptor, leading to activation of G proteins (gustducin, phospholipase C and hydrolysis of phosphatidylinositol-4,5-biphsophonate), generating second messengers (inositol-1,4,5-triphosphate and diacylglycerol) and gating of transient receptor protein M5 (TRPM5) ion channels which leads to nerve depolarisation.[4] From the taste buds, sensory afferents in cranial nerves V (trigeminal), VII (facial), IX (glossopharyngeal) and X (vagus) project to the rostral aspects of the solitary tract of the medulla and via the thalamus to the post-central gyrus-facial area and olfactory cortex.[3] Taste from the anterior 2/3 of the tongue is transmitted by the chorda tympani nerve (cranial nerve VII), and the lingual branch of the trigeminal nerve. The posterior third of the tongue, oropharynx, and esophagus are innervated by the glossopharyngeal and vagus nerves.

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Table 1
Taste sensation.

Taste	Function	Receptor
Sweet (sugar)	Energy rich nutrients; calories	T1R 1,2,3; T2R
Sour (acid)	Noxious/poisonous agents	Acid sensing proton channel
Bitter	Toxic/noxious/ poisonous agents	
Salt	Electrolyte balance	Na, K, Cl channels
Umami (monosodium glutamate; aspartate)	Amino acids: enjoyment/pleasure	T1R 1,2,3; T2R

Taste disorders

There has been limited study of taste disorders in oncology. Often patients may be unaware of taste change and not report these complaints,[5] and taste alterations may go unrecognized, particularly if specific testing is not conducted. While quantitative taste disorders are difficult to recognize, complete loss of function or abnormal function are more readily identified. Changes in taste intensity, loss or abnormality may be assessed with patient-reported outcomes (PRO). Dysgeusia may present as a variety of complaints including metallic, bitter, sour, salty or, more rarely, sweet taste that may be triggered, reduced or not affected by eating. The NCI CTCAE 3.0 provides a patient-reported scoring of perceived taste dysfunction as part of adverse event reporting (Table 2).

Impact of local factors on taste

Hyposalivation may affect taste as saliva dissolves food particles allowing presentation of tastants to the receptors. However, the impact of hyposalivation upon taste in cancer patients is not clear due to conflicting evidence in the literature.[6–9]

Other local oral conditions such as regional pathosis or damage to cranial nerves subserving taste may also lead to gustatory changes. Similarly, oral hygiene, dental and periodontal disease, mucosal infection and diet may affect taste. Infection and other diseases in the upper aerodigestive tract may lead to taste and smell alterations. In addition, changes in touch and temperature sensation mediated by the trigeminal nerve, and smell mediated by the olfactory nerve may alter taste perception. For cancer patients, oral infections associated with therapy include candidiasis and other fungal diseases, rampant dental and periodontal disease and herpes viridae reactivation.

Malignant disease in the head and neck may cause taste alterations. Patients with upper aerodigestive tract cancer, tissue necrosis, oral bleeding and/or post-surgical wounds commonly have taste disturbances.[10] Head and neck cancer (HNC) patients treated with radiotherapy may experience alteration or complete loss of smell depending on treatment fields and change in olfaction may affect taste. This change may be caused by the tumor or by tissue necrosis or infection, blockage of the nostrils or the cribiform plate or direct impact of radiation upon receptors. Patients will often report anosmia, altered smell, or loss of odor discrimination often with incomplete recovery after therapy.[13]

Impact of systemic and central factors on taste

Taste disorders occasionally represent signs of potentially life-threatening conditions including central nervous system (CNS) tumors, lung cancer, or severe anemia. Tumors that involve the CNS at the ponto-cerebellar angle may lead to taste change, as do tumors involving the middle ear, such as cholesteatoma.[11] Paraneoplastic syndromes may also cause altered taste including reports of sweet sensitivity.[12] Lesions of the CNS may result in unilateral or bilateral taste loss.[5,14]

Co-morbid conditions that may impact taste include cerbrovascular accidents, Bell's palsy and Ramsay–Hunt syndrome.[5,14] Degenerative neurologic conditions including Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, myasthenia gravis, and multiple sclerosis (MS) may affect taste and smell.[15–17] Similarly, metabolic diseases may influence taste, including diabetes mellitus, hepatitis/liver failure and renal disease.[18]

Impact of cancer therapy upon taste

Systemic medications are common causes of taste disorders. Many drugs, including cancer chemotherapeutics are secreted in saliva and gain direct contact with taste-receptors. Patients may

Table 2
Taste evaluation.

Subjective: patient report	
CTCAE v3.0 criteria	
Score	Taste alteration (dysgeusia)
Grade 0	None
Grade 1	Altered taste but no change in diet
Grade 2	Altered taste with change in diet (e.g. oral supplements); noxious or unpleasant taste; loss of taste
Grade 3	–
Grade 4	–
Scale of Subjective Total Taste Acuity (STTA)	
Grade 0	Same taste acuity as before treatment
Grade 1	Mild loss of taste acuity, but not inconvenient in daily life
Grade 2	Moderate loss of taste acuity, and sometimes inconvenient in daily life
Grade 3	Severe loss of taste acuity, and frequently inconvenient in daily life
Grade 4	Almost complete or complete loss of taste acuity
Quality of life scales	
Taste testing	
Chemical gustometry	
Solutions applied via drops, paper disks, swabs	
Detection of the lowest concentration (threshold)	
Supra-threshold concentrations also used	
Electrogustometry	
Recognition of electrical change – but does not define taste quality	
Imaging: PET, Functional MRI	

Table 3
Prevention and management of taste change.

Preventive approaches
Radioprotectants (impact poorly defined)
Amifostine suggested to be useful: taste receptor protection; reduced hyposalivation
Radiation treatment planning: sparing of sites of taste-receptors; reduced hyposalivation
IMRT and tomotherapy
Therapy for taste change
Dietary counseling/modification
Add seasoning, avoid unpleasant foods, extend dietary choice (pleasing colour, form, smell)
manage hyposalivation
Diagnose/mnage oral disease
Diagnosis/manage gastrointestional, upper aerodigestive tract disease
Rule out potentially related systemic disease
Zinc sulphate supplimentation

experience metallic or "chemical" taste when chemotherapy is delivered, which is consistent with drug secretion in saliva. Dysgeusia may persist after drug clearance, due to damage to the taste buds.[19]

Taste disorders may occur following surgical procedures for HNC, dental treatment, ear, nose and throat procedures, particularly if surgery or administration of local anesthesia traumatize nerves associated with taste.[20] These may include the lingual branch of the glossopharyngeal nerve or the chorda tympani.[17,20] Middle ear surgery may also lead to damage to the chorda tympani. Invasive diagnostic procedures of the upper airway, particularly rigid endoscopy may lead to transient taste disturbances in approximately 10% of patients.[21] In such cases, post-surgical taste changes are ipsilateral to the procedure and may resolve without treatment. Under-reporting of taste disturbances may reflect redundancy in taste sensation, as well as the bilateral taste function that obscures unilateral post-surgical change, but can be detected with specific testing.

Taste disorders are present in the majority of HNC patients undergoing radiation therapy (RT) as well as in cancer patients receiving chemotherapy (CT). In the former group, taste complaints have been reported in 75–100%.[9,10,22] Taste complaints are often present prior to treatment due to the malignancy. One review suggests that up to 89% of patients prior to RT have some taste disturbance.[23] Subjective assessment prior to RT shows alteration of bitter (35%), salt (18%) and/or sweet (6%) sensation.[24] RT to the head and neck commonly impacts saliva production and taste receptor function, typically after 10–14 days of treatment, consistent with the taste receptor turnover. Following RT, taste may recover within several months of resolution of mucosal damage. However, taste change may remain due to hyposalivation and receptor damage. Antibiotics may contribute to taste change due to a shift in normal oral flora. In oncology patients, multiple causes of taste change may be present.

All four basic tastes and umami are affected during RT to the oral cavity.[22] Sweet sensation is typically lost first, resulting in reports of increased bitter and salt taste, followed by general abnormal taste and reduction in taste acuity.[9,22–28] A prospective study of 52 HNC patients assessed taste loss by threshold testing for umami using whole-mouth rinsing. Umami declined in the 3rd week of RT and improved by the 8th week. Another study found umami loss in approximately half of patients early in the course of RT, and all patients were affected by the end of the treatment.[22] Loss of umami taste may be important in oral intake because it affects interest in eating (enjoyment, pleasure) and may have the strongest correlation with quality of life.[27] Taste dysfunction was not associated with mucositis or its treatment. As summarized above, persistent taste change has been assessed in QOL studies and along with hyposalivation is a common HNC patient complaint.

RT can lead to direct damage to taste-receptors, synaptic uncoupling, and other possible neurologic damage.[29,30] In addition, radiation typically causes hyposalivation, thus reducing delivery of molecules to receptor sites, and reducing exposure of receptors to salivary-delivered growth factors. Post-treatment recovery of taste is variable, in some studies improving in 2–6 months following cancer therapy, but may continue indefinitely.[23,28,30,31] RT-associated taste changes are highly variable and have been described as: soapy, burning, oily, powdery, chemical, reduced or absent, or "awful".[9,28–32] Parotid sparing IMRT has been associated with more consistent recovery in eating, which may reflect improvement in maintenance of both salivary secretion and taste following head and neck cancer therapy.[32]

In one study, patients with HNC who had completed RT more than 6 months earlier reported dry mouth (92%) and change in taste (75%) as the most common symptoms.[33] Another study found physical functioning, taste/smell, dry mouth and sticky saliva significantly altered up to 3 years following RT.[34] A small prospective study of naso-pharyngeal cancer patients assessed before and up to 24 months following treatment reported poorer overall health, fatigue, loss of appetite, and dysphagia (all $P \leqslant 0.01$), xerostomia ($P \leqslant 0.001$), taste change, dental problems (both $P < 0.05$), pain and altered emotional function ($P < 0.005$)[35].

The temporal pattern of taste loss is variable however, few studies conducted specific taste testing or accounted for differences in cancer therapy.[24] According to these studies, taste recovery may be seen by six months post-therapy.[9,26,31] However, long term follow-up of head and neck cancer patients has shown taste disturbances persisting up to 7 years in those treated with RT.[25]

Taste changes in CT-treated patients with solid tumors require further exploration.[10,36] Breast cancer patients receiving adjuvant CT frequently report taste complaints.[36] Altered taste was reported during treatment (metallic or drug taste 33% and hypogeusia 22%) and symptoms persisted at six months in 20% and at 12 months in 16% of patients. Dysgeusia was the most distressing symptom reported by 22% of the patients during therapy and by 10% at one year follow-up.[36]

Taste has received limited evaluation in hematopoietic stem cell transplant (HSCT) patients. Symptoms including dry mouth and taste alteration are common following induction CT.[10,37,38] Graft-versus-host disease (GVHD) has also been associated with hyposalivation, mucosal lesions and taste change.[10,38] Taste and smell dysfunction as well as nausea impact appetite and affect desire for food intake that may lead to nutritional compromise and weight loss. Persistent salty and sour taste has been reported in HSCT patients following treatment.[39] Other studies report taste recovery in this population after one year.[40]

Patient evaluation

Patient evaluation requires a history of the complaint, medication and nutritional supplement intake, a thorough past medical history, oral intake or habits and recent medical or dental management. The patient should be queried regarding onset of symptoms (sudden or gradual) and their progression, precipitating event and/or treatment. Other potentially related symptoms including smell changes and co-morbidities including tobacco, alcohol, and exposure to medications or toxins should be identified. Other helpful questions include: Is there a relationship in time to delivery of CT and/or RT? Is the taste of food altered or the taste in the mouth changed? What is the nature of the taste change: can salt, sour, sweet and bitter be distinguished? Attention should be given to neurological symptoms that may lead to the need for imaging of

the region, including assessment of such conditions as dental disease, sinus problems, and CNS disease.

A detailed head and neck and oral examination should be conducted to detect possible local/regional pathology. Head and neck examination should include assessment of cervical lymph nodes, salivary glands, and cranial nerve function. Oral examination should assess the mucosa, teeth and periodontium, oral hygiene, and oro- naso-pharyngeal status. Taste bud density can be assessed with methylene blue staining of the dorsal tongue (the buds remain blue after rinsing off the tissue stain). Salivary flow rates should be assessed. Palatal movement and gag reflex indicate glossopharyngeal nerve integrity. Otologic examination may include middle and external ear examination and a hearing test. Further neurological examination should include cranial nerves sensory and motor function and, if indicated psychiatric evaluation.

Olfactory testing

Threshold detection of the lowest concentration of an odorant can be conducted. Phenyl–ethyl alcohol or butyl alcohol (1–4%) and water in different sniff bottles are presented from low to high concentration until detection occurs. Commercial kits are available in squeeze bottles, felt-pens or "scratch and sniff" formats. Odor identification tests are typically provided at supra-threshold levels and may have better quantity-related sensitivity. The Connecticut Odor Identification test presents 10 odorants that commonly include: baby powder, chocolate, cinnamon, coffee, mothballs, peanut butter and soap. A more commonly used but similar method is the University of Pennsylvania Identification Test (UPSIT) (Sensonics, Inc., Haddon Heights, NJ).[41] This is a "scratch and sniff" card with 10 odorants, for which norms have been established. Alternatively, an abbreviated test with 4 odorants is available.[42]

Taste testing

Whole-mouth testing and spatial taste testing can be conducted. The former is performed by applying the tastant as an oral rinse followed by thorough water rinsing. Spatial taste testing is conducted by localized application of specific tastants to various areas of the mouth. Filter paper of standard sizes can be soaked with the stimulus and applied randomly on the tongue and the soft palate or cotton-tipped applicators or eye droppers can also be used to deliver the tastant.[42,43] Differentiation of true taste disorders from phantom taste can be assessed by using local anesthetic. Application of topical lidocaine can eliminate sensation by a tastant and interfere with local causes of taste dysfunction. If no changes are detected following such application, the taste disturbance is likely of central origin and CNS imaging studies may be indicated.

Taste threshold or supra-threshold testing can be conducted.[43] The five fundamental taste sensations can be tested: sour (citric acid), sweet (glucose), salt (sodium chloride), bitter (guanine or local anesthetic) and umami (monosodium glutamate). Recommended concentrations of tastants are sucrose 300 mg/ml; citric acid 60 mg/ml; sodium chloride 80 mg/ml; guanine 20 mg/ml. Umami is typically assessed by taste recognition threshold using 10 ml monosodium glutamate whole-mouth rinses (25, 50, 75 and 100 mM)[22,44] The mouth is first rinsed with distilled water, then increasing concentrations of MSG are provided until taste is detected.

Spatial taste testing can be conducted by applying the test solution with a dropper or impregnated strips using four concentrations of each taste and two blanks. This process requires approximately 8 min and provides the opportunity to test both sides of the tongue separately. This approach has provided reproducible results in 69 subjects.[45] Electrogustometry consists of application of a weak electric oral stimulus that produces a sour taste.[46,47]

Laboratory testing

Laboratory investigations of anemia, vitamin B12, folate, glucose, thyroid hormone, electrolytes, renal function, hepatic function, autoimmune disease may become necessary in selected cases. Microbial culture may also be indicated to assess bacterial or fungal infection.

Prevention and management of taste disorders (Table 3)

Specific conditions related to taste dysfunction such as hyposalivation, poor oral hygiene, use of tobacco products and/or alcohol has relatively simple solutions. Discontinuing the etiologic habit, chewing sugarless gum or candy for taste and salivary stimulation or prescribing sialogogue can be used for individuals with residual salivary gland function. Chewing gum or candy may also cover unpleasant taste and provide symptomatic relief. Patients should be counseled to increase taste or flavor of food by adding seasoning or rotating their diet.[48]

In selected cases, modification of cancer therapy may be possible. In HNC patients, radiation fields that avoid exposure to critical sites for taste can be chosen when not detrimental to tumor management. Advances in radiation therapy, including intensity modulated radiotherapy (IMRT) and image guided radiotherapy (IGRT-tomotherapy) can spare high dose exposure of salivary glands and taste-receptors in part of the oropharynx,[32] although wider regions of low dose RT exposure occur. The impact of IMRT or IGRT upon taste function has not been adequately studied. Radioprotectors such as amifostine can also contribute to taste maintenance, either directly through taste bud protection or indirectly by salivary gland protection.[49–52]

Zinc supplementation has shown variable results in studies of RT HNC patients. Zinc sulphate (45 mg tid) was compared to placebo during RT in 18 patients and improvement in taste was seen in those on zinc based upon whole-mouth threshold taste testing.[53] Another trial compared zinc sulphate (45 mg/day) versus placebo in 169 patients during RT, and found fewer patients in the zinc group reporting taste change (73% vs. 84%; $P = 0.16$).[28] Zinc supplements may be considered in patients with persisting taste complaints.[23]

Clonazepam, which has been used in management of neuropathic oral conditions, including burning mouth syndrome was also reported to reduce taste and smell complaints.[54,55] Based on these anecdotal publications, the impact of clonazepam in cancer patients with taste complaints should be further explored.

Necrotic tumors present with smell and taste changes that may be secondary to Gram-negative bacterial overgrowth. In such cases, use of topical antiseptics (e.g. chlorhexidine gluconate), or systemic antimicrobials (e.g. metronidazole) may be considered.

Conclusion

Cancer can significantly affect taste sensation, either due to the disease itself or, more commonly, by effects of cancer therapies. These effects can be of central and/or peripheral origin and are often challenging to diagnose. Despite potentially morbid consequences, taste disturbances in cancer patients and their possible treatments have not been sufficiently studied.

Conflicts of interest statement

None declared.

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