Received: 25 June 2024 | Revised: 3 July 2024 | Accepted: 9 July 2024

DOI: 10.1111/odi.15074

INVITED REVIEW

WILEY

Head and neck complications of cancer therapies: taste and smell

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Abstract

Sensory deficits affect awareness of the environment and information processing, leading to dysfunction that may have significant consequences. Deterioration of taste and/or smell sensation has been linked to impaired nutritional intake, and overall decreased quality of life (QoL). Recent data suggest that loss of these senses is also associated with cognitive decline and worse overall cancer treatment prognosis. Cancer therapies have commonly been associated with sensory deterioration. We review these associations with taste and smell in light of new findings and discuss potential prophylactic and therapeutic modalities for taste and smell function.

KEYWORDS
cancer, chemotherapy, radiation, smell, taste

1 | INTRODUCTION

A broad variety of medical conditions and iatrogenic factors have been shown to affect taste and smell, most of them temporarily. More than 200 drugs and supplements have been reported to produce dysgeusia (Bromley & Doty, 2015; Wang et al., 2017). Normal aging has been associated with gradual onset of dysgeusia/ageusia and anosmia, although recent data have shown no direct age correlation (Egan, 2024; Hur et al., 2018; Culen & Leopold, 1999). Taste and smell dysfunction may be present in many chronic conditions such as diabetes, renal disease, and Parkinson's disease, and with many medications including some used for oncology care (Ciancio, 2004; Doty, 2015; Epstein & Barasch, 2010; Ponticelli et al., 2017).

Cancer patients undergoing cytoreductive therapy represent a distinct population in which taste and smell are potentially affected by numerous factors such as regimen-related mucosal damage, therapeutic and supportive medications, and alterations of the oral and gastrointestinal microbiome (Doty, 2015; Ponticelli et al., 2017; Scordo et al., 2018; Steinbach et al., 2009). Targeted antineoplastic treatments have also been reported to affect these senses (Albiges et al., 2020), as have immune checkpoint inhibitors (Al-Eryani et al., 2024). The prevalence of taste and smell disorders in cancer patients under treatment for their disease has been reported between 20% and 100%, largely dependent on the specific therapy (Sevryugin et al., 2021). Hormone therapy also has a potential impact upon taste and smell (Di Meglio et al., 2022). Dysgeusia has been shown in a cross-sectional study to be present in up to half of patients on chemotherapy and has been associated with diarrhea, anorexia, oral mucositis, nausea, constipation, vomiting, fatigue, and risk of death (Silva et al., 2024). It is important to note that the severity of chemosensory decline in hospice cancer patients has been associated with the time of death (Hutton et al., 2007).

Despite being one of the most frequently experienced cancer treatment-related side effects, taste and smell have not been extensively studied in this context, and articles in the peer-reviewed literature have described heterogenous populations and clinical characteristics (Ciancio, 2004). In the current article, we review the extant evidence on the effects of cancer therapies on taste and smell and suggest areas of future exploration.

2 | PHYSIOLOGY OF TASTE AND SMELL

The vernacular meaning of the word "taste" is akin to "flavor," which in turn is a composite of sensations from several chemosensory systems during eating, including olfaction, taste, oral somatosensation (e.g., spiciness, texture, and temperature), as well as hearing and vision (Deems et al., 1991; Epstein & Barasch, 2010). Thus, patient's

complaints about taste loss are complex and do not necessarily reflect the underlying pathology.

The sense of taste (gustation) derives from afferent information received from the oral cavity and oropharynx and is typically perceived after exposure of oral sensory cells to tastants. It comprises five known basic qualities: sweet, bitter, salty, sour, and umami (savory, activated by monosodium glutamate) (Chaudhari et al., 2000). Additional taste qualities have been proposed, including fat "taste" that may be mediated by receptor transduction and non-specific transport across the cell membrane (Doty, 2019; Hummel et al., 1997; Matsuo, 2000), and spicy "sensation" (e.g., capsaicin) mediated by small nerve fibers. Other receptors may be activated in *Kokumi* taste, which enhances additional flavor sensations. A water/fluid receptor has also been described (Zocchi et al., 2017).

Taste-receptor cells are abundant in the taste buds on tongue papillae and other mucosal sites, primarily within the oral cavity, but they are also found in numerous extraoral sites including the nose, esophagus, stomach, pancreas, and lungs. The gustatory system is highly redundant, with bilateral distribution and transmission along multiple cranial nerves. It is currently accepted that in humans the entire tongue perceives each of the taste qualities. Nevertheless, there are areas, such as the tip and the rear of the oral tongue that display higher taste sensibilities (Egan, 2024).

The sense of smell relies on 6–10 million ciliated bipolar receptor cells located in a specialized neuroepithelium spanning the cribriform plate and sectors of the superior and middle turbinates of the nose. Nearly 400 different types of receptor proteins are located on these cilia, with a given cell expressing only one type of receptor. In general, a specific smell sensation depends upon a combination of the activity of subsets of these receptor cells. Analogous to the taste receptors, these receptors are not confined to the olfactory epithelium, but are found in other regions of the body, including the lung, intestine, skin, and heart. Bundles of axons from the olfactory receptor cells course into the brain via the cribriform plate of the ethmoid bone, making their first contacts within the olfactory bulb, from which information is passed to higher brain structures.

2.1 | Types of taste and smell disorders

There are several ways of classifying taste and smell disorders. The method most commonly applied in clinical practice is to distinguish qualitative from quantitative disturbances (Hutton et al., 2007; Welge-Lüssen et al., 2011). For taste, these disturbances are as follows:

- Dysgeusia: the general terminology for any kind of taste disorder.
- Parageusia: qualitative taste impairment, which delineates a triggered taste distortion (e.g., bitter, metallic, or other taste perception occurs with eating/drinking).
- Phantogeusia: qualitative taste impairment, which delineates a non-triggered, permanent, or intermittent taste distortion.
- Hypogeusia: a quantitative taste disturbance producing reduced taste function.
- Ageusia: a quantitative taste disturbance producing absence of taste.

Smell disorders are classified in parallel fashion using the terms dysosmia, parosmia, phantosmia, hyposmia (sometimes termed microsmia), and anosmia.

A number of factors can impact such symptoms, with the exception of ageusia and anosmia. In the case of taste, these include the intake of liquids, foods, and medications, and hormonal imbalances.

These quantitative and qualitative disorders can occur together or alone (e.g., a patient with bitter parageusia can have a normal or altered measured taste function). Importantly, genetics may be involved in some cases. For example, expression of the T2R40 gene is significantly reduced in many persons with hypogeusia (Onoda et al., 2011), whereas it is elevated in many of those with Phantogeusia (Hirai et al., 2012).

2.2 | Etiology of taste disorders

A broad variety of causes may produce taste disorders. For many of those, mechanistic processes await elucidation. Sensory disorders may accompany classic neurologic diseases, such as stroke or peripheral nerve lesions.

Alterations in taste perception can be an early symptom of significant or life-threatening illness including amyotrophic lateral sclerosis, multiple sclerosis, lung cancer, myasthenia gravis, or coronavirus disease (COVID-19) (Boscolo-Rizzo et al., 2020; Heckmann et al., 2003, 2005; Leon-Sarmiento et al., 2013; Petzold et al., 2023; Qiu et al., 2020; Sharetts et al., 2024; Tong et al., 2020), although a number of such cases reflect smell, rather than taste loss (Doty, 2015; Leon-Sarmiento et al., 2013; Sharetts et al., 2024). In fact, over 90% of patients coming to taste and smell disorder clinics with complaints of taste loss actually have smell loss and intact taste (Deems et al., 1991). Importantly, a significant number of taste complaints are due to medications, including cardiovascular medications such as ACE-2 inhibitors (Doty et al., 2003).

Although upper respiratory tract infections classically lead to olfactory dysfunction, taste function may also be compromised (Heckmann et al., 2005). In many instances, such taste disorders are transient and reversible. Chronic middle ear infections and inflammation may also affect afferent taste fibers of the chorda tympani (Heckmann et al., 2003).

Altered gustatory function may arise secondary to surgery if the procedures are close to or affect the afferent neural pathways. Surgical etiologies are among the most frequently encountered in specialized smell and taste disorder outpatient clinics (Deems et al., 1991;Kveton & Bartoshuk, 1994; Landis et al., 2005).

Procedures that may be complicated by postsurgical taste distortions or ageusia include:

- Dental: procedures involving the mandibular teeth located in inferior alveolar and/or lingual nerve proximity (Heiser et al., 2012).
- Tonsillectomy (approximately 35% of patients report transient taste disorders directly after tonsillectomy) (Kveton & Bartoshuk, 1994; Landis et al., 2005).
- Middle ear surgery (Heckmann et al., 2005).
- Upper airway endoscopy (Kveton & Bartoshuk, 1994).
- Maxillofacial and cranial surgery (Klasser et al., 2008; Landis et al., 2007).

Paradoxically, persons who have had third molar extractions years before testing outperform those who have not had such extractions, conceivably reflecting long-term sensitization of CN VII nerve afferents or partial release of tonic inhibition exerted on CN IX by CN VII (Klasser et al., 2008). In such surgery, CN VII can be compromised given its close proximity to the retromolar pad.

2.3 | Etiology of smell disorders

Many of the same etiologies that influence taste function also impact the ability to smell. These impacts can result in permanent loss. Among common causes are as follows:

- Acute viral upper respiratory tract infections from coronaviruses, parainfluenza virus type 3, and such rhinoviruses as SARS-CoV-2.
- Head trauma from acceleration/deceleration of the brain, even from minor accidents such as hitting the back of the head from slipping on ice.
- Sinonasal diseases.
- Toxic exposures, including those from air pollution.
- Tumors within the nasal cavity as well as in the brain.
- Nasal and cranial facial surgeries.
- Autoimmune disorders (e.g., myasthenia gravis and Sjogren's syndrome).
- Neurodegenerative diseases (e.g., Alzheimer's and Parkinson's diseases).

2.4 | Taste and smell testing

Validated taste and smell tests are available commercially. Accurate taste testing can be easily performed using chemical or low microamp electrical taste tests (electrogustometry) (Malkoc et al., 2024; Matsuda et al., 2023). Chemical gustometry may be applied in drops to the tongue, by oral rinsing, or by technologies based on disposable taste strips. Electrogustometry involves stimulation of the tongue with brief pulses of current that trigger gustatory sensations, but rarely true taste qualities such as sweet (Doty et al., 2019; Kim & Doty, 2021; Malkoc et al., 2024). Nonetheless, electrogustometric thresholds correlate well with measures of sensitivity to all taste qualities. Recently, a 53-item self-administered taste test that requires no liquid stimuli or rinsing between trials was developed using disposable plastic strips containing dried tastants of various concentrations (Doty, 2019). Test scores are compared to age- and sex-related normative data from hundreds of subjects, allowing for both absolute (e.g., ageusia, hypogeusia, normogeusia) and relative percentile determinations of an individual's taste function (Doty, 2024).

The two most popular olfactory tests are those that measure odor identification and threshold tests (Doty, 2015, 2019). The most widely used test involves the presentation of a series of microencapsulated odorants (scratch and sniff), each accompanied by a list of four written alternative possibilities. A response is required even if no smell can be detected or identified (Doty et al., 1984). Based on the number of correct responses, the patient can be categorized as normosmic, mildly hyposmic, moderately hyposmic, severely hyposmic, or anosmic. Norms allow for percentile determinations of performance relative to subject's sex and age (Doty et al., 1984, 1995). Malingering can be detected based on the avoidance of correct answers beyond chance. Because familiarity with odors can be culture-specific, this test has been modified in content for different cultures.

Other popular tests determine the lowest concentration of an odorant that can be reliably perceived, that is, its detection threshold. Threshold tests are analogous to pure-tone threshold tests in audiology and are not influenced by familiarity with odors (Doty et al., 1995). A number has normative data similar to that available for olfactory tests (Doty, 2020). Although exceptions exist, most odor threshold tests are more time-consuming and less sensitive than odor identification tests. In general, the sensitivity and reliability of any olfactory test depends in large part on test length, with shorter tests being less reliable than longer ones (Doty et al., 1995).

2.5 | Chemotherapy

Cytotoxic pharmacological agents may directly damage epithelium, including taste buds and olfactory mucosa, as these tissues have a relatively high cellular turnover rate. Specific drugs may also cause neurotoxicity, hyposalivation, and mucosal inflammation. Microbiological changes in the oral cavity have been reported and may also contribute to gustatory dysfunction. There are conflicting data regarding which chemotherapy drugs are associated with higher prevalence of taste and smell disorders. In general, the effect is correlated with dose and duration of treatment (Boer et al., 2010; Epstein & Barasch, 2010; Spotten et al., 2017).

In hematopoietic stem cell transplantation (HSCT), patients treated with conditioning protocols typically receive high-dose chemotherapy. Specific regimens may also include total body irradiation (TBI). There is significant myelosuppression with resultant neutropenia, anemia, and thrombocytopenia in this patient population. Supportive therapy consisting of analgesics, anti-inflammatories, sedatives, antibiotics, and targeted drugs is also commonly used.

Post-transplantation graft-versus-host disease (GVHD) may significantly involve oropharyngeal tissues and saliva function. Additionally, management of GVHD may impact taste and smell. Hence, these senses may be adversely affected by both the cytotoxic treatment and by other oral complications such as infection, hyposalivation, GVHD, and/or mucositis (Boer et al., 2010; Haverman et al., 2014; Scordo et al., 2022; Shouval et al., 2020).

Chemotherapy-induced taste alterations, both objective and subjective, appear to peak during immune nadir. These alterations are also typically associated with the onset of oral and gastrointestinal mucositis (Hovan et al. 2010). These findings suggest a direct impact of the toxic drugs on the taste receptor cells. Indirect chemotherapy-associated contributors to sensory deficit may include oropharyngeal mucosal infections and saliva characteristics. In the case of the latter, higher drug concentrations in saliva correlate with increased subjective dysgeusia (Epstein & Barasch, 2010; Scordo et al., 2022). As most (oral) complications after HSCT develop in clusters, it remains difficult to identify the exact relations and causative mechanisms.

2.6 | Radiation therapy (RT)

Ionizing radiation is an integral part of many antineoplastic regimens, used both as a primary and an adjuvant therapy. It is a non-specific cytotoxic therapy used in both hematology and oncology. Cell killing is produced mostly by sublethal damage to the cell structure and nuclear contents, followed by apoptosis. The two main methods of radiation delivery are external beam (EBRT) and internal radiotherapy (Baskar et al., 2012; Wang et al., 2018). The latter includes radioactive implants and brachytherapy, whereas the former encompasses parallel ports, dimensional conformal radiotherapy (3DCRT), intensity modulated radiation therapy (IMRT), volumetric modulated arc therapy (VMAT), stereotactic body radiation therapy (SBRT), image-guided radiotherapy (IGRT), and particle therapy (PRT) (Moreno et al., 2019). In addition, radioactive iodine used in the treatment of thyroid cancer can impact saliva and taste function (Epstein & Barasch, 2010).

Radiation can directly damage taste buds, nerve cells, and salivary glands, especially when it is targeted to the head and neck. RT may alter the structure of taste pores, leading to a disrupted delivery of flavor molecules to receptor cells, or a thinning of the papilla epithelium. The hypotheses to explain irradiation-induced taste impairment include inflammation of afferent nerves that supply taste buds, direct damage to differentiated taste cells, and ablation of proliferating progenitors, preventing the renewal of taste cells. The loss of taste progenitor cells may result in a reduced recovery rate of damaged taste buds (Nguyen et al., 2012). By virtue of its production of reactive oxygen species (ROS), RT can also cause inflammatory cytotoxicity and neurotoxicity, which can further damage mucosal tissue (Koka et al., 2022). The addition of adjuvant chemotherapy for radiosensitization (chemo-RT) has been associated with increased severity of side effects, including taste and smell dysfunction (Epstein & Barasch, 2010).

Radiation-induced sensory deficits are dose and field related. Furthermore, taste symptoms have been associated with treatment modality (RT vs. chemo-RT), cumulative radiation dose, and past and current smoking status. Radiation hyperfractionation has been associated with an increased profile of side effects, including taste and smell, while SBRT, IGRT, IMRT, and PRT produced less dysgeusia but had no benefit on smell alteration. Currently, head and neck cancer RT is delivered via IMRT or IGRT while PRT is used mostly for recurrent tumors (Koka et al., 2022; Togni et al., 2021).

Generally, dysgeusia and dysosmia are reported starting in the 4th and 5th weeks of treatment when a dose of more than 40 Gy has been delivered to the tongue. Recovery of sensation may begin about 6 months post-therapy, but deficits may persist indefinitely, often for the rest of the patient's life. There are many discrepancies in the literature regarding which taste sensing is most affected by RT. This is likely due to heterogeneous methodology and differing variables between studies (Bardow et al., 2001; Togni et al., 2021).

2.7 | Saliva

Taste is an important stimulus for the production of saliva and in turn, saliva is necessary for the perception of taste. Saliva is the natural oral solvent for food components to reach the taste receptors. Salivary composition may also affect taste, as a specific tastant quality must be above normal saliva concentration to be perceived. Thus, alterations in both saliva quantity and quality can influence gustatory sensation. Saliva secretion is regulated by the autonomic nervous system pathways (Bardow et al., 2001).

Physiologic, pathologic, psychologic, and iatrogenic processes may interfere with salivary output and thus contribute to dysgeusia. Major salivary gland tumors will indubitably affect secretion. However, cancer therapies can produce profound alterations in both quantity and quality of saliva through pathologic, psychologic, and iatrogenic mechanisms (Vistoso Monreal et al., 2022).

Chemotherapy, immune therapy, and RT can impact salivary production. Numerous cytotoxic medications have a direct effect on the salivary glands, including anthracyclines, antimetabolites, and vinca alkaloids. These effects are usually reversible and of relatively short duration (Epstein & Barasch, 2010). By virtue of their immune mechanism, ICIs may affect many organs, including the salivary glands. This type of impairment typically manifests as a sicca syndrome associated with severe mouth and eye dryness and appears 3–6 months after treatment initiation. These effects may ameliorate after treatment cessation, but usually last a lifetime (Warner et al., 2019).

RT has a direct effect on the acinar cells of the serous parotid glands, which produce about 70% of the salivary volume. This may lead to permanent damage in patients receiving cumulative RT doses >40 Gy. The less pronounced effect on the mucous glands contributes to clinical detection of ropey, thick saliva responsible for dysphagia, nausea, and vomiting (Baskar et al., 2012; Moreno et al., 2019). Introduction of computer-aided technology in RT

delivery has contributed to a significant reduction in severity of side effects, including hyposalivation. Programs are built to spare the parotid glands to the extent possible (Koka et al., 2022). PRT has the lowest profile of deleterious effects on salivation (Deshpande et al., 2019).

Given its composition of enzymes and immune components (sIgA) saliva has both digestive and protective roles. Decreased salivation is associated with increased risk for malnutrition as well as oropharyngeal infectious processes. As described below, in the setting of hyposalivation infectious agents may have a detrimental effect on gustation and smell.

2.8 | Infection

Most non-specific chemotherapies affect the immune system. Some targeted therapies may also blunt the immune response. Between infusion of the transplant and engraftment, most HSCT patients go through a period of profound myelosuppression. Under normal conditions, the oral cavity is home to millions of microorganisms, so naturally, it is a common location for infection; microbial shifts may also occur due to therapy including antimicrobials (Spotten et al., 2017). Organism motility with gut flora may occur, in addition to nosocomial infection. In patients with mucositis, oral care is compromised, microbial load may increase, and microbial shifts occur (Epstein & Barasch, 2010; Scordo et al., 2022). Systemic spread of the infection is also possible. Some of these infections affect taste and smell sensations (Fluitman et al., 2021).

Opportunistic and/or commensal organisms may become pathogenic and produce local and/or systemic disease. Candida spp. are a prime example of this process. Oropharyngeal candidiasis is one of the most common infections diagnosed in cancer patients. While some authors have associated candidiasis with decreased taste, recent studies have found only a negative effect on smell (Fluitman et al., 2021).

Bacterial strains may accelerate dental caries or periodontal bone loss, and on rare occasions produce tissue necrosis. Overgrowth of anaerobic bacteria may produce an excess of sulfur-containing metabolites, which are responsible for halitosis and altered taste. In the setting of immune suppression, viral organisms, particularly those from the Herpesviridae, may produce local and severe atypical recurrent lesions. Herpetic recurrence may affect the mucosa of the dorsal tongue and destroy the existing taste buds. These sensory changes are typically transient and may dissipate with resolution of the infection.

2.9 | Other factors

Drugs used to treat complications of cancer therapy can also cause dysgeusia and dysosmia. Anticholinergic medications used to prevent or treat nausea, vomiting, and/or diarrhea have anti-sialogogue effects, as do tricyclic antidepressants, antihistamines, and opioid analgesics. Clinical depression is common in cancer patients and has been identified as a possible cause of dysgeusia and dysosmia (Amsterdam et al., 1987; Hur et al., 2018).

2.10 | Prevention and treatment

There is a dearth of prophylactic measures specific to chemosensory deficits. General prevention of injury to normal tissues includes those important to sensorial function, such as mucosa, nerves, salivary glands, and the immune system. Additionally, impeccable oral hygiene and appropriate dietary changes are common sense measures required for improved outcomes.

A number of protocols for prevention of mucositis have been described. Among these, cryotherapy, palifermin, superoxide scavengers, and photobiomodulation (PBM) (low-level laser or light therapy) have shown significant benefits (Barasch & Epstein, 2011). Acupuncture has limited data supporting utility in taste/smell management following cancer therapy (Kumbargere Nagraj et al., 2017; Thorne et al., 2015). While there is evidence that PBM can help protect salivary glands, taste buds, and nerves, and thus reduce gustatory damage (Malta et al., 2022), the influences of this treatment on human taste function remains enigmatic for several reasons. Data are limited, the quality of taste testing is questionable, and findings are variable. For example, in the case of COVID-19-related taste loss, one report of positive effects lacked a control group (Panhoca et al., 2023) and a better designed study found no significant influences of PBM on long-term COVID taste dysfunction (Cardoso Soares et al., 2023). A well-controlled recent study suggests that PBM therapy may minimize taste changes due to hematopoietic cell transplantation (Ferreira et al., 2024). Zinc and other nonpharmacological means have been tested with mixed results while amifostine delayed taste recovery in a radiation group (Hsieh et al., 2022; Kumbargere Nagraj et al., 2017; Thorne et al., 2015).

Over two dozen therapies for smell loss have been described in the literature (Doty, 2019). Although several are efficacious in specific instances (e.g., antibiotics for bacterial infections, corticosteroids for sinonasal inflammation), the vast majority fall short based on lack of strong evidence, double-blinding, appropriate control groups, and failures of replication. These include supplements using selenium, zinc sulfate, polaprezinc, alpha lipoic acid, turmeric, glutamine, glutathione, and lactoferrin, as well as the currently popular "smell training" intervention. In smell-training studies, drop-out rates—which likely reflect persons not experiencing improvement—are known to be high, although rarely reported. Two studies have suggested that PBM therapy improves smell function in patients with loss due to Alzheimer's disease (one subject) (Salehpour et al., 2019) or unreported causes (Panhoca et al., 2023). However, given the lack of double-blinding and untreated controls, these reports are unconvincing. It is well known that a significant number of persons regain considerable smell function over time independent of any intervening systematic therapies or treatments (London et al., 2008).

As detailed above, taste and smell alterations associated with cancer therapies have a complex etiology, which makes pinpointing a specific cause a daunting task. Nevertheless, identifying the most likely culprit(s) is of utmost importance when deciding what treatment is appropriate. Taste and smell changes in the setting of oral or nasal infection may be alleviated by antimicrobial therapy. Salivary hypofunction may respond to sialagogues like cevimeline and pilocarpine, positively impacting taste function. Neural damage may respond to neuromodulatory medications such as gabapentin, pregabalin, and clonazepam.

2.11 | Future directions

Taste and smell dysfunction is one of the most common complaints from patients under treatment for malignant diseases. Yet, there is a paucity of studies exploring both the mechanisms and potential therapeutics for these conditions. An initial study using genome-wide assessment to predict onset of dysgeusia may provide predictive testing for taste dysfunction and could become a tool to predict response to therapeutic trials (Cardoso Soares et al., 2023).

Moreover, the results of existing studies are often controversial or divergent. Gaps in the current literature include a notable lack of consideration of potential confounding, mediating, and moderating effects, as well as the potential complexity of symptom etiology.

Acquiring new data at the cellular and molecular level could clarify the pathways of therapy-induced sensory deficits and point toward targeted interventions. Clinical studies, in higher risk cancer therapies including radiation-induced sensory dysfunction, chemotherapy, targeted therapy, and immunotherapy protocols should examine the effects of combined preventive and therapeutic strategies covering the protection and regeneration of all cell types involved in taste and smell. In addition, developing more targeted cancer treatments that spare sensory neural components could avoid this type of complication. As our knowledge of the morbidity of sensory dysfunction develops, renewed exploration of this topic comes into focus and must be pursued.

Endpoints of future clinical studies should be clearly defined. In addition to patient-reported outcomes, future studies should incorporate well-validated objective taste and smell tests. While many studies are sophisticated in other ways, their use of unreliable tests that fail to control for response biases undermines their effectiveness. Oral assessment including mucosal health, saliva function, and oral hygiene should be assessed and considered covariables in all studies.

AUTHOR CONTRIBUTIONS

Andrei Barasch: Conceptualization; writing – original draft. **Joel B. Epstein:** Conceptualization; methodology; validation; writing – review and editing. **Richard L. Doty:** Conceptualization; validation; writing – review and editing.

CONFLICT OF INTEREST STATEMENT

All authors have no conflicts of interest to disclose.

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How to cite this article: Barasch, A., Epstein, J. B., & Doty, R. L. (2024). Head and neck complications of cancer therapies: taste and smell. *Oral Diseases*, *00*, 1–8. https://doi.org/10.1111/odi.15074