Supportive Care in Cancer
https://doi.org/10.1007/s00520-019-05232-y

ORIGINAL ARTICLE

Oral examination findings, taste and smell testing during and following head and neck cancer therapy

Joel B. Epstein [1,2,3] · Dana Villines [4] · Geena L. Epstein [1] · Gregory Smutzer [5]

Received: 16 July 2019 / Accepted: 5 December 2019

Abstract

Purpose Diet and nutrition are critical in health and disease and are highly impacted by the presence and treatment for head and neck cancer (HNC). The purpose of this paper is to present oral examination findings and taste and smell test results in patients during and following HNC.

Methods Patients with HNC were evaluated during and following radiation therapy with/without chemotherapy. Oral examination findings including mucositis, saliva, oral hygiene (plaque levels, gingivitis), and taste and smell testing was completed on all subjects. NCI Common Terminology Criteria for Adverse Events (CTCAE) 4.0, and the Scale of Subjective Total Taste Acuity (STTA) were used to provide patient report of symptoms.

Results Mucositis and pain affected oral diet during therapy and improved in follow-up. Weight loss of 5% during and 12% following treatment was identified. Tobacco use was associated with increased severity of mucositis and increased weight loss. The subjects maintained excellent oral hygiene as reflected in plaque levels and gingivitis. Spicy/pungent perception was the most strongly disliked of testing stimuli. *Umami* and fat taste perception were reported of highest intensity during HNC treatment and rated as moderate in intensity after treatment. These results suggest improvement in these taste functions over time following treatment. Salt taste was of high intensity and associated with strong dislike in follow-up.

Conclusions In HNC patients, oral status and taste change occurs throughout the cancer trajectory and represent potential concerns in cancer survivorship. Taste change (as evaluated by taste testing) occurred in all HNC patients, whereas olfactory changes occurred in 30% of cases. Management of oral changes and symptoms should be considered in all HNC patients in addition to dietary and nutritional guidance in patient care to promote oral intake. Continuing study of taste changes may further define this problem and support dietary and nutritional guidance and product development.

Keywords Oral and pharyngeal function · Head and cancer therapy · Gustation · Olfaction

Introduction

Head and neck cancer (HNC) and HNC treatment affects oral and pharyngeal functions that impact oral intake. Appetite is affected by taste and smell function, tactile stimulation, and awareness of flavor [1, 2]. Flavor is multidimensional and involves interactions of taste, touch, temperature, all of which requires saliva production, and smell. Anticipated or experience of flavor stimulates interest in eating and affects appetite. Eating is considered a social construct with sociocultural influences [3, 4].

Five primary taste qualities have been identified in humans that include salt, sweet, sour (acid), bitter, and savory (*umami*) [3, 4]. An additional taste quality is fat taste [5]. *Umami*, sweet, and bitter taste are detected by G protein–linked seven transmembrane domain receptors, while salt and sour taste are thought to be detected via membrane channels. Oral chemosensory responses also include trigeminal stimuli that activate transient receptor potential channels for detecting spicy sensation and cooling sensation via C-fiber signaling [6].

Dysgeusia (altered taste) may be caused by direct damage to the taste or olfactory systems, systemic disease, loss of

✉ Joel B. Epstein
joel_epstein@hotmail.com

1 Beverly Hills, CA, USA
2 Cedars-Sinai Medical Center, Los Angeles, CA, USA
3 City of Hope Comprehensive Cancer Center, Duarte, CA, USA
4 Department of Research, Advocate Health Care, Chicago, IL, USA
5 Department of Biology, Temple University, Philadelphia, PA 19122, USA

Published online: 07 January 2020

saliva production, and oropharyngeal conditions [4, 7–10]. Dysgeusia is commonly reported in HNC patients [1, 4, 11, 12]. In HNC, dysguesia may begin with mucosal damage due to cytotoxicity and neurotoxicity from radiation therapy and systemic medications [1, 4]. Chemotherapy (CT) may have cytotoxic effects on taste and smell via systemic distribution, and may have direct effects via secretion in saliva and gingival crevice fluid causing damage to mucosa and taste receptors [4, 13]. While taste receptors undergo constant turnover in the oral cavity, impaired taste bud cell proliferation, repair, and cytotoxicity may underlie taste changes associated with HNC treatment [1, 3, 4].

Sensory and hedonic factors contributing to altered flavor perception leading to diet modifications may be due to change in specific taste qualities [3]. For example, some HNC patients may experience a bitter or metallic taste that affects diet [13]. Taste changes negatively impact quality of life and contribute to increased morbidity [10, 14]. Taste changes have been reported to reduce treatment compliance [15], are associated with impaired immune function [14], altered food intake [14], and may cause social and emotional distress [1].

A recent report of HNC patients identified oral intake in subjects during a median of 44 months (range 7–198 months) post-radiation therapy (RT) with or without CT [16]. Only 28% of HNC survivors reported consuming a normal full diet. This study concluded that dysphagia and dental problems were significantly associated with maintaining a normal diet. Eating experience following HNC treatment is altered and the social impact of this alteration is documented [10, 16, 17].

Despite the general acceptance that oral and oropharyngeal function is frequently affected in HNC care, there is limited literature addressing oral health and taste function in oncology patients during and following cancer treatment. Potential multiple toxicities of cancer treatment including mucositis, saliva change, and oral hygiene have not been clinically assessed in relation to taste and smell function in HNC treatment. In this prospective study, we examined HNC patients in order to evaluate oropharyngeal health and its impact upon measures of taste and smell.

Methods

Ten patients were included in this study. Patients were evaluated during cancer treatment (4–6 weeks after starting treatment) and up to 2 years after treatment. Some patients had visits during and following treatment, while some completed one visit (either during or following treatment). The data collected during cancer treatment were defined as the acute treatment group ($N = 6$) and the data collected after treatment were defined as the post-treatment group ($N = 8$): four patients completed both visits, two patients completed the acute visit only and four patients completed the post-treatment visit only. Three patients completed early follow-up visits (within 3 months after therapy) and 5 completed follow-up visits after 3 months and up to 24 months post-treatment. All patients received intensity-modulated radiation therapy (IMRT) and 9 combined IMRT and platinum-based CT.

Enrollement criteria were patients age 18 or above with HNC who were scheduled to receive radiation therapy with/without platinum-based CT for up to 24 months following the completion of cancer treatment. Exclusion criteria included history of prior treatment for HNC, induction CT, and cancer involving more than 50% of the dorsal tongue surface.

Oral examination included mucosal examination and completion of the oral mucositis assessment scale (OMAS) [18] which is a validated mucositis scale that includes ulceration and erythema in eight areas of the oral mucosa at risk during treatment. This examination allowed a total score to be developed. This observational scale was completed by one examiner using standard halogen lighting and a dental mirror.

Oral hygiene was evaluated by assessing plaque scores (plaque index) and gingivitis score (gingivitis index) [19] using halogen lighting and dental examination instruments as part of routine dental examinations.

Unstimulated (resting) and stimulated saliva was assessed by saliva collection in pre-weighed plastic containers. Patients were seated with their back at a 70–90^{o} angle and asked to swallow the saliva in their mouth. They were then asked not to swallow again and spit any accumulated saliva into a pre-weighed cup every 30 s for 3 min (unstimulated flow). For measurement of stimulated saliva, patients followed the same procedure except that after the initial swallow, patients were given a pre-weighed piece of unflavored/un-powdered vinyl glove to chew and spit for 3 min. Containers (including pre-weighed with vinyl piece) were then re-weighed after collection and the salivary flow per minute was calculated. Due to variation in salivary function, all assessments occurred 1 h or more after breakfast or after lunch (e.g., at least 1 h after eating). No liquid was allowed for 30 min prior to collections.

Suprathreshold taste and olfactory testing was conducted to assess responses to stimuli that are above threshold for most individuals. Taste perception was assessed by two methods. One taste test used liquid taste stimuli presented in drops and the other used edible films that incorporated chemosensory stimuli [20]. Diluted "Cool Blue Gatorade" (The Gatorade Co, Chicago, IL) was used as a rinse between each tastant. Taste drops were applied by alternating between the left and right sides of the tongue midway between the tongue tip and circumvallate papillae. Taste strips composed of the polymers pullulan-hydroxypropyl methylcellulose dissolve rapidly on the tongue and provide a localized taste test for different oral sensations including fat taste and spicy/pungent perception. The aqueous test solutions and gradients were formulated using distilled water and the following constituents: sweet taste; 300 mg/ml sucrose, sour taste; 0.3 mg/ml citric acid, salt taste; 80 mg/ml NaCl and bitter taste; 0.06 mg/ml quinine HCl. *Umami* taste was identified by presenting 50 g/l solutions of L-monosodium glutamate (MSG). Edible taste strips were used for identifying *umami* (25.2 μmol MSG per one-inch square strip), fat (35 μmol of linoleic acid per strip), and spicy/pungent perception (5.0 nmol of capsaicin per strip).

Patients selected the taste experienced (taste recognition) from a table containing the words sweet, salty, bitter, sour, tasty (savory), and no taste. Patients were asked to rank the strength of the stimulus on a 7-point Likert scale, from none to strong. Patients also were asked to rate the "pleasantness" of the taste experience on a 7-point Likert scale. Olfactory function was assessed using the Smell Identification Test® (UPSIT), a 40-item forced-choice "scratch and sniff" test that is a standardized and validated test of smell function [21]. Smell tests were obtained from Sensonics Inc. (Haddonfield, NJ). Patient report of taste function was recorded using NCI Common Terminology Criteria for Adverse Events (CTCAE) 4.0, and the Scale of Subjective Total Taste Acuity (STTA). The CTCAE provides patient report of dry mouth as part of adverse event reporting; the STTA is a scoring tool to assess the overall acuity of taste, where zero reflects no change, and four represents almost complete loss of taste function [4].

Descriptive statistics are presented as counts and percentages for dichotomous and categorical variables, and as percentage of change for continuous variables (change from prior to the visit and at the visit). Western Institutional Review Board approval was obtained prior to study initiation (WIRB, Puyallup, WA) and informed consent was completed by all patients.

Results

Ten patients were enrolled: 7 male, 3 female (Table 1). All had Human Papilloma Virus (HPV) p16 positive squamous-cell carcinoma (SCC). Using AJCC 8th Edition, HPV Positive Staging, 5 patients were stage I, 4 were stage II, and 1 was stage III [22].

Table 1 Demographics of study participants

		$n = 10$	%
Gender	Male	7	70
	Female	3	30
Mean age (y)		59.9 ± 7.0	N/A
Ethnicity	Caucasian	8	80
	Hispanic	1	10
	Asian	1	10
Smoker	Current or former	3	30
Cancer location	SCC tonsil p16 positive	6	60
	Base of tongue p16 positive	3	30
	Oral tongue p16 positive	1	10

All patients were dentate without dentures. Oral hygiene, mucositis, and saliva production are shown in Table 2. Patients maintained good plaque control and presented low gingival inflammation during and after HNC treatment. The mucositis ulcer score and total mucositis score increased during treatment ($x = 0.86 \pm 0.37$ and 2.1 ± 0.45, respectively); and ulcerations were fully resolved by the post-treatment visits ($x = 0.0 \pm 0.0$) and total mucositis score decreased by approximately 85% ($x = 0.31 \pm 0.43$). Whole resting saliva (WRS) increased after treatment (acute $x = 1.54 \pm 1.76$ and post-treatment $x = 5.27 \pm 11.32$) while whole stimulated saliva (WSS) decreased slightly (acute $x = 3.19 \pm 3.56$ and post-treatment $x = 2.64 \pm 2.13$).

Three patients reported tobacco use (> 15 packs/year history), and social alcohol use (2–4 drinks/week) was reported by half of the patients. Oral hygiene was good in all patients and was similar for smokers and non-smokers (Table 2). Mucositis scores were higher in the smoking group ($x = 0.61 \pm 0.79$) than the non-smoking group ($x = 0.30 \pm 0.43$). Saliva production was higher in the non-smoking group (WRS $x = 4.43 \pm 10.30$; WSS $x = 3.26 \pm 3.17$) than in the smoking group (WRS $x = 0.90 \pm 0.52$; WSS $x = 1.47 \pm 1.53$). Smokers also lost more weight when compared to non-smokers ($x = 18.00 \pm 8.66$ and 11.30 ± 13.87, respectively).

As reported by subjects on the STTA, all smokers reported severe taste loss (two smokers in acute group and one smoker in post-group, Fig. 1) while only 9% of non-smokers reported a severe taste loss and 27% reported a moderate taste loss (two non-smokers in acute group and one non-smoker in post-group). Change in smell function was limited to three patients who reported decreased smell function during treatment but increased smell function following treatment.

Taste intensity and pleasantness testing results are shown in Table 3. Spicy/pungent perception yielded the strongest intensity and most strongly disliked of the stimuli. Subjects had the most frequent reaction to a spicy stimulation during treatment and follow-up. Bitter taste response was in the weak intensity range in the acute phase, but was most frequently reported as strong intensity in follow-up. Additionally, fat taste and sweet taste were most frequently reported as producing strong intensity during treatment. However, at follow-up, fat taste was most frequently reported as moderate, and sweet taste ranged from weak to strong intensity. Sweet was the only primary taste quality to receive a positive pleasantness (hedonic) rating as the most frequent response. Taste intensity and pleasantness testing via taste drops produced primarily neutral results as the most frequently reported taste with the exception of salt. Salt taste caused strong intensity responses in both groups, and was most frequently reported as extreme dislike in the follow-up group. Finally, body weight decreased an average of 5% during treatment and 12% at follow-up.

Table 2 Oral hygiene mucositis and saliva production by treatment and smoking groups

	Acute group ($n = 6$)	Post-treatment group ($n = 8$)	Non-smoker ($n = 11$)	Smoker ($n = 3$)
Plaque index	0.37 ± 0.54	0.41 ± 0.45	0.41 ± 0.57	0.30 ± 0.27
Gingival index	0.34 ± 0.43	0.45 ± 0.38	0.37 ± 0.42	0.54 ± 0.48
Mucositis ulcer score	0.86 ± 0.37	0.0 ± 0.0	0.30 ± 0.43	0.61 ± 0.79
Total mucositis score	2.1 ± 0.45	0.31 ± 0.43	0.86 ± 1.037	1.86 ± 0.55
Saliva WRS	1.54 ± 1.76	5.27 ± 11.32	4.43 ± 10.30	0.90 ± 0.52
Saliva WSS	3.19 ± 3.56	2.64 ± 2.13	3.26 ± 3.17	1.47 ± 1.53

Discussion

Acute complications of HNC treatment include mucositis, pain, taste change, dysphagia, aspiration, fatigue, nausea, limited jaw opening, decreased saliva output, and social and psychological effects including depression and isolation [23]. As mucositis resolves following treatment, chronic toxicities continue to impact oropharyngeal function. The impact of HNC treatment on taste is multifactorial and is expected to be compounded when RT and CT are provided [1, 4, 16, 23].

In a recent survey of HNC survivors, the most impactful symptoms following cancer treatment were dry mouth, difficulty swallowing, mucus secretion, taste change, and choking/coughing with eating [16]. This study concluded that dysphagia and problems with teeth/gums were significantly associated with maintaining a normal diet [16].

The current study provides supporting evidence that symptoms that affect food consumption differed between patients during treatment and following treatment; however, generalization of these findings are limited by the small sample size in this study. During treatment, throat pain and mouth/tongue pain due to mucositis affected two-thirds of patients, and pain was less impactful following HNC treatment. Evaluation and management of the oral conditions and modifications of diet and food product development are needed to address the trajectory of oral function during and following cancer therapy.

Saliva quantity and quality affect taste function [1]. Hyposalivation may limit saliva food-coating, mastication, and decreased food particle delivery to taste receptors [24]. Hyposalivation and viscous secretions also affect oral comfort, swallowing, and speech. Increased risk of local oropharyngeal mucosal infection (e.g., candidiasis) and increased plaque levels can affect taste and oral comfort. More viscous (mucus) secretion has impact upon taste as found in the current study and was previously reported [10]. Therefore, saliva quantity and quality should be assessed in HNC patients and managed when possible. Other studies state that saliva change based upon patient report, caused by cancer therapy may lead to taste loss [10, 16, 24, 25].

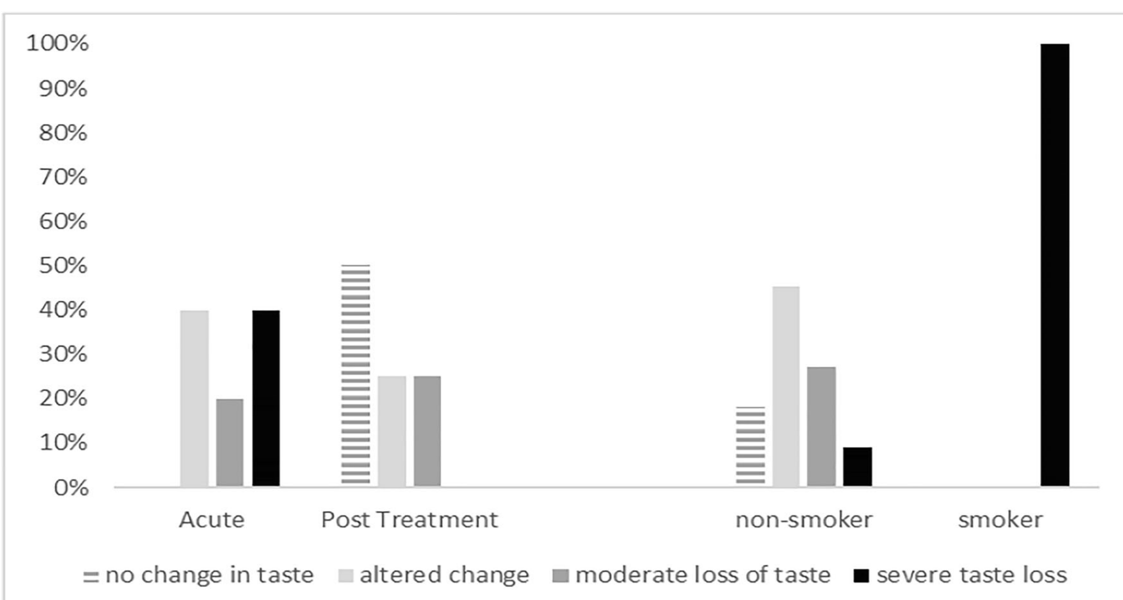

Fig. 1 Taste changes by treatment and smoking groups

Table 3 Most frequently reported flavor intensity and pleasantness for edible strip and drop testing

	Acute group ($n = 6$)	%	Post-group ($n = 4$)	%
Strip flavor—intensity				
Control	No taste	50	Barely detectable	50
Fatty	Strong	30	Moderate	50
Fatty control	No taste	70	No taste	75
Spicy	Strongest sensation	39	Strongest Sensation	50
Bitter	Weak	20	Strong	50
Sweet	Strong	30	(No mode)	–
Umami	Barely detectable	20	(No mode)	–
Strip flavor—pleasantness				
Control	Neutral	40	No taste	75
Fatty	Neutral	30	Dislike slightly	75
Fatty control	Neutral	70	Neutral	50
Spicy	Strongest dislike	30	Strongest dislike	50
Bitter	Neutral	20	Neutral	50
Sweet	Like somewhat	40	Like very much	50
Umami	Dislike somewhat	20	(No mode)	–
Drop flavor—intensity				
Salt	Very strong	30	Very strong	75
Sour	Neutral	30	Barely detectable	50
Sweet	Neutral	30	Moderate	50
Drop flavor—pleasantness				
Salt	Neutral	30	Extreme dislike	75
Sour	Neutral	60	Neutral	50
Sweet	No taste	50	(No mode)	–

"No mode" represents data with more than one mode

Taste change during RT and RT/CT, typically occurs concurrent with mucosal damage, which suggests damage to taste receptor cells in epithelial taste buds. Persisting change in taste may reflect decreased turnover rates of taste receptor cells, lack of connectivity between receptor cells and neurons, and possible neuronal damage. Physiological changes in the oral environment and loss of taste progenitor cells may result in decreased recovery of damaged or lost taste buds over time [2, 16, 25, 26]. Evaluation of recovery of taste function should be based upon taste testing, as it is unpredictable, and may never fully recover [10, 26–28].

In our current study, reduced saliva production was observed in 50% of patients in the post-treatment group. Taste change during RT/RT-CT was concurrent with mucositis that may reflect thinned/inflamed ulcerated mucosa and neuropathy (C-fiber activation) and atrophic mucosa and neuropathy that may continue post-treatment in half of subjects.

Along with taste, olfactory function contributes to the flavor of food. Smell function may be affected in HNC therapy, particularly when RT includes the nasopharynx and the olfactory bulb and with chemotherapy [1, 15]. Changed olfactory function was noted only 3 HNC patients, none of whom involved the nasopharynx, treated with RT and CT (33%) who were seen at 3 to 4 months after treatment.

As in the current study, all HNC patients in a prior report had moderate to severe taste disturbance and dry mouth. Some patients showed improvement in salivary production over time and with treatment [10]. Taste studies with electrogustometry have reported that taste qualities are affected with a high number of reported "no taste" or "abnormal taste" and a correlation between decreased sweet and increased sour taste [10, 29]. We identified similar findings in the current study. In our prior report [10], we found bitter taste function was altered in most HNC patients, which was seen in the current study particularly in subjects' post-treatment. In the current study, sensitivity to spicy and acidic (sour tasting) foods was highly impactful during and following treatment.

In prior studies, *umami* taste was the most affected taste sensation in HNC patients [10, 29], which may affect appetite and oral intake, and resulting in decrease in quality of life [30]. In the current study, *umami* taste was abnormal during therapy with some recovery in *umami* taste post-treatment. Changes in fat taste perception with linoleic acid as the stimulus were also identified during and following treatment. The potential recovery in *umami* and fat taste over time suggests potential recovery affecting dietary guidance. Some studies have shown improvement in some studies by the eighth week following HNC treatment [29, 31], while other studies found that taste changes may persist indefinitely [1, 30]. In our current paper, continuing taste changes were present 2 years post-treatment. We also found taste dysfunction and mucositis was more severe in tobacco users.

Current approaches to nutrition and diet management have emphasized nutritional supplementation with little attention to oropharyngeal factors that influence comfort, taste and dietary choices [10]. Management clearly requires a multidisciplinary team effort. The current study shows that changes in the oral condition occur throughout the cancer treatment continuum. We also show long-term needs for HNC patients are complex involving oropharyngeal health and function, nutrition and diet information, potential swallow, taste, and saliva management. We do not report here assessment of dental health (dentate/partially dentate, edentulous, cavities, broken teeth, oral hygiene), cavity and periodontal disease risk, and osteonecrosis risk, which has been reported in the study by Kamal et al. [16]. Our subjects experienced weight loss during treatment and continued weight loss during follow-up. No correlations with weight loss were identified due to common weight loss in study subjects attributed to small sample size.

Taste management involves strategies with a goal of reduced acute mucosal damage (mucositis), pain management, good oral hygiene, and addressing dental/oral disease and saliva management hyposalivation. Mucositis and tobacco use impacted taste function. Current guidance for medical intervention in taste change is based on preliminary studies. [10, 32].

This report is the first study to assess oral mucosa, oral hygiene, saliva production, and taste and smell testing which are all factors in taste function, flavor, and oral function. We identify differences between acute and chronic complications, which may guide future research, clinical care, and product development to better support patient needs. The study is limited by small numbers of participants, although they all had HPV 16 positive HNSCC, all treated with RT and all but one with combined RT/CT. The study however included detailed assessment of oral toxicities and objective taste and smell testing. We identified challenges in conducting taste testing during active therapy for HNC when affected by mucositis, oral pain, and fatigue approaching the end of cancer treatment. In this study, participants were highly motivated, had good prior oral/dental care and had excellent oral hygiene. These attributes may not reflect the general HNC population. The role of saliva in taste function, infection prevention, tissue repair, and maintenance also may be an important factor in the treatment and follow-up setting. Longitudinal study and follow-up of HNC patients is needed.

Our findings suggest that attention to diet and nutrition should include assessment and management of oral conditions and modifications of diet and food product development. These factors should be considered in diet and nutritional advice and products, seeking high calorie and nutrient content meals and supplements. Finally, future studies should include patient-reported measures, evaluation, and management of the oral condition and taste and smell.

Acknowledgments We acknowledge assistance in data entry by Dr. Sifira Marques de Andrade e Silva, DDS, PhD, Medical Dental at Clion CAM Group, Salvador BA, Brazil, visiting dentist, Beverly Hills, CA.

Funding information We received funding provided by the Cancer Nutrition Consortium, and Hormel Inc.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

The authors have full control of all primary data and agree to allow the journal to review the data if requested.

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