Taste and smell alterations, quality of life and food characterization among patients treated for head and neck cancer

by

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Abstract

Taste and smell alterations (TSAs) are among the most frequent and troublesome side effects reported by head and neck cancer (HNC) patients after treatment. The purpose of this research was to investigate TSAs among HNC patients, study the association of TSAs on patient quality of life (QoL) and the association between Physical-Function (PF) and food characterization among HNC patients.

Intensity and liking for the basic tastes and smell were evaluated before (n=32), upon completion (n=31), 6 weeks (n=31) and 3-6 months (n=31) after treatment for HNC using suprathreshold solutions representing sweet, salty, sour, bitter and umami in commercial beverages. Milk and cream were used to test for creaminess perception and liking. Smell intensity and liking were evaluated using the Modified Brief Identification Smell Test. Vanilla solutions in water were used to assess retronasal intensity perception. Results revealed that taste intensity perception was impaired after treatment for all basic tastes, especially salty and umami. Liking scores did not respond to changes in tastant concentration after treatment. At 6 weeks and 3-6 months post-treatment, participants disliked the most concentrated solutions of salty, sour and bitter. Participants were able to perceive changes in retronasal intensity olfaction at all the time points.

Repertory grid interviews were performed with orally-fed HNC patients (n=19) between 4-10 months post-treatment to characterize foods commonly eaten, avoided and eaten sometimes. Patients were stratified as better or worse PF (respectively ≥ or <61.7 on the Physical Function domain of the University of Washington Quality of Life (UW-QoL)). All patients used descriptors of taste, ease of eating, convenience, texture, potential to worsen symptoms and liking to characterize foods. Overall, avoided foods were characterized as having dry texture,

while foods commonly eaten were characterized by their ease of eating and low potential to worsen symptoms. Descriptors of nutrition and smell were significant only for patients with worse PF to discriminate among foods.

The association of TSAs with the overall QoL of HNC patients was analyzed using self-report measures of both TSAs (Chemosensory Complaint Score [CCS]) and QoL (UW-QoL version 3) before (n=126), upon completion (n=100) and at 2.5 months after treatment (n=85). CCS was a significant predictor of overall QoL (β= -1.84, $p<0.0001$), physical-function-QoL (β= -1.11, $p=0.001$), social-emotional-QoL (β= -1.74, $p<0.0001$) and overall function-QoL (β= -1.15, $p<0.0001$) regardless of whether patients were tube-fed or orally-fed. Taste was reported as an important symptom for both groups at the end of treatment and 2.5 months follow-up.

This research reveals that intensity perception for salty and umami is impaired after treatment, while smell intensity perception was not affected. TSAs are perceived by patients as an important symptom at the end of treatment and 2.5 months post-treatment, and are an independent predictor of overall QoL, social-emotional-QoL and physical-function-QoL. Physical function influences the characterization of foods among post-treatment HNC patients, with descriptors of nutrition and smell being especially important for patients with worse physical function. Findings from this research highlight the need to incorporate assessment and management of taste and smell alterations within HNC patient nutrition education programs.

Preface

This thesis is an original work by Mirey Alvarez-Camacho. The research project, of which this thesis is a part and reported in Chapters 2 and 4, received research ethics approval on October 28th, 2011, from the Alberta Cancer Research Ethics Committee, ACREC (presently known as Health Research Ethics Board of Alberta, HREBA), Project Name "The role of taste & smell alterations in the resumption of oral intake after treatment in head and neck cancer patients", No. ETH25818. In addition, results from Chapter 4 are based on data previously collected from a study approved by the former Alberta Cancer Board (ACB) Ethics Committee and closed on March 2nd, 2012, Project Name "Nutritional Status and Barriers to Dietary Intake in Head and Neck Cancer Patients Prior to, on Completion of and Six Weeks after Oncology Treatment", No. ETH23028, supported by the Minton Endowment Fund. The research project reported in Chapter 3, received ethics approval on June 11th, 2012 from The Health Research Ethics Board - Health Panel at the University of Alberta, Project Name "Understanding patient food choice through characterization of foods", No. 28634.

From the study reported on Chapter 2, I was responsible for data collection, analysis and manuscript composition. Dr. Sunita Ghosh assisted with data analysis and interpretation. Silvia Gonella contributed with manuscript edits. Dr. Rufus A. Scrimger and Dr. Karen P. Chu contributed with patient recruitment. Dr. Vera Mazurak and Dr. Vickie Baracos contributed to the interpretation of the data and manuscript edits. Dr. Wendy V. Wismer was the supervisory author and was involved with concept formation and manuscript composition. This manuscript will be submitted to the Journal of Pain and Symptom Management.

Chapter 3 was submitted to European Journal of Oncology Nursing on March 17th, 2015. I was responsible for data collection and analysis as well as the manuscript composition. Lorelei Martinez-Michel assisted with data analysis and interpretation and contributed to manuscript edits. Silvia Gonella contributed with manuscript edits. Dr. Rufus A. Scrimger and Dr. Karen P. Chu contributed with patient recruitment and manuscript edits. Dr. Wendy V. Wismer was the supervisory author and was involved with concept formation and manuscript composition.

Chapter 4 was submitted to the Quality of Life Research Journal on January 23rd, 2015 and revisions requested by the Journal are in progress. I was responsible for data collection and analysis as well as the manuscript composition. Catherine Kubrak contributed with data collection and manuscript edits. Silvia Gonella and Dr. Sunita Ghosh assisted with data analysis, interpretation and manuscript edits. Dr. Rufus A. Scrimger and Dr. Karen P. Chu contributed with patient recruitment and manuscript edits. Dr. Wendy V. Wismer was the supervisory author and was involved with concept formation and manuscript composition.

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CHAPTER 1: Literature review and research plan

1.1 Introduction

It is estimated that 2 out of 5 Canadians will develop cancer in their lifetime (1). In addition to the high economic cost in healthcare and productivity, cancer has immediate and long-term consequences on the physical, functional and emotional life areas of the patients (1). Tumors of the head and neck include those affecting the oral cavity, salivary glands, pharynx, larynx, paranasal sinuses and nasal cavity. World-wide, head and neck cancers are the sixth most common type of cancer representing 1%–4% of all cancers in North America and 25% in Southeast Asian countries (2-4).

The most important risk factors for head and neck cancer (HNC) include alcohol, tobacco, human papillomavirus, diet and exposure to toxic substances (5). Survival rates are improving due to better diagnosis, treatments and prevention programs, including smoking cessation. This has been reflected in the 5-year survival rate for oral and larynx cancer in Canada, which changed from less than 60% during 1992-1994 to 63% during 2006-2008 (1). As a result, more HNC survivors are adapting to their new physical, functional and lifestyle changes after treatment, which include changes in food behaviours. This chapter presents a summary of the current knowledge of food choices, taste and smell perception and quality of life among HNC patients.

1.2 Determinants of food choice

Furst et al. investigated how people make food choices and created a model explaining the process with three levels of determinants: life course, influences and personal system (6). Life course refers to the stage of life (e.g. childhood or adolescence) and how different events and experiences such as changing roles (e.g. parenthood) can have an impact on lifestyle and the foods chosen. Influences comprises “ideals” or the social and cultural norms that establish the type of foods that should be eaten, “personal factors” including physiological and psychological drivers, “resources” such as income or time, “social factors” or the impact of family and community and “context” such as the weather. The third determinant or personal system refers to the values that are negotiated when selecting certain foods (e.g., quality vs. price) as well as to the strategies and routines that are part of our daily life when choosing foods (6).

Food choice decisions are dynamic and complex and lead to food behaviors that include acquiring, preparing, serving, eating, storing, giving away and cleaning up foods (7). Food choice and food behaviors change during major illnesses (7, 8). For instance, it is estimated that 48-58% of cancer patients make changes to their food intake after diagnosis, motivated by their need to increase well-being, maintain health, prevent recurrence and avoid causes of cancer (9, 10).

HNC patients are among those patients compelled to make changes to their food intake due to their symptoms. While previous studies have quantified the impact of symptom severity on daily energy intake (11), it is important to understand how symptom severity shapes perception of foods, preventing or promoting food intake when patients re-initiate oral intake after treatment.

1.3 Dietary changes among head and neck cancer patients

Localization of the tumour, side effects of treatment and the physiological response to the malignancy, can produce several nutrition impact symptoms which interfere with normal food intake (12). Some of the common nutrition impact symptoms among HNC patients are pain, difficulty swallowing, sore mouth, decreased appetite, dental problems, xerostomia, feeling full quickly, constipation, diarrhea, nausea, vomiting and taste and smell alterations (TSAs) (12). Having multiple nutrition impact symptoms leads to a reduced dietary intake, weight loss and reduced survival in radio/chemo naïve HNC patients (13).

Nutrition impact symptoms can become more severe as treatment progresses with a significant effect on food intake. Da Cruz et al. reported that 39% of patients undergoing treatment for HNC could not eat some of their usual foods and required changes in food preparation, while an additional 33% had major restrictions and reduced their food variety to half of what they would normally consume (14, 15). Factors associated with greater food restrictions during treatment for HNC include having a large tumor with posterior location, loss of tongue mobility, loss of teeth and radiotherapy (RT) (14, 15). Xerostomia and mucosal sensitivity have been identified as two symptoms that lead to reduced oral energy and protein intake (16). Symptom alleviation after treatment, such as a reduction in chronic mucositis, leads to improved oral intake and the ability to eat a normal diet (17). Individual nutritional counselling helps to improve energy and protein intake, QoL and physical functioning compared to no nutritional advice or standard nutritional advice (18).

1.4 Factors leading to weight loss among head and neck cancer patients

Weight loss is related to poor nutritional and clinical outcomes among HNC patients. Ganzer et al. reported a mean weight loss of 7.91 ± 4.06 Kg from diagnosis to treatment completion and a further 3.35 ± 4.29 Kg from treatment completion to 3.9 months post-treatment (16). “Critical weight loss,” defined as more than 10% in the last 6 months or 5% in the last month, is related to fatigue and decreased physical function among HNC patients (19). Weight loss beyond 20% of the pre-diagnosis weight leads to higher treatment interruption, increased risk of infection, hospital readmission and higher mortality rates (20).

Pre-treatment predictors of critical weight loss include loss of appetite, dysphagia, loss of taste and taste aversion (21). Once RT-treatment for HNC patients has begun, pain and oral mucositis contribute to increased weight loss. For HNC patients with chemoirradiation (ChemoRT), systemic inflammation, appetite loss, oral mucositis, pain, xerostomia, reduced swallowing capacity and TSAs contribute to weight loss during and after treatment (11).

1.5 Physical Function

Physical Function (PF), is the ability to perform daily life activities, important for Quality of Life (QoL) and independence (22). The University of Washington Quality of Life (UW-QoL v. 4), is one of the most commonly used questionnaires in HNC (23). Factor analysis from Rogers et al. indicated that a composite score can be calculated to represent the Physical Function, resulting from the average of taste, chewing, swallowing, speech, saliva and appearance (23). Higher scores indicate better physical function. Previous studies have investigated the impact of symptoms on food intake and weight loss among HNC patients (11), but have not studied the impact of the Physical Function on food characterization.

1.6 Smell, taste and texture: perception and assessment

1.6.1 Smell perception and assessment

Olfaction provides vital information about one's surroundings, such as the presence of food, smoke or toxins (24, 25). Smell perception starts when odor molecules reach the nasal cavity during breathing or sniffing (orthonasal olfaction) or when odor molecules from food pass through the nasopharynx during chewing and swallowing (retronasal olfaction) (24, 26). Odor molecules activate the olfactory sensory neurons at the olfactory epithelium, triggering an action potential that is propagated to the olfactory bulb, ascends to the amygdala and primary sensory cortex (24, 25, 27).

The olfactory epithelium is replaced by respiratory epithelium through the years, reducing the olfactory capacity (24, 28). The majority of odors stimulate both the olfactory and trigeminal (cranial nerve V) system (25), leading to somatosensory sensations of cooling or stinging with scents like menthol or onion (29). Odor sensitivity has a genetic component (30), but in general, peak olfaction performance is reached at 30-50 years, declining after 70 years of age (31).

Olfactory function is tested through odor detection threshold, odor identification and odor discrimination tests (32). Odor detection threshold is defined as the lowest concentration of an odorant that can be detected reliably (33). A solution of butyl alcohol or phenyl ethyl alcohol is commonly paired with water blank and the subject is asked to sniff both samples and identify the odorant through a series of ascending concentrations (34).

Odor identification consists of the presentation of various stimuli at supra-threshold levels. Subjects are asked to name the odor or choose a name from a list (32). The University of Pennsylvania Identification Test (UPSIT) (35) and the Brief-Smell Identification Test (B-SIT) (36) are some of the most widely used identification tests. They consist of microencapsulated odors that are scratched and sniffed and participants select an identity from four options. In the modified version of the B-SIT tests, three items investigate strength, pleasantness and familiarity for each odor in a 7-point scale (37). The Scandinavian Odor Identification Test (SOIT), validated for Swedish and Finnish population, uses 16 liquid odors injected in a tampon filled to saturation placed in an opaque glass jar; participants have to choose the correct name among 4 options (38, 39).

Odor discrimination tests assess the ability to distinguish one odor among others (32). People are often less able to discriminate among unfamiliar than familiar odors, but the ability to discriminate improves with practice (40). The felt-tipped pens from the "Sniffin' Sticks" test (34) can be used to test for Odor detection threshold, Odor identification and Odor discrimination and results are combined to calculate a composite score, for threshold, discrimination, and identification. Other psychophysical olfactory assessments include quality recognition, quality identification and memory tests, described in detail elsewhere (41).

In addition to psychophysical tests, self-report tools are often used to assess subjective alterations such as dysosmia that cannot be captured with clinical techniques (28). The European Organization for Research and Treatment of Cancer (EORTC) H&N35 has a two item-scale on "senses" to evaluate problems of taste and smell together (i.e. "have you got problems with your sense of taste/ smell") in a scale from 1 to 4, where 1=not at all, 4=very much (42). However, a recent review found low reliability of the scale when taste and smell are evaluated together and suggested they should be evaluated separately (43). The Questionnaire on Odor, Taste and Appetite (QOTA) evaluates current perception and perception compared to the past (44). The Taste and Smell Survey quantifies smell alterations through the Smell Complaint Score (SCS, range= 0-6); the higher the score, the greater the number and severity of alterations (45).

1.6.2 Taste and texture perception and assessment

The human mouth possesses chemical, mechanical and thermal receptors to detect taste, touch, temperature, and pain (46). After ingestion, food is physically and chemically manipulated until a bolus is formed and swallowed (46, 47). Oral receptors contribute to the perception of food characteristics, such as taste and texture, and transmit the information to the central nervous system (46). Perception of taste starts when a stimuli (molecule) reaches a taste receptor cell, causing a depolarization or hyperpolarization of the receptor cell and triggers a release of neurotransmitters (24). Different mechanisms have been proposed for the perception of the basic tastes (i.e. sweet, sour, salty, bitter and umami), involving Na^+ or H^+ for the perception of saltiness and acids, respectively, or the involvement of specific membrane receptors activating a G-protein second-messenger system for sweet, bitter and umami (24).

Taste function can be evaluated by assessing detection and identification thresholds. The most common tests are known as "spatial tests," which evaluate different locations on the tongue and have different modalities. In the filter paper method, a piece of filter paper is soaked with a taste and dried before being placed (one at a time) in any of the four quadrants of the tongue and the subject is asked to identify the taste and rate the intensity from 1 to 10. Similarly, for the three-drop method, three drops are placed in the tongue (one with a taste stimulus and two blank) in increased concentration. Finally, in the whole-mouth method subjects are presented with ascending concentration series of basic tastes and invited to "sip and spit" to evaluate the ability to both detect and identify the taste (33). Electrogustometry is a non-spatial test method to evaluate taste in which an electrical stimulus is applied to the tongue producing a taste. However, this method evaluates only sourness (33). Among the self-report tools to evaluate taste, the Taste and Smell Survey has a component to quantify the severity of taste alterations through the Taste Complaint Score (TCS, range= 0-10) with a higher score representing a greater number and severity of alterations, and by collecting information on whether the change is due to an increased or decreased perception for sweet, salty, sour or bitter (45).

Texture perception is important for the appreciation and recognition of foods (46). Foods can be perceived as good or bad quality based on whether they have the expected texture (e.g. crunchiness in vegetables or the smoothness in a cream soup) (46). In addition, the ability to identify a food becomes more difficult after it has been blended and the defining textures lost (48). Different intra-oral factors influence texture perception, such as saliva, tongue movements, swallowing, dentition, mouth sensitivity and thermal perception (46), therefore, different texture parameters can be assessed during the eating process, from the first bite to post-swallowing mouth-feel (47).

1.7 Taste and smell alterations among head and neck cancer patients

TSAs can appear before the initiation of treatment (12) due to necrosis of the tissue and the invasion of tumour cells into functional areas related to normal taste or smell (49); however, TSAs are most commonly reported after treatment for HNC (50). TSAs are classified for diagnosis as a reduced perception of taste (hypogeusia) or smell (hyposmia); complete loss of perception of taste (ageusia) or smell (anosmia); heightened perception of taste (hypergeusia) or smell (hyperosmia); or distorted perception of taste (dysgeusia) or smell (dysosmia) (49). Among distorted perceptions, it is possible to differentiate between perception in the absence of any stimuli and perception that does not correspond to the stimuli (33). A summary of studies evaluating TSAs among HNC patients is presented in Table 1.1. The effects of oncologic treatment on taste and smell perception are discussed in the next section.

1.7.1 Factors affecting normal taste and smell perception

Several factors affect normal taste and smell perception. Aging is the most common factor, with one of every 4 people over 75 years-old being anosmic (51) and with the majority of people having lost half of their taste buds at the age of 60 years-old (52). Smoking affects smell perception by producing glutinous mucous that prevents odor molecules from reaching olfactory sensory neurons (51) and the degree of impairment is correlated to the number of cigarettes smoked (53). Head trauma (even slight) can compress olfactory nerves causing smell impairment (51). Poor oral hygiene, use of dentures and oral diseases can lead to infections and foul-smelling-breath that interfere with the normal taste and smell perception (54, 55). Micronutrient deficiencies such as vitamin A (56), B complex (57), zinc and copper (58) can lead to impairments that are reversible with supplementation. Other common factors include nasal obstruction (e.g. polyps), viral infections (e.g. viral hepatitis), hypothyroidism, exposure to toxic agents (e.g. lead, arsenic or some insecticides) (51) and medications (e.g. antihypertensive) (59).

1.7.2 Effects of radiotherapy, chemoirradiation and surgery on taste and smell perception among HNC patients

Some degree of alteration in taste is typically observed among HNC patients once treatment with RT or ChemoRT is started. A recent systematic review reported a prevalence of dysgeusia during cancer therapy among Chemo-, RT- and ChemoRT-treated cancer patients of 56.3%, 66.5% and 76%, respectively (60). All basic taste recognition thresholds appear to be significantly impaired when receiving 45 Gy (61).

The amount of radiation influences severity of TSAs. Patients with a greater area of the tongue irradiated tend to have more taste impairment (62, 63). Different explanations of the cause of taste alterations due to RT have been proposed, including a decrease in saliva production, alterations in protein or electrolyte content of saliva, reduction in proliferation of taste buds and lesions to neurons that transmit sensory signals (61). Yamashita et al. reported that recognition thresholds for sweet, salty, sour and bitter started to improve by the 11^{th} week after RT initiation, in a study where total RT treatment period ranged 8-12 weeks (58). In addition to RT, chemotherapy inhibits renewal of taste cells reducing the usual ability to taste, while under normal conditions taste cells are replaced every 10.5 days (61). Saliva has an important role in taste perception since it is involved in the transduction of flavors (65). RT alters the functionality of salivary glands when exposed to the radiation field. Surgery for submandibular gland transfer helps to preserve their function by positioning them outside of the radiation field (66) resulting in prevention of xerostomia, better swallowing and QoL (67).

The lifespan of olfactory receptor cells can extend beyond 30 days (28, 60, 68) and there is evidence of smell impairment after chemotherapy as it affects fast dividing cells in the body (69, 70). Furthermore, RT has been identified as an independent predictor of reduced olfactory function (71). The proposed mechanisms behind smell alterations in RT-treated HNC patients include a reduction in the number of receptors, alteration of cellular structure, changes in the surface of receptors and/or interruption in neural coding (72). Surgery for HNC is also known to affect perception according to the area resected. Subjects with laryngectomy have been reported to have a reduced or complete loss of olfactory function. Despite this, food flavour may be experienced by retronasal perception (73). Patients reconstructed with forearm free flap surgery lack taste perception in the area reconstructed when measured >3 years after surgery, but a compensatory mechanism may take place in the unaffected area of the tongue (74).

The evaluation of detection and recognition thresholds is useful to detect a taste or smell loss, but the assessment of perceived intensity may reflect patients' real complaints with taste alterations as highlighted by Bartoshuk as patients can relate more easily to foods when exposed to higher concentrations of stimuli (75). In addition, an improvement in clinically assessed taste thresholds may not imply changes in self- perceived intensity (75).

1.7.3 Liking and perceived intensity of the basic tastes and smell

Studies of liking and perceived intensity of food tastes and aromas during malignancy are valuable to understand the challenges experienced by HNC patients in obtaining adequate and enjoyable food intake. Liking is defined as the pleasure obtained from the oral stimulation of eating a food (76). It can be influenced by appetite, hunger and learned food aversions and can be measured with the nine-point hedonic scale (77). Liking and disliking influence changes in nutritional, gastronomical and social patterns (78). Despite the importance of the topic, liking for tastes and aromas among cancer patients has received little study. Only three studies have examined taste intensity among HNC patients and two studies have examined liking among non-HNC patients.

The three studies that evaluated taste intensity among HNC patients used aqueous solutions of the basic tastes at suprathreshold concentrations. Schwartz evaluated patients between 0.5-19 years post-RT and found differences only in sour intensity as compared to a healthy control group (79). Zheng reported impairment in the intensity of sweet, salty, sour and bitter after RT-initiation, which started to recover after a 2-3 week resting period at mid-treatment (80). Barhavand et al. assessed intensity before and 3 weeks after RT, reporting impairment for salt and bitter perception (81). None of these studies examined intensity perception of umami, liking for the basic tastes, or intensity and liking perception of aromas.

Two studies investigated liking and perceived intensity among non-HNC populations. Bossola et al. reported higher hedonic scores for salty and sour tastes among anorectic, non-HNC cancer patients without recent treatment (i.e. surgery, Chemo or RT) as compared to a healthy control group. Perception for bitter and sweet were found to be more intense among gastrointestinal cancer patients (82). Trant et al. assessed the perceived intensity of sweet, salty, sour and bitter among gastrointestinal and thoracic cancer patients with and without recent treatment in the last month, reporting that scores for perceived intensity increased with greater stimuli (83).

1.7.4 Impact of taste and smell alterations on nutritional, clinical outcomes and QoL

Previous studies have found a relationship between TSAs and clinical outcomes in cancer patients. Among advanced cancer patients, severe self-reported TSAs have been associated with reduced energy, lower protein intake, and lower scores in quality of life questionnaires compared to patients reporting few TSAs (84). A stronger sense of smell is associated with a reduced energy intake and higher nausea (85). Among lung cancer patients, an increased bitter sensitivity is associated with weight loss (86). Among HNC patients, umami taste impairment has been associated with reduced sense of well-being (87). Taste alterations have ultimately been associated with shorter survival times (88).

Taste alterations may not initially be considered among the most important concerns by HNC patients before treatment (89); however, as treatment progresses, taste alterations become one of the top 3 most important issues reported after treatment (50). Baharvand et al. reported that quality of life significantly decreased after the occurrence of dysgeusia among HNC patients with partial or total taste loss (81). Kubrak et al. reported a trend of self-reported TSAs as a predictor for reduced QoL when following patients up to 2.5 months post-treatment (11). Previous studies exploring the impact of TSAs on QoL have assessed TSAs as individual items on QoL tools rather than using a comprehensive assessment tool (50, 90-93) or have defined QoL as the average of symptoms (11) rather than using a health-related QoL approach, which considers the person as a whole (94).

1.7.5 Interventions tested to improve taste and smell perception

Different strategies have been tested to improve taste and smell perception with no success on improving energy intake. The use of flavor enhancers among elderly people with deficits in taste and smell perception was useful to improve food variety, but did not to improve energy, macro or micronutrient intake (95). In cancer patients, Haylard et al. and Lyckholm et al. tested zinc supplementation vs. placebo (220 mg oral zinc sulfate twice daily and 45 mg of oral zinc sulfate three times a day, respectively) and reported there was not an improvement in taste perception (96, 97). Brisbois et al. reported patients that received Marinol (delta-9-tetrahydrocannabinol) reported improvement in taste and smell perception, better appetite and reported that "food tasted better" vs. a group of patients receiving placebo, however, both groups had similar energy intake (98).

1.8 Summary

Previous studies of HNC patients have evaluated TSAs using detection and recognition thresholds, which evaluate the lower range of the concentrations that can be perceived. However, limited information has been collected about the intensity of the stimuli or the effect of these alterations on liking. Previous studies exploring the impact of TSAs on QoL have not used a comprehensive taste and smell assessment tool or have defined QoL as the average of symptoms rather than using a health-related QoL approach. Moreover, previous studies have investigated the impact of symptoms on food intake and weight loss among HNC patients, but have not studied the impact of the symptom experience on food characterization. The study of TSAs and their role in food intake can help capture the challenges faced by patients and aid in the creation of more effective strategies for nutritional counselling in order to improve nutritional and clinical outcomes.

1.9 Research plan: rationale objectives and hypothesis

CHAPTER 2: Intensity and liking of basic tastes and aroma among a prospective cohort of head and neck cancer patients

Rationale: Previous studies among HNC patients have used tests of detection and recognition thresholds, which evaluate the lower range of concentrations that can be perceived but have limited applications to draw conclusions about perception at higher concentrations, as would be found in food. In addition, there is limited information in the literature about liking and intensity perception of taste, creaminess and smell after treatment for HNC cancer.

The objective of this study was to evaluate intensity and liking of the basic tastes, creaminess and common aromas prior to, upon completion of, and after treatment follow-up, among HNC patients. It was hypothesized that intensity scores for taste, creaminess and retronasal perception would increase with increasing concentrations of stimuli. It was also hypothesized that liking scores for sour and bitter would follow an inverse function, sweet, umami and creamy follow a direct function and salty a parabolic function with the increasing concentrations, as reported by previous studies with other tumor groups.

CHAPTER 3: Physical-function of post-treatment head and neck cancer patients influences their characterization of food: Findings of a repertory grid study

Rationale: While the restrictions of symptoms on dietary intake and nutritional status among HNC patients is well documented, little is known about patient characterization of food as a consequence of their Physical-Function symptom experience.

The objective was to explore the association between Physical-Function and food characterization among post-treated HNC patients. It was hypothesized that patients with better Physical-Function perceive foods differently than patients with worse Physical-Function.

CHAPTER 4: The association of taste and smell alterations and quality of life in head and neck cancer patients

Rationale: Previous studies exploring the impact of TSAs on QoL have assessed taste and smell alterations as individual items on QoL tools, while others have defined QoL as the average of symptoms rather than use a health-related QoL approach (e.g. considering the person as a whole and including other areas that contribute to the sense of well-being). In addition, there are no published studies about TSAs among tube-fed patients.

The objective was to determine the impact of TSAs on quality of life among HNC patients, describe the overall QoL and the most important QoL issues before treatment, upon completion and 2.5 months follow-up. It was hypothesized that TSA would predict overall QoL among HNC patients.

The data presented in this thesis were collected from three trials: a longitudinal study that assessed patients before treatment, upon treatment completion and 2.5 months follow-up (Study I), a cross-sectional study that assessed patients at pre-treatment, upon completion, 6 weeks and 3-6 months post-treatment (Study II) and a study that evaluated patients at 4-10 months post-treatment (Study III). The studies had the same inclusion/exclusion criteria. Study I began accrual in February 2007 and closed in August 2009. Study II began accrual in January 2012, and closed in July 2014. Study III began accrual in July 2012 and closed in May 2014.

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Table 1-1 Studies evaluating taste and smell alterations among head and neck cancer patients.

Author, year	Study design	Patients		Measures of taste or smell (tool)	Time of assessment	Results
		(N, %) Age (years)	Treatment (RT dose)			
Barhavand et al. 2013 (81)	Longitudinal	N=22 M:14 (63) Age: 54.9 (19-79)	RT or RT chemo (tongue was partially/totally included in the RT field).	Taste recognition and intensity (low, medium, high) for aqueous solutions representing sweet (sucrose), salty (sodium chloride), sour (citric acid) and bitter (quinine) using AML.	Assessment before and 3 weeks after RT.	All patients had dysgeusia after RT. 27.2% had total taste loss. Salt and bitter perception were the most impaired, followed by sweet and sour.
Bindewald et al., 2007 (99)	Cross-sectional	n=205 M: 190 (93) Age: 64 (32-84)	LE+RT (n=72, 78%) LE only (n=20, 22%) PL+RT (n=36, 32%) PL only (n=77, 68%)	Self-report smell (EORTC QLQ-H&N35)	LE: 5.7 y (range 0.11-16.58) post-surgery PL: 4.5 y (range 0.19-15.14) post-surgery	LE had more impairment in smell than PT No differences in smell perception between irradiated and non-irradiated patients
Brämerson et al., 2013 (71)	Longitudinal	n=72 M: 51 (72) Age: 60.9 (35-86)	RT (n=39) CRT (n=32) Low RT-dose to olfactory epithelium (<10 Gy,	ODT , OI (SOIT) and subjective experience of olfactory capability	Before RT and 20 months after RT (range 12-35 months)	Significant decrease in ODT and OI before and after RT for both groups, a larger difference observed in the

			n=56) High RT-dose to olfactory epithelium (>10 Gy, n=15)			high RT group. After therapy, subjective olfactory capability declined in six (40%) high RT-dose patients and 4 (7%) low RT-dose patients. RT-dose was an independent predictor of declined olfactory function. Significant weight (Kg) decrease before and after treatment, however, the study does not specify the causes/predictors of the weight loss.
Chencharick et al., 1983 (91)	Longitudinal	N=74 M: 59 (79) Age: 55 (11-83)	RT	Questionnaire about subjective awareness of taste changes, dysphagia, appetite loss and food preferences.	Prior RT and every week for 6 weeks during treatment. 8 patients completed 24-hour dietary records early in therapy (after 1 week) and late in RT	14% of patients reported taste changes (prior to RT), which increased up to > 80% by the 5th week of therapy. Patients tended to sweeten food and fluids more frequently as RT progressed. Salt

					(after 6 weeks).	intake seemed to remain constant. High protein foods- meat, eggs, dairy referred as the most abnormal tasting foods. Tough foods, meats and hard/fried foods referred as the most difficult to eat.
Epstein et al., 1999 (100)	Cross-sectional	N=65 M:42 (64.6) Age: 52.2 (21–79) y	RT	EORTC QLQ-C30 with an added oral, symptom and function scale were sent to HNC patients.	More than 6 months following RT	Patients reported the following complaints: Change in taste: 75.4% Difficulty chewing or eating: 43% Dry mouth: 91.8% Dysphagia: 63.1% Altered speech: 50.8% Difficulty with dentures: 48.5% Increased tooth decay: 38.5% Pain: 58.4% Pain interfering with daily activities: 30.8% Mood complaints: 50% Interference of the

						social activities: 60%
Epstein et al., 2001 (101)	Longitudinal	N=20 M:12 (60) Age: 53.4 (38-78)	RT	EORTC QLQ-C30 with an added oral symptom and function scale	Completed at the beginning of RT, 1 month after completion of therapy and 6 months after RT.	Oral quality of life does not return to pre-treatment levels by 6 months after RT. 6-Months after RT: Change in taste reported by 90%
Fernando et al., 1995 (62)	Longitudinal	N=26 M: (NR) Age: (NR)	RT 6 (23%) patients treated with surgery prior to RT.	Taste detection threshold (whole mouth) for sweet, salt, bitter and sour. Questionnaire about taste loss and xerostomia.	Taste detection threshold: Pre-RT, end of RT. Questionnaire: Pre-RT, end of RT and 1-month post RT.	An increase in 28% of tongue volume irradiated resulted in one unit increase in threshold OTL (Objective taste loss). An increase in 12% of tongue volume irradiated resulted in one unit increase in Subjective Taste Loss (STL) score that ranged from 0 (complete taste loss) to 10 (normal taste).
Hahn, 2007 (102)	Retrospective study	n=1411 M (NR) Age (NR)	Surgery (n= 671, 47.6%) Surgery RT (n= 479, 33.9%) CRT (n= 207,	Smell impairment (5-point likert scale questionnaire)	6 months after treatment	Impairment of smell in patients irradiated vs. no irradiated.

			14.7%); Surgery and chemotherapy (n=54, 3.8%)			
Ho et al., 2002 (103)	Longitudinal	n=58 M 23 (40) Age: 46 (22-71)	RT (n=43) CRT (n=15)	OI, ODT and OD (Sniffin' Sticks - Asian version)	Before RT, end of RT, 3, 6 and 12 months post-RT	Deterioration of ODT and overall TDI score at 12 months No changes in OD, OI or self-reported hyposmia at 12 months.
Hölscher et al., 2005 (104)	Longitudinal	n=44 M 28 (64) Age: 55 (11-81)	RT (n=30) CRT (n=14) High-RT dose (OLF group) to olfactory epithelium (> 20 Gy, n=22) Low-RT dose (Non-OLF group) to olfactory epithelium (<12 Gy, n=22)	OI, ODT and OD (Sniffin' Sticks)	Before and bi-weekly during RT for 6 weeks. Long term information for 10 OLF (34 weeks post-RT) and 15 non-OLF (39 weeks post- RT)	During RT: No differences between OLF and non-OLF in OI, ODT. Two weeks after RT onset: Decreased OD in OLF vs non-OLF. Long term assessment: No difference in ODT between OLF and non-OLF. Lower OI scores in OLF vs non-OLF. Significant effect of RT dose for OD during RT but only a trend (p=0.096) after RT.

Hua et al., 1999 (72)	Controlled clinical trial	Study group (n=49) Control group (n=36) M (n=65, 76) Age: 43±9	RT	ODT (*n*-butyl alcohol and water) OQD test (five odorants offered in triads in random sequence) OR memory test (a vial contained an odorant from the discrimination test and a distractor. Subjects had to recognize the odor shown in the ODQ test) OVMT (subjects sniffed 15 odorants matching them with the corresponding item among an array of 15 objects) OTMT (subjects explored tactually 10 objects while an odorant was presenting and had to match the odor with the object) OI(a list of 20 names (10 objects and 10 distractors) and 10 odorants presented randomly)	Before and after RT: Before RT (n=24 NP and control group) Post RT (n=25 NP and control group)	ODT: Control group had the lowest threshold among the groups. No difference among the NPC groups. OQD: NPC post-RT group performed poorer that the other 2 groups (no difference when using average of two nostrils as covariate) OR memory: control subjects performed better than NPC groups OVMT, OTMT, OI, OFT: performance was better in the control group, followed by the NPC before RT

				OFT (20 items. Subjects sniffed the items and answered questions on edibility, function and identity)		
Maes et al., 2002 (105)	Cross-sectional	N=73 M: 67 (91) Age: 56 ±10	Surgery RT: 25 (34%) ChemoRT: 1(1.3%) RT: 47 (64%)	Detection and recognition thresholds by whole-mouth method for the 4 basic tastes. Subjective awareness of taste loss evaluated by a questionnaire (part of the Dutch translation of the Adapted symptom Distress Scale - ASDS). Total taste loss for a taste= absence of detection and recognition of the taste for the 3 different concentrations of the solute used. Partial taste loss= If subject could detect and recognize at least one concentration.	- Prior initiation of RT - 2 months after RT - 6 months after RT - After 1-2 years of RT	Before RT: Moderate to serious partial taste loss observed for sweet (6%), salt (18%) and bitter (35%). 2-Months after RT: Majority of patients with moderate partial to total loss for different taste qualities (53-88%). Prevalence of taste loss was most pronounced for bitter and salt. 6 Months after RT: Partial taste loss observed in 41-71% of the patients. 12-24 months after RT: Partial taste loss observed in 27-50% of the patients. At 12-24 Months after treatment, taste still not

						entirely restored as compared with the situation pre-RT.
Mirza, 2007 (106)	Longitudinal	N=8 17 controls: receiving RT for colon, prostate, breast or lung cancer.	M: 17 (94) Age patient group: 58.4 ± 8.7 Age control group: 62.1 ± 7.6 years. Patient group: ChemoRT: 1 (12%) RT: 7 (88%) Control group: ChemoRT: 1 (6%) RT: 16 (94%)	Taste identification using solutions representing sweet (sucrose), salty (sodium chloride), sour (citric acid) and bitter (caffeine). Each taste presented with micropipettes in four regions (anterior and posterior) of the tongue. Digital images of the tongue were collected using video microscopy and to count for papillae and pore.	All participants evaluated at 2 weeks before RT, 2 weeks, 2 months and 6 months after RT.	Sour was significantly affected after RT compared to the control group. Bitter, salty and sweetness were not significantly impaired after RT. There was a loss of lingual papillae and taste pores at 8 and 4 weeks after RT, respectively in the study group.
Ogama N., et al. , 2010 (107)	Longitudinal	117 HNC patients receiving RT.	RT M: 84 (71%) Age: 68.63 ±10.2	Detection thresholds using filter-paper disk method. Also evaluated: -Daily fluctuations in saliva production. -Analgesic use -Frequency of oral care -Appetite = 5-point ascending scale on a	Evaluations performed after 20, 30 and 50 Gy.	Analysis according to RT received: 20 Gy appetite affected by smoking frequency, age and sensitivity to taste. 30 Gy appetite affected by frequency of oral care, xerostomia

				given day. -Adverse events (dysgeusia, xerostomia, oral mucositis).		symptoms, age, sensitivity to taste and oral mucositis. 50 Gy appetite affected by low saliva production in the morning, frequency of oral care, xerostomia symptoms, sensitivity to taste, analgesic use and oral mucositis.
Olszewska, 2002 (108)	Longitudinal	n=20 M 18 (90) Age 60.5 (47-77)	RT (n=20) (60 Gy)	ODT (butyl alcohol) OI (seven commonly known smells)	Before and after RT	No differences in ODT before and after RT. Olfatometric examination of patients after laryngectomy showed different degree of hyposmia: mild and medium in 40%, advanced in 50% , anosmia in 5%, normosmia in 5%
Ophir et al., 1988 (109)	Longitudinal	n=12 M 9 (75) Age: 54.8 (38-	RT (n=12) (66 Gy total dose) Dose to	ODT (three-way forced-choice sniff technique using 5 ml of amyl acetate and	Before RT, within a week after termination, 1,	ODT increased for both compounds by the end of treatment.

		76)	olfactory area: 25-28 Gy (NPC), 18-22 Gy (Pituitary adenoma)	eugenol diluted in diethyl phthalate)	3 and 6 months later	The first week after RT termination was the worst moment. At 6 months after RT termination baseline levels for ODT were not yet recovered.
Oskam et al., 2013 (110)	Longitudinal study	n=80 M 47 (59) Age: 58 (23-74)	Free-flap reconstruction and postoperative RT (n=80)	Self-report taste/smell (EORTC QLQ-H&N35)	Baseline (post-diagnosis/ pretreatment), at 6 months, 12 months, and 8-11 years (known as survivors)	No difference for EORTC QLQ-H&N35 taste/smell mean scores between survivors and non-survivors. No difference between long-term taste/smell mean score versus taste/smell mean score at baseline, 6 months and 12 months follow up. However, at 8-11 years follow up taste/smell have not yet recovered the baseline level.
Qui, 2001 (111)	Longitudinal	n=100 M 50 (50) Age: 43 (19-70)	RT (n=100) (27-29 Gy to olfactory epithelium, maximum 72 Gy)	ODT (for amyl acetate, eugenol, and 3-methylindole, prepared at 1-10 levels)	Before treatment, and 3, 6,12,24,36 months after therapy.	Smell acuity had a significant decrease at 3 month time point, then acuity recovered a bit at 6 month and 12

						month, then decreased at 24 month (2 year) and 36 month (3 year).
Rhemrev, 2007 (112)	Cross sectional follow-up study	n=72 M 44 (61) Age: 57 (33-79)	All had radial forearm free flap RT (n=57, 79%) (66 or 70 Gy)	Self-report smell (EORTC H&N35)	43 ± 27 months post-treatment (range 2-120 months).	RT group scored significantly worse than non-RT group for the subscale 'senses' (problems with smelling and tasting)
Risberg-Berlin et al., 2009 (113)	Longitudinal study with control group	Intervention (n=18): M 15 (83) Age: 71 (57-83) Control (n=18): M 15 (83) Age: 72 (52-82)	Intervention: LE+ RT+NAIM Control: RT	OI (SOIT) Self-report smell (semi-structured interview, EORTC QLQ-H&N35 and QOTA)	Baseline (before NAIM rehabilitation), at 6 and 36 months Controls were examined only once	*Intervention group* SOIT score and categories Baseline: 11/18 (61%) patients were anosmic, 2 hyposmic, 5 normosmic. At 6 months: 7 of the anosmic became hyposmic. At 36 months: 4 anosmic, 6 hyposmic, 8 normosmic. The SOIT score statistically improved over time Patients' self-estimation: improvements on olfactory function at 6 and 36 months

						QOTA scale: improvements in "present sense of smell" over time *Intervention group vs control group* All control patients were normosmic and scored better than the intervention group for SOIT, QOTA scale (present sense of smell and present sense compared to before treatment) and EORTC QLQ-H&N35.
Sagar et al., 1991 (114)	Retrospective study with control group	Study group (n=25): M (NR) Control group (n=40): M (NR)	RT (n=65) Only the study group received RT on the olfactory region (50-75 Gy)	Unusual odor during RT (Postal ad hoc questionnaire)	During treatment	Control group: Did not experience odorous symptoms. Study group: 15 (60%) complained of an odor from the first treatment fraction and diminished toward the end of a course of treatment ceasing when the radiation was terminated Smell described as bleach, ozone,

						chlorine, ammonia, gas, celery, burning, acrid or pungent, 11 patients defined the experience unpleasant and 4 complained of severe disturbance
Sandow et al., 2006 (115)	Longitudinal study with control group	Study group (n=13): M 10 (77) Age: 51.6 (40-75) Healthy control (n=5): M 3 (60) Age: 47.9 (27-70)	RT	OR (UPSIT)	At baseline (prior to RT), 1 month, 6 months and 1 year post-RT	OR was unaffected by radiation
Schaupp et al., 1974 (116)	Cross sectional	n=24 M (NR) Age: NR (28-80)	RT	ODT (Elsberg' method)	19 participants tested 1-15 y after RT. 5 participants tested before, during and after RT.	Participants tested 1-15 years post-RT: thresholds did not exceed normal range (i.e., no permanent disturbance of smell after RT). Participants tested

						before, during and after RT: threshold rose to the upper margin of the normal limit and returned to baseline levels within 6-8 weeks. Up to 60 Gy, damage is not disruptive.
Schwartz, 1993 (79)	Cross-sectional with control group	15 HNC patients Age: 32-72 (mean 53.8) y. Control group: 23 healthy participants Age: 36-72 (mean 53.9) y.	RT	Evaluation of oral dryness, changes in food enjoyment, taste and smell through structured interview. Taste intensity test for sweet (sucrose), salty (sodium chloride), sour (citric acid) and bitter (quinine sulfate) solutions in water. Participants used a tape-measure to express the intensity perceived. Unstimulated and stimulated parotid saliva flow rates were calculated for each participant.	Study group: Evaluation at 0.5-19 years after RT	Patients were more likely to report changes in their taste and report that it had gotten worse from structured interviews, but there was not difference in the complaints between study and control groups for smell changes. There were differences in sour intensity between the groups and younger patients gave higher values than older patients. No differences in intensity were

						observed for the other tastes.
Shi et al., 2004 (87)	Longitudinal	34 patients with HNC	RT dose was 60-70 Gy	Recognition threshold evaluated for sweet, salty, bitter, sour and umami using whole mouth method. Subjective distress investigation (VAS): To evaluate subjective taste loss and appetite loss.	Pre-RT and then at 15,30,45 and 60 Gy	No statistical difference was found between thresholds at pre-RT and those at 15, 30, 45 and 60 Gy in any taste quality. Significantly impaired threshold of umami taste was revealed at 30 Gy and remained through the following treatment.
Yamashita et al., 2006(a) (61)	Longitudinal	51 HNC	ChemoRT: 40 (78%) RT: 11 (22%) M: 44 (86) Age: 64 (29–89).	Taste recognition threshold for 5 tastes. Sweet, salty, sour and bitter were evaluated by filter paper disc. Umami was also evaluated in only 13 patients by the whole mouth method.	Before, during and after RT	All thresholds significantly impaired at the 5th week of treatment (around 45 Gy) and these alterations improved by the 11th week of treatment with exception of umami. No difference between those patients receiving and not receiving

						concurrent chemotherapy.
Yamashita et al., 2006(b) (63)	Longitudinal	N=118	Chemo RT: 80 (68%) RT: 38 (32%) M: 93 (79) Age: 60.9 (19-89)	Taste recognition threshold for sweet, salt, sour and bitter using filter paper. Patients were grouped in two: -Group A: Radiation field included most of the tongue -Group B: Radiation field did not include the tip of the tongue.	Before, during, and after radiotherapy	Group A: Decreased sensitivity for the 4 basic tastes at 3 weeks after treatment and remained until 8 weeks for all 4 tastes. For both groups, the impairment was reduced at 4 months after treatment.
Yamashita et al. , 2008 (117)	Longitudinal	N=52	RT M:46 (88) Age: 64 (29–89).	Taste recognition threshold for umami (using a Polyethylene pipette, 10 ml of the lowest concentration was circularly dropped in the mouth of the subject).	Before RT and weekly thereafter from the 1st week to 10-12 weeks after start of RT.	Umami taste declined on the 3rd week after the start of RT (around 30 Gy) and improved on the 8th week. No difference in the effect with and without chemotherapy.
Zheng, 2002 (80)	Longitudinal	N=40	RT Age: 27-81 y (mean 59.3)	Taste recognition threshold and suprathreshold intensity with aqueous solutions	Evaluation before RT, at each 10 Gy increase in RT dose and 6	Taste recognition threshold: Bitter taste was the most affected at 30 Gy, while sour and salty

				representing sweet (sucrose), salty (sodium chloride), sour (tartaric acid) and bitter (quinine hydrochloride). A retractable tape measure was used to express taste intensity in terms of distance.	months after completion.	were somewhat affected. Suprathreshold intensity: After initiation of RT, intensity decreased, after a dose of 30 Gy, intensity tended to recover. Six months after completion, taste intensity had recovered fully.

Abbreviations: AML: Ascending Method of Limits ; ChemoRT, Chemoirradiation; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire; EORTC QLQ-H&N35, EORTC Quality of Life Head and Neck Module; Gy, Gray; HN, Head and Heck; HP, Hypopharynx; LC, Laryngeal carcinoma; LE, Laryngectomees; M, Male, NAIM, Nasal Airflow-Inducing Maneuver; NPC, Nasopharyngeal carcinoma; NR, Not reported; OC, Oral cavity; OI, Odor identification; OD, Odor discrimination; ODT, Odor detection threshold; OFT, Odor function test; OP, Oropharynx; OQD, Odor Quality Discrimination; OR, Odor recognition; OTMT, dour tactile matching test; OVMT, Odor visual matching test; PL, Partial laryngectomees; PU, Unknown primary; QOTA, Questions on Odor, Taste and Appetite; RT, Radiotherapy; SN, Sinonasal; SOIT, Scandinavian Odor Identification test ; TDI, Threshold, discrimination and identification total score; UPSIT, University of Pennsylvania Smell Identification Test.

CHAPTER 2: Intensity and liking of basic tastes and aroma among a prospective cohort of head and neck cancer patients[1]

2.1 Introduction

Taste and smell alterations (TSAs) are among the symptoms most commonly reported after treatment for head and neck cancer (HNC) (1), and have been identified as independent predictors of reduced energy intake and weight loss in orally-fed HNC patients (2). Maes et al. reported that at 2 and 6 months post-treatment, 64% and 42%, respectively, of radiotherapy-treated HNC patients complained of moderate to very serious taste alterations (3). Sagar et al. reported that 60% of HNC patients complained of smell alterations with the first dose of radiotherapy (RT) and alterations decreased when treatment was terminated (4).

Previous studies investigating TSAs among HNC patients have used clinical tests of detection and recognition thresholds (3, 5-13), which determine the lowest concentrations of stimulant that can be perceived (14). Threshold studies have identified that perception of the basic tastes and odors is reduced among HNC patients as a result of both RT and chemoirradiation (RTchemo). The ability to recognize umami taste (or the taste of some amino acids and food proteins) is generally impaired after 15-30 Gy of radiation (8, 15), whereas sweet, sour, salty and bitter are significantly impaired after 45 Gy (12). Mossman et al. reported a dose-response relationship between RT and taste loss, with a dose of 60 Gy causing a 90% loss in the perception (16). Additional treatment with chemotherapy (Chemo) inhibits the renewal of taste cells, reducing the ability to taste (17). Studies evaluating odor detection and recognition thresholds reported impairment in patients receiving radiation to the olfactory epithelium (6) with doses greater than 10 Gy (18).

In contrast to tests of detection and recognition thresholds, tests of intensity evaluate stimulus perception at higher concentrations (i.e. supra threshold) as would be perceived in food and daily-life situations (19). Three studies investigated taste intensity among HNC patients using aqueous solutions of the basic tastes. Schwartz et al. evaluated taste intensity among 15 men, 6 months to 19 years post-RT, and reported younger patients rated sour as more intense than healthy age-matched control subjects (20). Zheng et al. reported an overall

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reduction in the intensity performance for sweet, salty, sour and bitter starting at 30 Gy, and full recovery at 6 months after RT completion (21). Barhavand et al. assessed intensity before and 3 weeks after RT, reporting salt and bitter perception to be the most impaired (22). Results of studies using aqueous solutions have been difficult to extrapolate to real-life food (23), since under normal conditions food acts as a vehicle for flavors and it is rare to be exposed to aqueous solutions of the basic tastes. Moreover, liking for umami seems to be reduced when presented as an aqueous solution than when presented as part of a food (24).

Liking is the pleasure obtained from the multi-sensory (taste, smell, trigeminality and touch) stimulation of the oral cavity while eating a food (25, 26). Taste liking and disliking are drivers of food selection (25), and shape nutritional, gastronomical and social patterns (27). Previous studies of cancer populations other than HNC have shown higher liking for saltiness in tomato juice (Molar concentration: 0.25-1 M) and sourness in lemonade (Molar concentration: 0.006-0.1 M of citric acid) compared to healthy individuals (28). Concentration and liking are closely related and their relation can be plotted as an inverted U-shape graph or Wundt curve (29). As the concentration of a taste or smell increases, an optimum point is reached where the concentration is most liked. Levels beyond the optimal concentration can lead to aversion (29). Studies of optimal concentration can be used to compare people of different circumstances (30), such as in health and disease.

Viscosity plays an important role in perception of flavor (31) and food intake (32). Variation in viscosity alters the physiology of the swallowing process (33). As HNC patients experience oral discomfort and symptoms resulting from cancer and its treatment (e.g. xerostomia, mucositis, pain), the perception of optimal viscosity may change at different time points during and beyond treatment. Currently, there are no studies that have explored the perceived intensity and liking for tastants at different concentrations in beverage matrices, or intensity and liking for a variety of aromas among HNC patients before and at multiple time points after treatment. Perceived intensity and liking are more likely to relate to food choices than taste and smell thresholds. Therefore, the aim of this study was to evaluate the intensity and liking of the basic tastes in beverage matrices, viscosity and a variety of aromas before, upon completion of and after treatment for HNC.

2.2 Materials and Methods

2.2.1 Subjects

Patients diagnosed with HNC were recruited from the new patient and outpatient clinics at the Cross Cancer Institute, in Edmonton, Alberta, Canada between January 2012 and June 2014. Inclusion criteria were: older than 18 years, diagnosis of HNC (oral cavity, salivary glands, paranasal sinuses, oropharynx, nasopharynx, hypopharynx and larynx) with any histology and any stage, scheduled to receive or having received curative-intent RT with or without concurrent Chemo or cetuximab. Patients with tumors of the lip and thyroid were excluded. All patients spoke English and provided written informed consent. The study was approved by the Alberta Cancer Research Ethics Committee. Participants were invited to take part in one or more study time points, which included before treatment, end of treatment, 6 weeks and 3-6 months post-treatment.

Patients' main demographic characteristics, smoking status, presence of feeding tube, tumor site, tumor stage, treatment and body weight were extracted from medical records. Patients' food intake was recorded by a self-reported 3-day dietary record (34), a method that provides a valid and reliable estimate of cancer patients' dietary intake (35). Food Processor II Nutrient Analysis Program™ (Esha Research, Salem, OR) was used to determine caloric and protein intake from the dietary records.

2.2.2 Intensity and liking for basic tastes and creaminess

Taste intensity and liking were evaluated using solutions representing the basic tastes (i.e., sweet, salty, sour, bitter and umami) at five suprathreshold concentrations (28, 36), prepared with the addition of taste chemicals (tastants) into commercial beverages as follows:

1) Sweet taste: Sucrose was added to fruit punch-flavored beverage (Kool-Aid® drink mix, Kraft Foods Canada Inc., Ontario, Canada) prepared in water as per manufacturer's instructions. Sucrose concentrations ranged from 6.25×10^{-2} M to 1 M.
2) Salty taste: Sodium chloride was added to reduced-sodium tomato juice (Heinz, Ontario Canada) to generate a concentration range from 6.25×10^{-2} M to 1 M.
3) Sour taste: Citric acid in lemonade (ReaLemon®, Dr Pepper Snapple Group, Inc., Texas, USA) was prepared with 6.25% v/v lemon juice and 0.25 M sucrose. Citric acid concentrations ranged from 3.125×10^{-3} M to 5×10^{-2} M.
4) Bitter taste: Urea in blackcurrant juice (Ribena®, GlaxoSmithKline, UK) was diluted 1:5 in water as per manufacturer instructions. Urea concentrations ranged from 1.25×10^{-1} M to 2 M.

5) Umami taste: Monosodium glutamate was added to vegetable broth (Simply Vegetable Broth Knorr®, Unilever Canada Inc., Toronto ON) to generate concentrations ranging from 0.1% to 10% (w/w).

Beverages were chosen because they are normally associated with the taste being tested (28, 36). Solutions (20mL) in individual lidded containers (30 mL) were stored frozen and brought to room temperature on the day of the test. Viscosity was evaluated through creaminess perception using commercially available milks and creams (0.3, 3.25, 10, 18 and 33% milk fat (M.F.)) (Dairyland®, Saputo Foods Ltd, Canada) served in containers (30mL). Participants were instructed to rinse their mouth prior to and between tasting solutions presented from lowest to highest concentration. Perceived intensity was evaluated on a 9 point scale ranging from 1="Not very" (sweet, salty, sour, bitter, umami or creamy) to 9="Very" (sweet, salty, sour, bitter, umami or creamy) and expressed level of liking on a 9-point hedonic scale ranging from 1="Dislike extremely" to 9="Like extremely". The response "I cannot taste anything" was accepted and recorded.

2.2.3 Smell intensity and liking assessment

Smell intensity was assessed ortho- and retronasally. Orthonasal perception was evaluated using the "Modified Brief Identification Smell Test" (BSIT) (Sensonics, Inc. Haddon Heights, NJ), which consists of a booklet with 12 common micro-encapsulated aromas in scratching cards (37). Participants chose one option among four possible smell identities and rated intensity and liking on 7-point scales from 1="very weak" to 7="very strong" and 1="very pleasant" to 7="very unpleasant", respectively. Scores for intensity and liking were stratified as "high" (scores of 5-7), "neutral" (score of 4) or "low" (scores of 1-3). Participants were classified as normal, deficit or abnormal perception based on normative data for smell identification (38).

Retronasal intensity perception was assessed using aqueous solutions of vanilla flavor (Bonnie & Don, Mississauga, ON. Canada) in concentrations of 0.01%, 0.20% and 0.30% and a blank (water) (39). Participants were instructed to rinse their mouth with water before and in-between the samples, pinch their nose, try each solution from the lowest to the highest concentration, swallow the sample, and exhale through the nose. The perceived vanilla intensity of each solution was rated on a 9-point scale ranging from 1="Not at all" to 9="Very Strong".

2.2.4 Patients' self-reported taste and smell evaluation

The Taste and Smell Survey (40) collects information about the nature and severity of patients' self-reported taste and smell alterations. Here we report responses to five of the survey questions in which patients assessed their current intensity perception for sweet, salty, sour, bitter and smell as "stronger", "weaker/ cannot perceive", or "as strong" compared to before treatment.

2.3 Data analysis

Continuous variables were expressed as median and Inter Quartile Range [IQR] while categorical variables were summarized as sums and percentages. Mann-Whitney U test and Fisher exact tests were used to evaluate differences in energy, protein intake and percent of weight loss among orally-fed and tube-fed patients at each time point, as well as the proportion of participants who reached the recommendation of energy and protein at each time point. Kruskal-Wallis and Fisher 2 by 5 tests compared differences in age and the proportion of males vs. females, smoking, tumour site, tumor stage and treatment across time points. Friedman test was used to evaluate differences of intensity and liking scores within each time point. Chi-square test was used to compare the proportion of participants with normal vs. deficit/abnormal smell perception across time points. Regression analysis tested the hypothesis that intensity scores would increase with rising concentrations and predicted the relationship (linear or quadratic) between liking scores and the increasing concentrations at each time point. Correlation coefficients were interpreted using Dancey and Reidy's categorization, where correlations of ±0.7 to ±0.9 are interpreted as strong, ±0.4 to ±0.6 are moderate and ±0.1 to ±0.3 are weak (41). All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS V.22 for Windows, IBM, New York). Figures were plotted using Tableau (Tableau Software, Version 8.2. Seattle, WA).

2.4 Results

Seventy-eight participants were included in the study. Demographics and patient characteristics before treatment are shown in Table 2-1. Most patients were male (n=60, 76.9%) and the mean age was 59 years. Forty-nine (62.8%) had a pharynx neoplasm. Main therapies were RTChemo ± pre-treatment surgery (n=37, 48.4%) and RT ± pre-treatment surgery (n=27, 34.6%). There were no differences on gender (p=0.847), age (p=0.998), smoking status (p=0.309), tumor stage (p=0.759) or tumor site (p>0.05) among participants across time points. There were no differences in the treatment received among the groups evaluated upon and after treatment completion (p>0.05).

There was no difference in the proportion of tube-fed and orally-fed patients who reached vs. those who did not reach their recommendation of energy and protein intake according to ESPEN guidelines (i.e. 30-35 kcal/kg BW/day, protein: 1.2-2 g/kg BW/day) (42) at each time point (p>0.05). Before treatment, 44% (n=12/23) of orally-fed and 0% (n=0/4) tube-fed patients participants reached their recommendation of energy and protein intake. At the end of treatment, energy and protein intakes were met by 20% (n=2/10) and 30% (n=3/10) of orally-fed patients, respectively, and by 56% (n=5/9) of tube-fed patients for both energy and protein. At 6 weeks post-treatment, 53% (n=10/19) and 58% (n=11/19) of orally-fed patients reached their recommendation of energy and protein intake, respectively, compared to 25% (n=1/4) of tube-fed participants. All participants at 3-6 months post-treatment were orally-fed, and 54% (n=13) and 58% (n=14) reached their recommendation of energy and protein intake, respectively. There were no significant differences in the median energy, protein intake or percentage of weight loss between tube-fed and orally-fed groups at any time point (p>0.05).

2.4.1 Taste intensity and liking

Before treatment, participants were able to distinguish among the increasing concentrations of each taste as indicated by the significant differences in the increasing median intensity scores of each concentration (Table 2-2). Regression analyses showed moderate to strong significant (p<0.0001) correlations between intensity scores and the increasing concentrations for sweet (r=0.707), salty (r=0.498), sour, (r=0.555), bitter (r=0.746), umami (r=0.441) and creamy (r=0.820) (Table 2-3).

At end of treatment, participants were less able to discern among increasing concentrations of the basic tastes, as no differences were found for the median intensity scores of the five concentrations of each of sweet, salty and umami and no differences were found for the intermediate concentrations of sour and bitter (Table 2-2). Correlations between perceived intensity and increasing concentrations for the basic tastes were weak for sweet (r=0.267, p=0.002), sour (r=0.298, p=0.002) and bitter (0.334, p<0.0001) and non-existent for salty or umami (Table 2-3).

At 6 weeks and 3-6 months post-treatment, participants were able to distinguish among concentrations of the basic tastes, as indicated by the significant correlation coefficients

(Table 2-3). Sweet, sour and bitter displayed moderate strength correlation coefficients between intensity and increasing concentration (sweet, r=0.563 and r=0.640, p<0.0001; sour, r=0.485 and r=0.496, p<0.0001; bitter, r=0.475, r=0.461, p<0.0001), while umami displayed weak correlation coefficients (r=0.368 and r=0.312, p<0.0001) at 6 weeks and 3-6 months, respectively. Salty had a weak correlation coefficient at 6 weeks post-treatment (r=0.376, p<0.0001) and the correlation was non-existent at 3-6 months post-treatment (Table 2-3). In contrast, creaminess had a medium-to-strong relationship between intensity and the increasing concentrations at all time points (range, r=0.686 to r=0.820, p<0.0001) (Table 2-3). Median scores indicated that participants were able to distinguish among the different concentrations of milk fat at all time points (Table 2-2).

Liking of increasing concentrations followed different patterns among the basic tastes. Before treatment, liking for saltiness in tomato juice, sourness in lemonade, and bitterness in blackcurrant juice followed inverse functions, with higher concentrations being the least liked (salty, r=-0.526, p<0.0001; sour, r= -0.336, p<0.0001; bitter, r= -0.692, p<0.0001). In addition, liking for sweet and umami, followed quadratic functions, with the least and most concentrated solutions receiving lower liking scores, as indicated by regression analysis results (Table 2-4).

At the end of treatment, there were no significant differences in the median liking scores of the concentrations of the basic tastes (Table 2-2). Linear regression results showed weak inverse functions of liking for sour (r=-0.249, p=0.010) and bitter (r=-0.204, p=0.036) and flat relations of liking for sweet, salty, umami and creamy (Table 2-4).

At 6 weeks and 3-6 months post-treatment, there was a flat relation between the increasing concentrations of sweet and umami and their liking scores. Liking for saltiness, sourness and bitterness followed inverse functions, with the most concentrated beverages being the least liked. For creaminess, regression analysis indicated a quadratic function at 6 weeks post-treatment, but there was high variability in the data (Table 2-4).

2.4.2 Smell intensity and liking

The majority of participants had normal orthonasal perception at all-time points based on BSIT score guidelines (38). Before treatment, 81% (n=22) of participants had a normal ability to identify aromas. At the end of treatment, 6 weeks and 3-6 months post-treatment, the percentage of patients with normal smell identification ability was 74% (n=17), 86% (n=24) and 77% (n=20), respectively. The proportion of participants with normal vs. deficit/abnormal smell perception was not different across time points.

Orthonasal intensity and liking perceptions differed before and after-treatment time points. Before treatment, aromas of smoke, banana and gasoline were generally perceived as very strong as indicated by the high intensity scores given by 23 (88%), 20 (80%) and 18 (69%) participants, respectively. At all the other time points, aromas of banana, smoke and onion were frequently rated with high intensity scores by 48% or more of the participants (Figure 2-1). Smells of banana, cinnamon and chocolate were perceived as very pleasant before treatment, as indicated by high liking scores given by 20 (80%), 19 (70%) and 18 (72%) of the patients, respectively, while cinnamon, rose and lemon were rated with high liking scores at all the other time points by 48% or more of the participants. The aromas perceived as very unpleasant at all time points were gasoline, paint-thinner and smoke. For retronasal test perception, patients were able to distinguish between the water blank and the vanilla solutions, however, they were not able to distinguish among the 0.1, 0.2 or 0.3 % vanilla concentrations, as indicated by their median intensity scores.

2.4.3 Self-assessed intensity of basic tastes and smell

Before treatment, the majority of participants reported no changes in their perception of sweet, salty, sour or bitter on the Taste and Smell Survey (Figure 2-2). At the end of treatment, participants most frequently reported weaker/ cannot perceive for all tastes except for bitter (n=3, 15%). At 6 weeks post-treatment, participants frequently reported weaker/cannot taste for sweet (n=15, 50%), salty (n=16, 52%) and sour (n=12, 39%). Perception of bitter was divided among those patients with no change (n=12, 39%) and weaker/cannot perceive (n=12, 39%). At 3-6 months post-treatment, participants frequently reported weaker/ cannot perceive for salty (n=12, 44%) and a stronger perception of sour (11, 37%). Perception of sweet and bitter was divided among patients with no change and weaker/cannot taste.

The pattern for self-reported smell intensity perception was similar to the pattern of self-reported taste. Twenty-seven (87%) participants reported no changes in the perception before treatment, however, at the end of treatment, 15 (48%) patients reported weaker/cannot smell. At 6 weeks and 3-6 months post-treatment, participants frequently reported no changes in smell (n=14, 45%; n=14, 48%).

2.5 Discussion

This is the first study that investigates concurrently intensity and liking perception for the basic tastes among HNC patients using suprathreshold concentrations of tastants in food matrices. In addition, this study evaluated creaminess intensity and liking perception using several concentrations of M.F., orthonasal intensity and liking perception with common aromas, and retronasal intensity perception with vanilla solutions. Results indicate that patients had a reduced perception of all the basic tastes at the end of treatment, whereas creaminess and smell perception were less affected. Patterns of liking of increasing concentration were unique to the tastant.

Our results contribute to the understanding of taste intensity perception at different time points after treatment for HNC. While intensity scores for all the beverages increased directly with added tastant concentration before treatment, the perception of all the basic tastes was impaired at the end of treatment, especially salty and umami. Participants at 6 weeks and 3-6 months post-treatment were able to perceive changes in intensity, suggesting partial recovery in the ability to differentiate among suprathreshold concentration of the basic tastes. An ability to perceive changes in intensity for sweet, sour, salty and bitter has been reported in gastrointestinal and thoracic cancer patients with and without previous chemotherapy (28, 36).

Liking perception was unique for each basic taste. Sweet and umami liking followed quadratic functions before treatment, with intermediate concentrations being the most liked. At the end of treatment, despite the increasing concentrations of sweet or umami, patients were less able to perceive the tastes and there were no "optimal" concentrations that were generally liked. In addition, there was patient variability in sweet and umami liking despite consistent intensity perception at 6 weeks and 3-6 months post-treatment. Liking for sweet following quadratic function has been reported among gastrointestinal and thoracic cancer patients (36) but a reduced liking for sweet after chemotherapy has been reported among breast cancer patients (43). Umami taste has been associated with hunger stimulation by increasing food palatability in healthy people (44), thus reduced umami perception may lead to reduced appetite and food enjoyment among HNC patients. Salty, sour and bitter perception followed similar patterns of liking and concentration both before and at after treatment time points. Patients were able to perceive increasing concentrations and disliked the most concentrated solutions. Disliking for higher concentrations of salty, sour and bitter has been reported among gastrointestinal and thoracic cancer patients (28, 36).

Different mechanisms have been studied to explain the effect of HNC treatment on the physiology of taste perception (45). Treatment with RT can cause morphologic changes in the gustatory papillae (12, 46) and damage in the taste cell surface (47) with the greater area of the tongue irradiated, the more taste impairment (5, 11). In our study, we found that patients at 3-6 months post-treatment were able to perceive basic tastes, suggesting a certain degree of recovery after treatment. Similarly, Zheng et al. reported a recovered perception when evaluated with aqueous solutions at 6 months post-treatment (21). Patients undergoing reconstructive surgery with free flap (9) or additional chemotherapy have a reduced taste perception (17).

Creaminess intensity perception was similar at all time points with patients able to perceive differences in viscosity. In contrast, creaminess liking was heterogeneous. Liking for increased viscosity followed a quadratic function before treatment and 6-weeks post-treatment. The non-significant correlations at the end of treatment and 3-6 months post-treatment, and the low coefficients of determination at all the time points, suggests high variability in the perception of creaminess liking, which may be determined by symptoms affecting the oral cavity and perception of the optimal level of viscosity (48). Commercial and home-made food products such as oral nutritional supplements or pureed diets may not appeal to HNC patients if the optimal viscosity is not selected. Therefore, future studies should explore liking for different viscosities and textures at different time points after treatment.

In contrast to taste intensity findings, we did not observe smell impairment after treatment. The majority of participants had normal orthonasal perception at all time points and the proportion of participants with normal vs. deficit/abnormal smell perception was not different across time points. Participants were able to distinguish between the blank and the vanilla solutions at all-time points, but were not able to distinguish among concentrations, which suggests a functional retronasal perception that may have adapted after the presentation of the first vanilla solution (45) In our study we did not to calculate the mean radiation dose received by the olfactory epithelium, however, previous studies report impairment in the ability to identify odors after 10 Gy (10, 18). The proposed mechanisms of smell alterations due to RT include a reduction in the number of olfactory receptors, alteration of cellular structure, changes in the surface of receptors and/or interruption in neural coding (6).

Addition of chemotherapy can affect smell perception by affecting olfactory receptor cell division (49, 50). Twenty percent of our participants (n=16) were smokers before treatment and smoking is known to affect smell perceptionby producing glutinous mucous that blocks odor molecules from reaching the olfactory mucosa (51).

Self-reports of taste and smell perception captured changes in intensity perception, as seen with the beverages matrices and modified B-SIT tests. Before treatment, participants frequently reported no changes in the perception of sweet, salty, sour, bitter or smell. After treatment, reduced perception of sweet, salty sour and smell was reported by patients on the Taste and Smell Survey. At 6 weeks and 3-6 months post-treatment, participants reported a variety of perceptions that deserve further study to elucidate if similar results are obtained from both assessment methods (self-reports vs. solutions of tastants).

Participants had an overall difficulty reaching their recommendations of energy and protein intake at all time points, independently of their main source of nutrition (i.e. orally-fed or tube-fed). Before treatment, less than half of the participants reached their recommendation of energy and protein intake according to ESPEN guidelines and this percentage decreased even further at the end of treatment. Energy intake among orally-fed participants at the end of treatment corresponds to previous reports of HNC populations (2). At 6 weeks and 3-6 months post-treatment, half of the participants reached their energy and protein intakes, with weight loss reaching a median of 10% at 3-6 months post-treatment and corresponding to previous reports of weight loss in post-treated HNC patients (2). HNC patients at our institution have access to a registered dietitian and speech and language pathologist who provide weekly follow-up during and after treatment with the goal of maintaining energy and protein requirements, and minimizing weight loss, which may have influenced our results and therefore be different from patients with less access to information.

Results from this study help us to recognize the complexity of liking perception after treatment for HNC. The high variability in taste liking perception as indicated by moderate to weak correlation coefficients and low coefficients of determination at all time points, revealed the differences in opinion among HNC patients and the challenges of providing general dietary modification suggestions or developing products with tastes that will be accepted only by a small group of patients. Smell liking results can help to shortlist the aromas rated with high scores for inclusion in food preparation or food product development, especially if supra threshold perception remains unaffected after RT.

2.5.1 Strengths and limitations of the study

The assessment of patients' taste and smell intensity perception provides useful information to appreciate the complexity of the TSA experience and reveals the difference in perception at different points in time among HNC patients that are unique to this population. Traditional tests of detection and recognition thresholds are helpful to diagnose a loss in the ability to perceive taste or smell. In this study, we observed differences in the ability to perceive intensity and liking. The use of food matrices as carriers for tastants helps participants relate more easily to foods, as the evaluation of liking using aqueous solutions is difficult to extrapolate to real food. Assessment of liking illustrated differences in preference at different time points after treatment, which cannot be obtained through traditional tests and are useful to understand food selection (25). Our cross-sectional design allowed us to gather data more quickly than a longitudinal study and reduce patient burden by scheduling assessments according to patient's standard of care.

Due to the study design, we were not able to observe changes in personal preferences over time or to account for genetic or cultural factors that are known to influence intensity (52) and liking (53), respectively. We did not collect treatment specific information (e.g. volume of tongue irradiated or amount of radiation to the olfactory epithelium) or have sufficient participants to ascertain specific treatment effects (e.g. surgery, targeted therapies or additional Chemo) on taste and smell perception, and liking, as recently reported (27). We present summarized data but as indicated by participants, perceptions of stronger, weaker and no change are unique to the individual. Future studies should study long-term changes in intensity and liking and assess their impact on food patterns.

In conclusion, we observed a loss of ability to discriminate tastant intensity at the end of treatment that was partially resolved at 6 weeks and 3-6 months post-treatment. Patterns of liking of increasing concentration were unique to the tastant and least distinct at end of treatment for sweet, salty, umami and creamy. Smell perception was minimally affected. The study of intensity perception of taste and smell can help healthcare professionals understand patients' experience of TSAs allowing the provision of better information and strategies for their management.

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Table 2-1 Demographics and patient characteristics

	All participants (n=78)
Gender (N,%)	
M	60 (76.9)
Age, year (mean ± SD)	59 (10)
Smoking status (N,%)	
Never smoker	12 (15.4)
Former smoker	50 (64.1)
Current smoker	16 (20.5)
Tumor site (N,%)	
Pharynx	49 (62.8)
Larynx	8 (10.3)
Oral cavity	9 (11.5)
Salivary glands	6 (7.7)
Other[a]	6 (7.7)
Tumor stage (N,%)	
T1/T2	43 (59.7)
T3/T4	29 (40.3)
Not classified	6 (7.6)
Treatment (N, %)	
RT chemo ± surgery	37 (48.4)
RT ± surgery	27 (34.6)
RT cetuximab ± surgery	7 (9.0)
Surgery only	4 (5.1)
No treatment	3 (3.8)
Energy intake, Kcal/KgBW/day (median [IQR]) [b]	
Orally-fed [c]	
Baseline (n=23)	31.4 [23.2-41.3]
End of treatment (n=10)	25.0 [17.7-30.2]
6 weeks post-treatment (n=19)	30.1 [19.3-32.9]
3-6 months post-treatment (n=24)	30.9 [22.5-35.9]
Tube-fed [d] (n=26)	
Baseline (n=4)	22.5 [16.7- 26.5]
End of treatment (n=9)	36.6 [22.4-44.2]
6 weeks post-treatment (n=4)	21.3 [18.3-31.9]
Protein intake, g/KgBW/day (median [IQR]) [b]	
Orally-fed [c]	
Baseline (n=23)	1.23 [1.0-1.6]
End of treatment (n=10)	1.1 [0.9-1.5]
6 weeks post-treatment (n=19)	1.37 [1.1-1.7]
3-6 months post-treatment (n=24)	1.34 [1.0-1.7]
Tube-fed [d]	
Baseline (n=4)	0.9 [0.6-1.2]
End of treatment (n=9)	1.6 [0.9-1.8]
6 weeks post-treatment (n=4)	0.9 [0.7-1.3]
% Weight loss compared to pre-treatment (median [IQR])	
Orally-fed [c]	6.2 [0.6-8.0]
End of treatment (n=20)	5.1 [2.9;12.9]
6 weeks post-treatment (n=26)	10.0 [6.1-16.5]

3-6 months post-treatment (n=31)	
Tube-fed [d]	
End of treatment (n=11)	6.4 [4.9-11.9]
6 weeks post-treatment (n=5)	8.7 [7.3-12.4]

Abbreviations: KgBW, Kilograms of Body Weight; IQR, Inter Quartile range; RT, Radiation Therapy; RTchemo, Chemoirradiation; SD, Standard Deviation.

[a] Including nasal cavity and paranasal sinuses (n=3), unknown primary (n=2) and orbit (n=1).

[b] Food records available for 27 participants at baseline, 19 at end of treatment, 23 at 6 weeks post-treatment and 24 at 3-6 months post-treatment.

[c] 26/78 participants were tube-fed.

[d] 52/78 participants were orally-fed. No participants were tube-fed at 3-6 months post-treatment.

Table 2-2 Taste and smell intensity and liking for five concentrations of basic tastes, creaminess in milk and retronasal perception of vanilla

Taste	Concentrations	Intensity			
		Pre-treatment (median, IQR)	End of treatment (median, IQR)	6 weeks post-treatment (median, IQR)	3-6 mo. post-treatment (median, IQR)
Sweet	6.25 x 10^{-2} M	2.0 [1.0-3.0] a	2.0 [1.0-4.25] a	3.0 [1.0-5.0] a	2.0 [1.0-3.75] a
	1.25 10^{-1} M	4.0 [2.75-5.25] ac	2.0 [1.0-4.0] a	4.0 [2.0-5.0] a	3.75 [2.0-5.0] ac
	2.5 x 10^{-1} M	6.0 [4.0-7.0] bc	2.0 [1.75-5.0] a	5.0 [3.0-7.0] ac	5.0 [3.25-6.75] bc
	5.0 x 10^{-1} M	8.0 [7.0-9.0] bd	3.0 [2.0-6.5] a	8.0 [5.0-8.0] bc	7.0 [5.25-8.5] d
	1 M	9.0 [8.0-9.0] d	3.5 [1.25-8.0] a	8.0 [6.75-9.0] b	8.0 [6.625-9.0] d
Salty	6.25 x 10^{-2} M	6.0 [3.75-7.25] a	3.5 [1.0-6.0] a	6.0 [4.0-8.0] a	4.0 [3.0-8.0] a
	1.25 10^{-1} M	7.0 [6.0-8.0] ac	2.0 [1.0-4.75] a	7.0 [4.0-9.0] ac	5.25 [3.125-8.0] a
	2.5 x 10^{-1} M	8.0 [7.25-9.0] bc	2.0 [1.0-7.0] a	8.0 [5.5-9.0] ab	6.25 [5.0-8.0] ac
	5.0 x 10^{-1} M	9.0 [9.0-9.0] b	2.0 [1.0-7.5] a	8.5 [7.0-9.0] bc	8.0 [0.5-9.0] ac
	1 M	9.0 [9.0-9.0] b	2.0 [1.0-8.5] a	9.0 [8.0-9.0] b	9.0 [0.5-9.0] bc
Sour	3.125 x 10^{-3} M	1.0 [1.0-4.0] a	2.5 [1.0-3.0] a	4.0 [2.0-6.0] a	2.0 [1.0-4.5] a
	6.25 x 10^{-3} M	3.0 [2.0-5.0] ac	3.0 [1.25-4.75] a	5.0 [3.75-7.0] ab	3.5 [2.0-5.5] ab
	1.25 x 10^{-2} M	5.0 [3.75-7.0] bc	3.0 [2.0-4.0] ab	6.0 [4.0-7.0] ab	5.0 [4.0-7.0] bc
	2.5 x 10^{-2} M	7.0 [4.0-8.0] bd	3.0 [1.0-6.0] ab	7.0 [5.0-8.0] b	6.0 [3.25-7.37] c
	5 x 10^{-2} M	8.0 [6.0-9.0] d	5.0 [2.0-8.0] b	9.0 [7.0-9.0] c	8.0 [6.0-9.0] d
Bitter	1.25 x 10^{-1} M	2.0 [1.0-3.0] a	2.0 [1.0-3.0] a	3.0 [1.0-4.0] a	2.5 [1.0-5.0] a
	2.5 x 10^{-1} M	3.0 [2.0-4.0] a	2.0 [1.0-4.0] ab	4.0 [2.0-6.0] a	4.0 [2.0-6.0] ab
	5 x 10^{-1} M	4.0 [3.0-5.0] a	2.0 [1.0-6.0] ab	5.0 [3.0-6.25] ab	4.25 [3.0-6.0] bc
	1 M	7.0 [5.75-8.0] b	3.0 [1.0-6.75] ab	7.0 [5.0-8.0] bc	7.0 [4.625-7.5] cd
	2 M	9.0 [8.0-9.0] b	5.5 [2.0-9.0] b	8.0 [6.0-9.0] c	8.5 [7.0-9.0] d
Umami	0.1 % w/w	4.0 [2.0-6.0] a	4.0 [2.0-6.0] a	5.0 [3.5-6.5] a	4.25 [2.625-6.0] a
	0.3 % w/w	4.0 [3.0-6.0] ab	3.0 [2.0-5.0] a	5.5 [2.25-6.0] a	4.75 [3.0-6.75] a
	1.0 % w/w	5.0 [3.75-6.25] ac	4.0 [3.0-6.0] a	5.0 [3.0-7.0] a	5.0 [3.25-5.875] a
	3.0 % w/w	6.5 [4.0-7.0] bcd	5.0 [2.0-7.5] a	6.0 [4.0-7.0] ab	5.5 [4.0-6.875] ab
	10 % w/w	8.0 [5.75-9.0] d	4.0 [1.5-8.5] a	7.5 [5.25-8.0] b	7.0 [6.0-8.0] b
Creamy	0.3% MF	1.0 [1.0-2.5] a	1.5 [1.0-3.0] a	2.5 [1.25-3.0] a	2.0 [1.0-2.5] a

	3.25% MF	3.0 [2.5-4.5] ab	3.0 [2.0-5.0] ab	4.0 [3.0-5.0] ab	3.0 [2.0-4.5] ab
	10 % MF	6.0 [5.0-7.0] bc	5.0 [3.0-7.0] bc	5.5 [4.0-6.75] bc	5.0 [4.0-6.0] bc
	18% MF	7.0 [7.0-8.0] cd	7.0 [4.0-7.0] cd	7.0 [5.0-7.0] cd	6.0 [5.25-7.0] cd
	33 % MF	9.0 [9.0-9.0] d	9.0 [7.0-9.0] d	9.0 [8.0-9.0] d	8.25 [7.0-9.0] d
Vanilla	0 % v/v	1.0 [0-1.25] a	1.0 [0-2.0] a	1.0 [0-2.0] a	1.0 [0.5-2.0] a
	0.1 % v/v	3.0 [2.75-5.25] b	3.0 [2.0-4.0] b	3.0 [2.0-6.0] b	4.0 [2.0-5.0] b
	0.2% v/v	4.0 [2.0-6.0] b	3.0 [2.0-5.0] b	4.0 [2.0-5.0] b	4.0 [2.5-6.0] b
	0.3 % v/v	4.0 [2.5-6.5] b	3.0 [2.0-5.0] b	3.0 [2.0-6.0] b	5.0 [2.0-6.0] b

Note: Different superscript letters indicate a significant difference ($p<0.05$, with correction) among intensity or liking scores for the individual tastes, milk creaminess and vanilla at each time point. Taste intensity was rated on a 9 point scale ranging from 1="Not very" (sweet, salty, sour, bitter, savory or creamy) to 9="Very" (sweet, salty, sour, bitter, savory or creamy). Taste liking was rated on a 9-point hedonic scale ranging from 1= "Dislike extremely" to 9="Like extremely". Vanilla intensity was rated on a 9-point scale ranging from 1="Not at all" to 9="Very Strong". Smell intensity and liking were rated on 7-point scales from 1="very weak" to 9="very strong" and 1="very unpleasant" to 9="very pleasant". Abbreviations: M, Molar; w/w, weight/weight; MF, milk fat; v/v, volume/volume.

Table 2-2 Taste and smell intensity and liking for five concentrations of basic tastes, creaminess in milk and retronasal perception of vanilla (continuation)

Taste	Concentrations	Liking			
		Pre-treatment (median, IQR)	End of treatment (median, IQR)	6 weeks post-treatment (median, IQR)	3-6 mo. post-treatment (median, IQR)
Sweet	6.25×10^{-2} M	5.0 [4.0-6.0] a	5.0 [3.5-6.0] a	5.0 [3.0-6.0] a	5.0 [4.0-6.0] a
	$1.25\ 10^{-1}$ M	6.0 [5.0-7.0] a	5.0 [4.0-5.5] a	5.0 [4.0-6.0] a	5.0 [4.125-7.0] a
	2.5×10^{-1} M	6.0 [6.0-7.0] a	5.0 [3.5-5.5] a	6.0 [4.0-7.0] a	6.0 [5.0-7.0] a
	5.0×10^{-1} M	6.0 [4.0-7.0] a	5.0 [4.0-5.0] a	5.0 [4.0-7.0] a	6.0 [4.625-7.0] a
	1 M	3.0 [2.0-5.25] b	5.0 [4.0-5.0] a	5.0 [4.0-7.0] a	6.0 [4.0-7.0] a
Salty	6.25×10^{-2} M	6.0 [3.75-7.0] a	4.0 [3.0-5.0] a	4.0 [2.0-5.75] a	4.0 [2.5-5.0] a
	$1.25\ 10^{-1}$ M	4.0 [3.0-6.0] ac	4.5 [3.0-5.0] a	3.5 [2.0-5.25] a	4.0 [2.125-5.0] a
	2.5×10^{-1} M	2.5 [2.0-6.0] bc	4.0 [2.75-5.0] a	4.0 [2.0-5.5] ab	3.0 [2.0-4.875] ac
	5.0×10^{-1} M	2.0 [1.0-4.0] bd	4.0 [2.5-5.0] a	2.5 [1.25-5.0] ab	2.0 [0.25-3.0] bc
	1 M	1.0 [1.0-2.0] d	3.5 [2.25-5.0] a	2.0 [1.0-4.0] b	1.0 [0.250-2.0] b
Sour	3.125×10^{-3} M	6.0 [5.0-7.0] a	5.0 [4.0-5.75] a	5.0 [4.0-6.0] a	5.0 [4.0-6.0] a
	6.25×10^{-3} M	5.0 [4.0-7.0] a	5.0 [4.0-6.0] a	5.0 [4.75-6.0] a	5.0 [4.0-6.0] ab
	1.25×10^{-2} M	5.0 [4.0-7.0] ab	5.0 [4.0-5.0] a	5.0 [3.0-6.75] ab	4.5 [3.0-5.0] ab
	2.5×10^{-2} M	4.0 [2.75-6.25] ab	4.0 [3.0-5.0] a	4.0 [3.0-7.0] ab	4.0 [2.625-5.0] b
	5×10^{-2} M	4.0 [1.75-6.0] b	4.0 [3.0-5.0] a	3.0 [1.25-4.0] b	2.0 [2.0-4.0] c
Bitter	1.25×10^{-1} M	6.0 [5.0-7.0] a	5.0 [3.0-6.0] a	5.0 [3.0-6.0] a	5.5 [3.75-6.5] a
	2.5×10^{-1} M	6.0 [5.0-7.0] a	5.0 [3.0-6.0] a	5.0 [4.0-6.0] a	5.0 [3.25-6.0] a
	5×10^{-1} M	5.0 [4.0-6.5] a	5.0 [3.0-5.5] a	5.0 [3.0-6.0] ab	4.25 [3.0-5.0] ab
	1 M	3.0 [2.0-4.0] b	5.0 [3.0-5.75] a	4.0 [2.0-5.0] b	3.0 [2.0-4.0] bc
	2 M	1.5 [1.0-3.0] b	4.0 [2.0-5.0] a	3.0 [1.0-5.0] c	2.0 [1.0-2.75] c
Umami	0.1 % w/w	6.0 [4.0-6.0] ab	5.0 [4.0-7.0] a	5.0 [3.0-7.0] a	5.0 [3.0-5.0] a
	0.3 % w/w	6.0 [4.0-7.0] ab	4.0 [3.0-6.0] a	5.0 [3.25-6.0] a	4.0 [3.0-5.375] a
	1.0 % w/w	6.0 [5.0-7.0] ab	5.0 [4.0-6.0] a	5.0 [3.0-6.0] a	5.0 [4.0-5.375] a
	3.0 % w/w	6.5 [4.0-7.0] a	5.0 [3.25-6.0] a	5.0 [3.25-6.0] a	5.0 [3.625-6.0] a
	10 % w/w	3.0 [2.0-6.0] b	5.0 [2.5-6.0] a	5.0 [3.0-6.0] a	4.0 [2.0-6.0] a

Creamy	0.3% MF	5.0 [3.0-6.5] a	5.0 [3.0-6.0] a	5.0 [4.25-6.0] a	5.0 [3.0-6.0] a
	3.25% MF	6.0 [4.0-7.0] ab	5.0 [5.0-6.0] ab	6.0 [5.0-6.0] a	5.0 [4.0-6.5] a
	10 % MF	7.0 [6.0-7.0] b	6.0 [5.0-7.0] ab	6.0 [5.0-7.0] a	5.0 [4.0-6.0] a
	18% MF	7.0 [5.0-7.0] b	6.0 [5.0-7.0] b	7.0 [5.0-7.0] a	5.0 [4.0-7.0] a
	33 % MF	5.0 [3.5-7.5] ab	6.0 [5.0-8.0] ab	6.0 [4.0-7.0] a	4.0 [3.0-6.0] a
Vanilla	0 % v/v	-	-	-	-
	0.1 % v/v	-	-	-	-
	0.2% v/v	-	-	-	-
	0.3 % v/v	-	-	-	-

Note: Different superscript letters indicate a significant difference ($p<0.05$, with correction) among intensity or liking scores for the individual tastes, milk creaminess and vanilla at each time point. Taste intensity was rated on a 9 point scale ranging from 1="Not very" (sweet, salty, sour, bitter, savory or creamy) to 9="Very" (sweet, salty, sour, bitter, savory or creamy). Taste liking was rated on a 9-point hedonic scale ranging from 1= "Dislike extremely" to 9="Like extremely". Vanilla intensity was rated on a 9-point scale ranging from 1="Not at all" to 9="Very Strong". Smell intensity and liking were rated on 7-point scales from 1="very weak" to 9="very strong" and 1="very unpleasant" to 9="very pleasant". Abbreviations: M, Molar; w/w, weight/weight; MF, milk fat; v/v, volume/volume.

Table 2-3 Linear regression between perceived intensity and increasing concentrations of sweet, salty, sour, bitter, umami, creamy and vanilla

	Before treatment				End of treatment				6 weeks post-treatment				3-6 months post-treatment			
	R	Adj. R^2	B	S.E.	R	Adj. R^2	B	S.E.	R	Adj. R^2	B	S.E.	R	Adj. R^2	B	S.E.
Sweet	0.707*	0.496	0.017	0.001	0.267*	0.064	0.006	0.002	0.563*	0.312	0.013	0.002	0.640*	0.405	0.014	0.001
Salty	0.498*	0.243	0.056	0.008	0.061	-0.007	0.009	0.015	0.376*	0.133	0.044	0.011	0.119	0.007	0.019	0.014
Sour	0.555*	0.304	0.471	0.058	0.298*	0.080	0.216	0.068	0.485*	0.229	0.378	0.062	0.496*	0.246	0.397	0.059
Bitter	0.746*	0.553	0.050	0.004	0.334*	0.103	0.023	0.006	0.475*	0.220	0.031	0.005	0.461*	0.207	0.033	0.005
Umami	0.441*	0.189	0.283	0.047	0.114	0.004	0.079	0.067	0.368*	0.128	0.226	0.052	0.312*	0.091	0.187	0.049
Creamy	0.820*	0.671	0.196	0.011	0.686*	0.465	0.158	0.017	0.766*	0.583	0.161	0.013	0.727*	0.525	0.162	0.013
Vanilla	0.438*	0.185	9.291	1.772	0.321*	0.093	6.131	1.910	0.358*	0.119	7.681	2.026	0.439*	0.185	9.175	1.830

***p-value <0.05**

Table 2-4 Regression analysis between liking and increasing concentrations of basic tastes and milk creaminess.

Taste	Before treatment				End of treatment				6 weeks post-treatment				3-6 months post-treatment			
	R	Adj. R^2	B	S.E.	R	Adj. R^2	B	S.E.	R	Adj. R^2	B	S.E.	R	Adj. R^2	B	S.E.
Sweet [a]	0.451*	0.192	0.007 -3.587 x 10-5	0.005 0.000	0.113	-0.004	-0.004 8.203 x 10-6	0.005 0.000	0.140	0.005	0.008 -2.063 x 10-5	0.005 0.000	0.146	0.007	0.009 -2.298 x 10-5	0.006 0.000
Salty [b]	-0.526*	0.271	-0.061	0.008	-0.163	0.016	-0.013	0.009	-0.230*	0.044	-0.023	0.009	-0.420*	0.171	-0.045	0.008
Sour [b]	-0.336*	0.107	-0.205	0.047	-0.249*	0.053	-0.123	0.047	-0.281*	0.072	-0.171	0.053	-0.451*	0.197	-0.243	0.041
Bitter [b]	-0.692*	0.475	-0.035	0.003	-0.204*	0.032	-0.009	0.004	-0.422*	0.172	-0.018	0.004	-0.538*	0.284	-0.026	0.003
Umami [a]	0.306*	0.081	0.284 -0.041	0.210 0.020	0.097	-0.009	-0.156 0.011	0.252 0.024	0.076	-0.011	-0.039 7.864 x 10-5	0.232 0.022	0.109	-0.003	0.189 -0.022	0.221 0.021
Creamy [a]	0.286*	0.069	0.154 -0.004	0.044 0.001	0.261	0.048	0.103 -0.002	0.048 0.001	0.233*	0.038	0.108 -0.003	0.046 0.001	0.134	0.004	0.066 -0.002	0.047 0.001

Note: Quadratic models have 2 B values representing coefficients ***a*** and ***b*** in the quadratic function $y=ax^2+bx+c$

*p-value <0.05

a. Quadratic model

b. Linear model

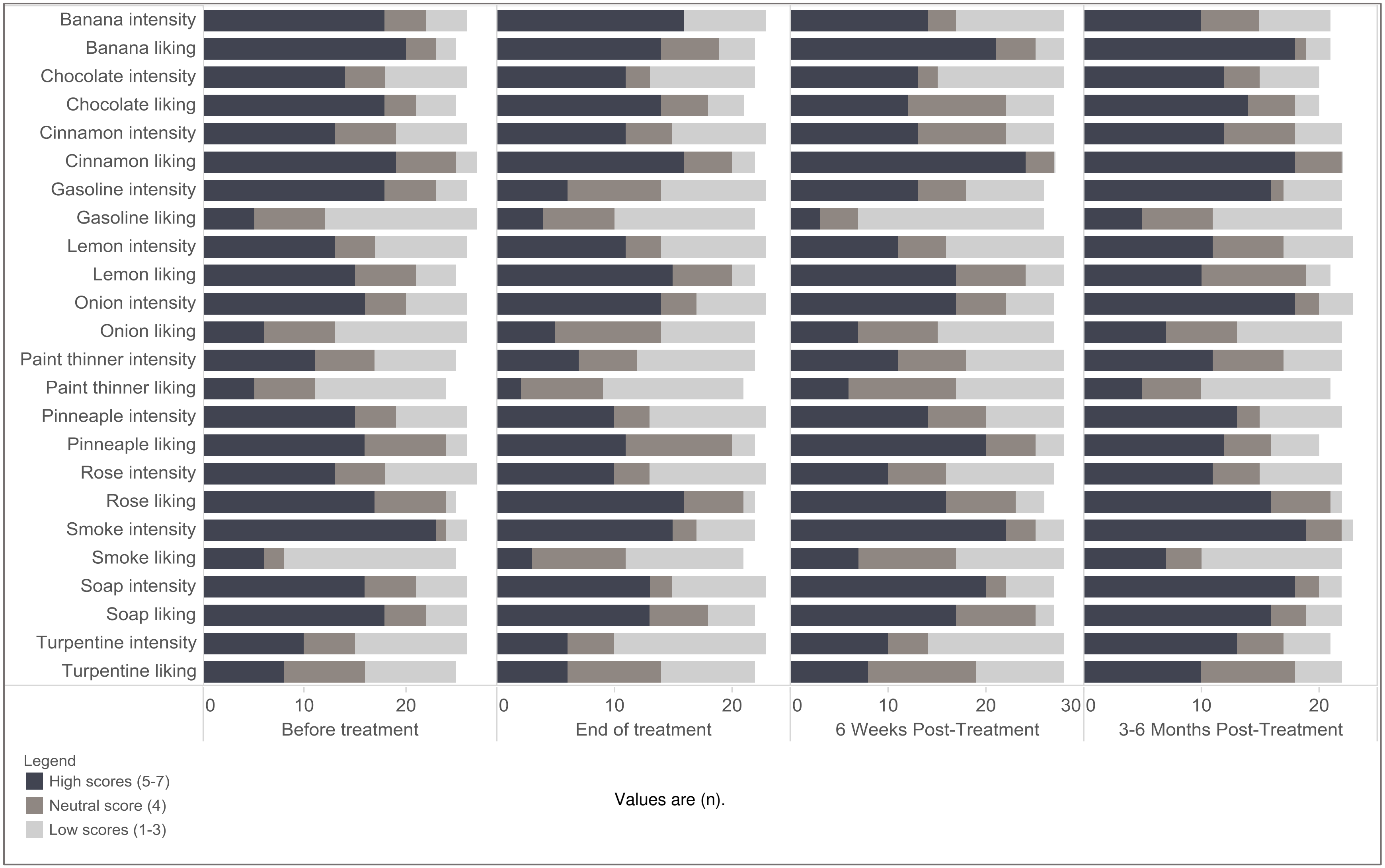

Figure 2-1 Number of participants selecting low, neutral or high scores in the smell intensity and liking scales for the 12 odors of the Modified Brief Smell Identification Test (BSIT).

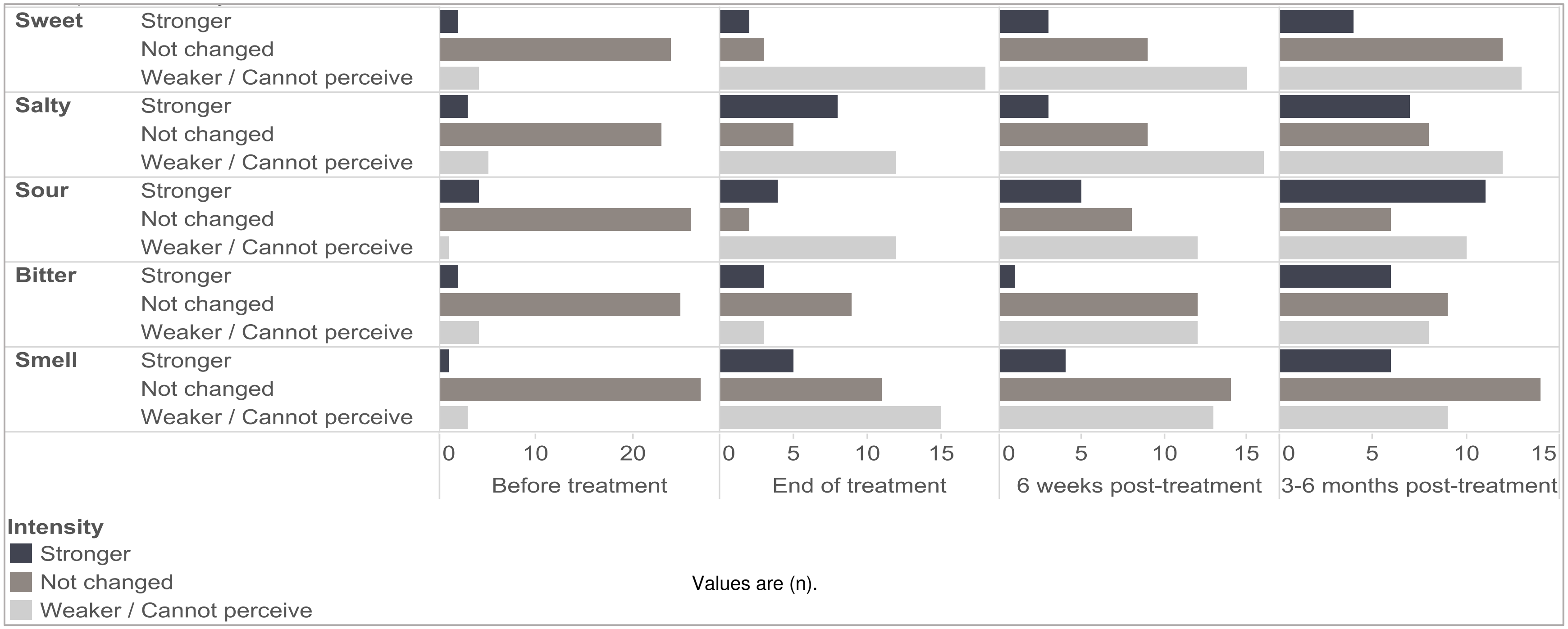

Figure 2-2. Self-reported intensity perception for the basic tastes and smell from the Taste and Smell Survey.

CHAPTER 3: Physical-function of post-treatment head and neck cancer patients influences their characterization of food: Findings of a repertory grid study.[1]

3.1 Introduction

Illness has been identified as a determining point when the reconstruction of food choice occurs (1, 2), and affects the negotiation and priority perception of food values (e.g. health vs. taste or convenience vs. cost) (2, 3). An estimated 48-58% of cancer patients change their eating habits after diagnosis (4, 5). Head and neck cancer (HNC) patients are among those commonly compelled to make changes as their symptoms and structures associated with the tumor often interfere with normal eating and drinking. During treatment, 72% of HNC patients have some type of food restriction that impedes their intake of foods they normally consume (6, 7). Many symptoms persist post-treatment, delaying return to normal eating habits, reducing food enjoyment (8), nutritional status and quality of life (9). Subsequently, eating behaviors evolve to deliberately avoid certain foods and preferentially consume others.

Symptom clustering after HNC treatment impacts nutritional outcomes (10). For instance, decreased swallowing capacity, increased pain, and mucositis lead to reduced energy intake (11) and xerostomia and mucosal sensitivity lead to reduced oral energy and protein intake (12). In addition, symptom severity affects patients' Physical Function (PF), or the ability to perform daily life activities, leading to a reduction in Quality of Life (QoL) and independence (13, 14).

During the 4-10 months following treatment, patients transition to food intake experienced prior to treatment, making alterations to their lifestyle and food choices (15). Patients use a variety of coping strategies, yet some symptoms persist and prevalence of critical weight loss has been estimated to be 13% (16). While the restrictions of PF symptoms on dietary intake and nutritional status among HNC patients is well documented, little is known about patient characterization of food as a consequence of their PF symptoms experience. Knowledge of how HNC patients perceive and characterize foods following treatment could aid nutrition education in all areas of eating behavior, including food acquisition, preparation and intake, and contribute

[1] A version of this chapter was submitted to the European Journal of Oncology Nursing as: Álvarez-Camacho M., Martínez-Michel L., Gonella S., Scrimger R.A., Chu K.P., Wismer W.V. Physical-function of post-treatment head and neck cancer patients influences their characterization of food: Findings of a repertory grid study.

to patients' QoL improvement. Therefore, the aim of this study was to explore the association of Physical-Function and food characterization among HNC patients after treatment is complete.

3.2 Methods

3.2.1 Participant recruitment

The study was conducted at the Cross Cancer Institute (CCI), in Edmonton, AB., between July 2012 and May 2014. Research procedures were approved by the Health Research Ethics Board - Health Panel and all participants completed informed consent. Outpatients who completed treatment for HNC (oral cavity, salivary glands, paranasal sinuses, oropharynx, nasopharynx, hypopharynx and larynx) with any histology and at any stage were invited to participate. Inclusion in the study required being at least 18 years-old, English-speaking, capable of oral intake and having completed treatment between 4 and 10 months prior to the interview. Recruitment continued until no new information emerged from the interviews indicating data saturation was reached (17).

3.2.2 Study design

Individual repertory grid interviews were performed to determine the characteristics of foods perceived by patients post-treatment. The repertory grid method (RGM) is based on the Personal Construct Theory of psychology developed by Kelly (1955) that seeks to understand individuals' perception of the world in their own terms (18). RGM has been used in health care research to explore beliefs about heart failure treatment (19), the meaning and impact of HNC (20), and to assess patient preferences for angina treatments (21).

Twelve foods were selected from a previous study in post-treatment with HNC patients (11) for use in the RGM interviews. These foods represented three categories: foods commonly eaten (milk, fish, eggs, and cooked vegetables), foods eaten sometimes (bread, meat, chicken and pulp fruits) and foods seldom eaten (rice, cheese, fresh vegetables and citrus fruits). The names of these foods were written on individual white cards, one food per card. Before each interview, cards were arranged into six triads by randomly selecting three cards from the initial pool of 12 (triad 1). The second triad was constructed by randomly selecting one of the cards from the first triad and including two more from the remaining nine. This procedure was repeated until all cards were included in a triad (22).

Triads were presented one at a time and participants were asked to think about "something that two foods had in common that the third did not have" in regards to their current food intake and then "how the third food differed from the other two", which prompted participants to elicit bi-polar descriptors known as constructs. When all possible constructs within a set of cards had been elicited, a new triad was shown and the same procedure was followed. To conclude the interview, each participant used their own constructs to rate each of the 12 foods on a 5-point scale, where 1 represented the first elicited construct (e.g. cheap) and 5 represented the opposite of that construct (e.g. expensive). Details of this methodology have been reported elsewhere (23). The interviews (approximately 1 to 1.5 hours) took place in meeting rooms at the CCI.

3.2.3 Socio-demographic status, taste and smell, appetite, food intake and quality of life

A questionnaire on socio-demographic status was used to collect data on education, housing, income, ethnic group and dietary restrictions. Self-reported taste and smell alterations (TSA) and associated factors were evaluated through the Taste and Smell Survey (TSS) (24) and a supplementary questionnaire modified for the study on potential triggers and symptoms that are known to affect taste and smell perception and the ability to eat (25). The TSS quantifies the nature and severity of TSA through a final score, the Chemosensory Complaint Score (CCS) that ranges from 0 to 16 (Insignificant/Mild (1-4), Moderate (5-9) and Severe (10-16) (26). Appetite and hunger were assessed using the Council of Nutrition Appetite Questionnaire (CNAQ) (27). Energy and protein intake were estimated from three-day food records (three consecutive days including one weekend day) using the Food Processor II Nutrient Analysis Program™ (Esha Research, Salem, OR).

Quality of Life was assessed using the University of Washington Quality of Life Questionnaire (UW-QoL) version 4 (28), a tool that evaluates overall QoL and severity of 12 common symptoms (i.e., chewing, swallowing, speech, taste, saliva, appearance, anxiety, mood, pain, activity, recreation and shoulder) in scores from 0 to 100, where higher scores indicate better QoL. The Social-Emotional Function domain is calculated as the average of anxiety, mood, pain, activity, recreation and shoulder scores, while the Physical-Function domain is calculated as the average of taste, chewing, swallowing, speech, saliva and appearance. Patient scores were stratified as “better PF” (i.e., ≥ 61.7) or “worse PF” (i.e. < 61.7) according to the overall median PF domain score, reflecting less or more PF impairment, respectively. The RGM characterization of food between the two PF groups was compared.

3.2.4 Data analysis

Data were analyzed by General Procrustes Analysis (GPA) (29) using Senstools for Windows V 1.2.2.0 (OP&P, Utrecht, The Netherlands). GPA identifies trends among participant’s own descriptors (configurations) through mathematical transformations of translation, rotation/reflection and stretching/shrinking, creating a multidimensional consensus map that represents the mean of the individual configurations for each PF group and illustrates the way participants characterize the 12 foods, i.e., closer foods share similar characteristics (22, 30, 31). Categories of constructs with a correlation value greater than ±0.70 were considered significant to label dimensions on the consensus maps, as they explain about 50% of the total variance (31). Foods were grouped by their proximity to each other in the consensus space and by the amount of variance explained by food for each dimension on the GPA (32). The Procrustes Analysis of Variance (PANOVA) test was used to estimate differences between individual and consensus configurations (33). A permutation test was used to estimate the probability that the resulting consensus could have been generated by chance (34).

3.3 Results

3.3.1 Participants’ characteristics

Nineteen HNC patients, 17 males and 2 females, took part in the study; all participants were enrolled within 17-46 weeks post-treatment and almost 80% (n=15) had oropharynx cancer (Table 3-1). Eleven patients were classified as better PF and eight as worse PF. Participants’ education level ranged from partial or completed high school to partial or completed graduate degree for both groups. Most participants (n=17) were Caucasians. Many participants (over 60% for both groups) prepared meals by themselves. Financial problems limited food choice for only one better PF patient. Four worse PF patients described their appetite as “poor” or “very poor” (Table 3-1). Median energy intake was 31 [29.7-36.9] and 27.6 [22.3-37.2] Kcal/KgBW/day for better and worse PF patients, respectively. Median protein intake was 1.5 [1.0-1.7] and 1.2 [1.0-2.0] g/KgBW/day for the better PF and worse PF patients, respectively. Overall QoL ranged from 60 “good” to 100 “outstanding” for better PF patients, and from 20 “poor” to 80 “very good” for worse PF patients. Nearly all better PF patients (n=10, 90%) and all worse PF patients experienced moderate to severe TSA (Table 3-2).

3.3.2 Repertory Grid Construct elicitation

A total of 233 constructs elicited during the RGM interviews were reviewed and classified into one of 72 categories of similar constructs (Table 3-3). The most frequent constructs elicited by both better and worse PF patients made reference to themes of taste, ease of eating, convenience, texture, potential to worsen symptoms and liking. For each of the PF patient groups, GPA generated two dimensions explaining close to 50% of the total variance and were used to plot the corresponding consensus maps (31). A total of 129 and 103 constructs categories could have been potentially used for interpretation of the better and worse PF groups’ consensus maps, respectively, but only those significantly correlated to each dimension were selected (31, 33). Permutation tests indicated that there was a probability of less than 5% that results found were due to chance.

3.3.3 Participant agreement

Individual configurations of participants 16 (better PF) and 13 (worse PF) differed from the average group agreements on dimension 1, as evidenced by higher residuals on the PANOVA tests for each group (1.47 and 1.62, respectively). This may be attributable to specific symptom experiences or personal preferences. For instance, participant 16 had the worse appetite score of the better PF patients, while participant 13 was among those reporting no saliva, feeling somewhat depressed and was among those with a low Social-Emotional score. However, as their socio-demographic, tumor and treatment data were not different from other participants they were not excluded from the analysis.

3.3.4 Better physical-function patients

Each better PF patient generated between 5-13 constructs (average 11). Along the two dimensions of the GPA, foods are separated into four different groups (Figure 3-1): (A) milk, eggs and fish; (B) citrus, pulp fruits, fresh vegetables and cheese; (C) rice, bread, chicken and meat; and (D) cooked vegetables. GPA's first two dimensions of the consensus explained 47.53% of the total variance (Dimension 1=25.16%, Dimension 2=22.37%).

Dimension 1 broadly separated foods that have dry texture and are difficult to eat (positive axis) from those that were easy to eat (negative axis); milk and meat were the most contrasting foods for this dimension. Dimension 2 discriminated foods that are convenient but have a potential to worsen symptoms (positive axis) from those with low potential to worsen symptoms and are easy to eat (negative axis); pulp fruits and fish were the most contrasting foods for this dimension.

Group A was comprised of foods that are commonly eaten, and were characterized by their ease of eating, liking and low potential to worsen symptoms. Groups B and C included a combination of foods that are sometimes eaten and seldom eaten. While group B foods were characterized by their convenience and potential to worsen symptoms, group C foods were characterized by their dry texture and eating difficulty, but acknowledged for their good taste. Finally, group D was positioned at the center of the consensus map as it was mostly characterized by descriptors of dimension 3, eating frequency and texture. Dimension 3 explained 11.08% of the total variance.

3.3.5 Worse physical-function patients

Each patient with worse PF generated between 6-22 constructs (average 13). Along the two GPA dimensions foods were separated into five different groups (Figure 3-2): (A) eggs and milk; (B) citrus fruits, fresh vegetables and pulp fruits; (C) cheese, rice and bread; (D) chicken, meat, and fish and (E) cooked vegetables. The first two dimensions of the consensus map explained 54.87% of the total variance (Dimension 1=38.08%, Dimension 2=16.79%).

Dimension 1 broadly separated foods that were easy to eat (positive axis), from those that have dry texture and are difficult to eat (negative axis); milk and bread were the most contrasting foods in this dimension. Dimension 2 separated those foods that are difficult to eat (positive axis) from those that are easy to eat, have a low potential to worsen symptoms and are nutritious (negative axis), with citrus fruits and fish the most contrasting foods in this category.

Similar to the better PF patients, group A foods were perceived positively and characterized by their low potential to worsen symptoms, ease of eating and good texture. Foods in groups B and C were characterized by the need to modify their texture; however, foods in Group B were further described by their ease of eating, convenience, good taste and nutritional value. Group D foods were characterized by their dry texture, but acknowledged as nutritious. Fish in particular was characterized by its strong smell but ease of eating. Finally, group E was mostly characterized by descriptors of dimension 3, fiber content and quality, which explained 14.3% of the total variance.

3.4 Discussion

Nineteen post-treatment HNC patients, stratified by UW-QOL PF score as better or worse PF, characterized 12 foods in repertory grid interviews. All patients, regardless of their PF, used constructs with themes of taste, ease of eating, convenience, texture, potential to worsen symptoms and liking to characterize foods, while nutrition and smell constructs were only significant among worse PF patients.

All patients characterized foods commonly eaten (milk, eggs, fish) by their low potential to worsen symptoms and ease of eating. Worse PF patients characterized these foods as having good texture and described fish by its strong smell. Foods eaten sometimes (meat, chicken and bread) were characterized by their dry texture and eating difficulty. In particular, worse PF patients characterized chicken and meat as having the potential to worsen symptoms, although they were recognized as nutritious. Pulp fruits were characterized as convenient and easy to eat by both groups and their good taste and nutritional value were recognized by the worse PF group. Worse PF patients described the foods seldom eaten (rice, cheese, fresh vegetables and citrus fruits) as requiring texture modification, while better PF patients described them as convenient. Rice, in particular, was described as dry by both groups. Cooked vegetables were characterized by their eating frequency and texture (better PF patients) and by their fiber content and quality (worse PF patients).

We identified differences in the characterization of foods according to patients' PF, confirming and deepening the understanding of food choice described in previous studies (9, 35, 36). Sorensen et al. observed that patients with severe eating-related symptoms (e.g. anorexia, nausea, xerostomia, dysphagia) preferred simpler foods with a consistency and texture that facilitates eating to meet nutritional requirements and “stay alive” (35). Similarly, in this study, the constructs of nutrition (i.e. “good source of protein”, “has fat on it”, “nutritious”), and smell (i.e. “strong smell) were significant for the worse PF patients only.

Not all frequently used constructs were significantly correlated with the two dimensions of the repertory grid; constructs of health, tradition/family, clean-up effort, temperature and price were not significant for either PF group indicating differences in the perception of these constructs. The majority of better PF patients (8 out of 11) had an annual income of $CAD 83,000 or more, which may allow them access to resources (e.g. ready-made meals or paid help at home) that would positively impact their eating experience, however, constructs on price were not significant for either group of patients. In addition, all participants had some or completed high-school education and only a few were living by themselves, therefore, different results may be expected from HNC patients with no formal education or living alone.

The construct “good source of protein” was frequently mentioned during the interviews (n=12). Three participants chose characteristics related to carbohydrates as opposites for “good source of protein” (i.e., “rich in carbohydrates”, “starchy food” or “natural sugars”). However, protein and carbohydrates are macronutrients not mutually exclusive, occurring in some plant and dairy based foods, and this misbelief should be clarified during nutritional counseling to reduce impact on food intake. The importance of detecting misconceptions around food in at risk populations has been reported previously (5, 37).

Almost all better PF patients reached the current European Society for Parenteral and Enteral Nutrition (ESPEN) recommendation of 30-35 Kcal/Kg/day of daily energy intake. However, both better and worse PF patients had difficulty reaching the recommended protein intake of 1.2-2 g/Kg/day (38), that may be partially explained by the presence of oral symptoms still prevalent at this period (12) including moderate to high TSA (39).

Between 4-10 months post-treatment, HNC patients experience improvement of some symptoms, although chewing difficulties, pain and xerostomia persist leading to adjustments to food intake (40, 41). Larsson et al. reported that 65% of HNC patients have two or more eating problems or causes of eating problems at 6 months post-treatment and this percentage remains unchanged until one year post-treatment (41). The prevalence and interference with eating of individual symptoms on food choice and dietary intake should be further explored and future studies could use the Head and Neck Symptom Checklist to identify a patient's most troublesome symptoms with respect to dietary intake (42).

Although a cancer patient's symptom experience is individual and the drivers of food choice are complex, this study highlights the influence of patient PF on the characterization of foods by post-treatment HNC patients. Knowledge of food characteristics as perceived by patients can help health care providers increase adherence to dietary counseling in two ways. First, seldom eaten foods may be more easily identified and strategies for food preparation promptly suggested, reducing the impact of symptoms on food intake. Second, misconceptions of food characteristics, such as the perception that protein and carbohydrates are mutually exclusive food components, can be clarified in a timely manner.

3.4.1 Strengths and limitations

The technique of RGM followed by GPA generated both qualitative and quantitative information about patients' food characterization. The RGM technique facilitates participants' communication using their own constructs, avoiding researcher bias. Our sample size was relatively small, however the number of participants is consistent with other repertory grid studies (21, 43) and was sufficient to achieve data saturation. Our sample was predominantly male and different descriptors may have been elicited with a greater number of female participants, as in general women tend to have a strong focus on healthy eating (44) and are generally more involved in food purchase and preparation. Our sample reflects the higher incidence of HNC among males relative to females in North America (45, 46). Finally, HNC patients at our Institution are invited to attend a post treatment symptom support group led by a multidisciplinary health care team, therefore, patients from centers who do not have this type of support may report different food characterizations.

The PF domain of the UW-QoL tool represents the level of performance/impairment for activities related to the head and neck areas. While four of its components are directly related to food intake activities (i.e. taste, chewing, swallowing and saliva), two of them (i.e. speech and appearance) may not directly affect patients' food intake or food characterization, but may still alter eating-related behaviours due to social isolation (47, 48). Further analysis should consider eating-related symptoms to discriminate between patient with better and worse performance.

The 12 foods used in this study represent a small selection of foods commonly eaten, eaten sometimes and seldom eaten which permitted the interviews to be performed within a reasonable time, and reduced participant burden. Future studies could explore a wider variety of foods or food products. Participation of HNC patients at a later time point between 12 and 24 months post-treatment could reflect a different food characterization, highlighting differences between patients with varying success in the resumption of pre-treatment oral intake.

3.5 Conclusions

HNC patients frequently used constructs with themes of taste, ease of eating, convenience, texture, potential to worsen symptoms and liking to characterize foods regardless of their PF. Constructs of nutrition and smell were significant only among worse PF patients. Foods seldom eaten were characterized for their dry texture, while those foods commonly eaten were characterized by their ease of eating and low potential to worsen symptoms.

Future studies should explore patient’s characterization of food beyond one year post-treatment, when symptom severity is further reduced and perceptions of foods may change reflecting the new context. Nutrition counseling for post-treatment HNC patients must incorporate their Physical-Function status and the perceptions that drive food selection or avoidance to provide appropriate advice for adequate, appropriate and enjoyable food intake.

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Table 3-1 Characteristics of study participants

		Better Physical Function[a] n (%) N=11	Worse Physical Function[b] n (%) N=8
Age (years)		58 [56-65]	57 [50-58]
Gender	Male	9 (81)	8 (100)
Time post-treatment (weeks)		32 [25-40]	24 [20-31]
Tumor site	Oropharynx	9 (81.8)	6 (75)
	Salivary glands	1 (9.1)	0 (0)
	Larynx	1 (9.1)	0 (0)
	Sinuses	-	1 (12.5)
	Primary unknown	-	1 (12.5)
Tumor stage	II	1 (9.1)	-
	III	3 (27.3)	1 (12.5)
	IV	7 (63.6)	7 (87.5)
Mode of treatment	Radiation therapy (RT)	1 (9.1)	1 (12.5)
	Concurrent, chemotherapy (chemo) RT	4 (36.3)	5 (62.5)
	Surgery, postoperative RT	2 (18.2)	-
	Surgery, postoperative chemoRT	1 (9.1)	1 (12.5)
	Concurrent, RT cetuximab	3 (27.3)	1 (12.5)
Education	Partial or completed high school	1 (9.1)	2 (25)
	Partial or completed college diploma/ university degree	8 (72.7)	5 (62.5)
	Partial or completed Graduate degree (Master's or Doctorate)	2 (18.2)	1 (12.5)
Household size	1 persons	1 (9.1)	1 (12.5)
	2 persons	7 (63.6)	4 (50)
	3 persons	3 (27.3)	1 (12.5)
	4 persons	0 (0)	2 (25)
Annual income ($ CAD)	41,544 or less	2 (18.2)	2 (25)
	41,544 - 83,088	1 (9.1)	2 (25)
	83,000 - 128,800	5 (45.4)	2 (25)
	128,800 or more	3 (27.3)	1 (12.5)
	Prefer not to answer	0 (0)	1 (12.5)
Ethnic group	Asian	1 (9.1)	0 (0)
	First Nations	0 (0)	1 (12.5)
	Caucasian	10 (90.9)	7 (87.5)
Food restriction	Yes	2 (18.2)	0 (0)
Appetite	Poor/ Very poor	1 (9.1)	4 (50)
	Average	5 (45.4)	2 (25)
	Good/Very good	5 (45.4)	2 (25)

"I feel hungry"	Rarely	0 (0)	4 (50)
	Occasionally/ Some of the time	10 (90.9)	3 (37.5)
	Most of the time	1 (9.1)	1 (12.5)
Meals	Meals prepared by self	7 (63.6)	5 (62.5)
	Eat meals alone	3 (27.3)	3 (37.5)
	Money problems often prevents them from eating food they enjoy	1 (9.1)	0 (0)

Abbreviations: CAD, Canadian Dollar.
Values represent median [IQR] or number of patients (%). [a] Defined as $\geq$ median score of 61.7 on the Physical Function domain of the University of Washington Quality of life v4. [b] Defined as < median score of 61.7 on the Physical Function domain of the University of Washington Quality of life v4.

Table 3-2 Quality of life, nutrient intake and Chemosensory Complaint Scores (CCS) of study participants

Participant number	UW-QOL				Nutrient intake		CCS	
	Physical function	Social-emotional	Overall score	Overall quality of life	Energy [Kcal/Kg BW/ day]	Protein [g/Kg BW/day]	Score/16	Category
Better Physical Function[a] (n=11)								
02	73	92	80	Very good	29.7	1.7	9	Moderate
05	86	87	80	Very good	38.1	1.3	6	Moderate
08	83	88	80	Very good	29.1	1	6	Moderate
09	62	83	60	Good	32.2	1.7	2	Mild
11	66	70	60	Good	-	-	7	Moderate
12	68	88	100	Outstanding	15.6	0.9	8	Moderate
14	62	58	60	Good	31.2	0.9	12	Severe
15	78	96	80	Very good	30.8	1.5	8	Moderate
16	72	83	60	Good	36.9	1.7	7	Moderate
17	63	83	60	Good	30	1.4	10	Severe
19	77	78	80	Very good	42.9	1.9	13	Severe
Worse Physical Function[b] (n=8)								
01	58	74	60	Good	22.1	0.7	13	Severe
03	51	50	40	Fair	22.5	0.9	6	Moderate
04	54	70	20	Poor	34.2	1.5	7	Moderate
06	48	58	40	Fair	46.7	2.7	8	Moderate
07	42	68	60	Good	40.2	2.5	9	Moderate
10	61	53	80	Very good	20.1	1.1	6	Moderate
13	49	50	60	Good	30.7	1.3	12	Severe
18	53	63	40	Fair	24.6	1	13	Severe

Abbreviations: CCS, Chemosensory Complaint Score; UW-QOL v4, University of Washington Quality of life version 4. The CCS total scores were stratified as Insignificant/Mild (1-4), Moderate (5-9) and Severe (10-16). UW-QOL v4: Scores range 0-100, higher scores indicate better quality of life. [a] Defined as $\geq$ median score of 61.7 on the Physical Function domain of the UW-QOL v4. [b] Defined as < median score of 61.7 on the Physical Function domain of the UW-QOL v4.

Table 3-3 Themes and categories of constructs stratified by patients Physical Function (PF)

Themes	Categories of constructs	Better PF[a]		Worse PF[b]		Total	
		N=11		N=8		N=19	
		n	%	n	%	n	%
Taste	Taste is good	7	5.4	3	2.9	10	4.3
	Taste is as remember	4	3.1	2	1.9	6	2.6
	Bland	3	2.3	5	4.9	8	3.4
	I could taste it right after treatment	1	0.8	2	1.9	3	1.3
	Needs sauces/ condiments	1	0.8	2	1.9	3	1.3
	Cannot eat by itself	1	0.8	1	1.0	2	0.9
	Taste increased	1	0.8	1	1.0	2	0.9
	Card board taste	1	0.8	0	0.0	1	0.4
	Did not change its taste during treatment	1	0.8	0	0.0	1	0.4
	After first bites, it is not the same	1	0.8	1	1.0	2	0.9
	Metallic taste	0	0.0	1	1.0	1	0.4
	Mixed-up flavors	0	0.0	1	1.0	1	0.4
Ease of eating	Easy to swallow	8	6.2	7	6.8	15	6.5
	Easy to chew	5	3.9	4	3.9	9	3.9
	Goes down easily	5	3.9	2	1.9	7	3.0
	Needs fluids	4	3.1	5	4.9	9	3.9
	Need to eat in small portions	4	3.1	2	1.9	6	2.6
	Takes longer to eat	1	0.8	0	0.0	1	0.4
Convenience	Easy to prepare/ cook	4	3.1	3	2.9	7	3.0
	Can be used in many preparations	3	2.3	1	1.0	4	1.7
	Can eat as a snack	2	1.6	0	0.0	2	0.9
	Can eat in the morning	1	0.8	1	1.0	2	0.9
	Easy to get	1	0.8	1	1.0	2	0.9

	Can eat raw	0	0.0	4	3.9	4	1.7
	Can use in a shake	0	0.0	1	1.0	1	0.4
	Don't have to wash before	0	0.0	1	1.0	1	0.4
Nutrition	Good source of protein	7	5.4	5	4.9	12	5.2
	Contains minerals	1	0.8	2	1.9	3	1.3
	Contains fiber	1	0.8	1	1.0	2	0.9
	Has calories	1	0.8	1	1.0	2	0.9
	Nutritious	1	0.8	1	1.0	2	0.9
	Rich in fatty acids	1	0.8	0	0.0	1	0.4
	Has fat on it	0	0.0	2	1.9	2	0.9
	Lifesaver food	0	0.0	1	1.0	1	0.4
	Good source of vitamins	0	0.0	1	1.0	1	0.4
Texture	Dry	8	6.2	6	5.8	14	6.0
	Hard texture	4	3.1	4	3.9	8	3.4
	Texture that I enjoy	2	1.6	0	0.0	2	0.9
	Needs to be pureed	1	0.8	1	1.0	2	0.9
	Grainy texture	1	0.8	0	0.0	1	0.4
	Rubbery texture	1	0.8	0	0.0	1	0.4
	Not starchy	0	0.0	2	1.9	2	0.9
Potential to worsen symptoms	Dries out my mouth	1	0.8	1	1.0	2	0.9
	I could have it even when I was sick	1	0.8	2	1.9	3	1.3
	An ingredient bothers me	0	0.0	1	1.0	1	0.4
	Got me sick during chemo	0	0.0	1	1.0	1	0.4
	Hurts my mouth/ throat	0	0.0	1	1.0	1	0.4
	Makes me feel nauseous after a bite	0	0.0	1	1.0	1	0.4
	Hard on my stomach	4	3.1	0	0.0	4	1.7
Liking	I have always liked it	5	3.9	1	1.0	6	2.6
	I don't enjoy it now	4	3.1	1	1.0	5	2.2
	Did not like it before	1	0.8	0	0.0	1	0.4

	I have regained my appetite	1	0.8	0	0.0	1	0.4
	I eat because I need	0	0.0	2	1.9	2	0.9
Eating frequency	I have it very often	5	3.9	1	1.0	6	2.6
	Have never eaten	4	3.1	1	1.0	5	2.2
	Not tried after treatment	2	1.6	3	2.9	5	2.2
	Used to eat this before	0	0.0	1	1.0	1	0.4
Health	Healthy	1	0.8	1	1.0	2	0.9
	Beneficial for cancer patients	1	0.8	0	0.0	1	0.4
	I am intolerant	1	0.8	0	0.0	1	0.4
	My doctor said to eat it	1	0.8	0	0.0	1	0.4
Freshness/ Quality	Freshness	2	1.6	0	0.0	2	0.9
	I need it fresh	0	0.0	1	1.0	1	0.4
	We don't have good quality in the city	0	0.0	1	1.0	1	0.4
Smell	Strong smell	1	0.8	1	1.0	2	0.9
	Bad smell	1	0.8	0	0.0	1	0.4
Tradition/ Family	It is a tradition to have	1	0.8	0	0.0	1	0.4
	My family likes it	0	0.0	1	1.0	1	0.4
Clean-up effort	Requires energy to clean up	0	0.0	1	1.0	1	0.4
Temperature	Need to eat warm	0	0.0	1	1.0	1	0.4
Price	Expensive	4	3.1	1	1.0	5	2.2
Total		129	100	103	100	232	100

Abbreviations: PF, Physical Function

[a] Defined as $\geq$ median score of 61.7 on the Physical Function domain of the UW-QOL v4

[b] Defined as < median score of 61.7 on the Physical Function domain of the UW-QOL v4.

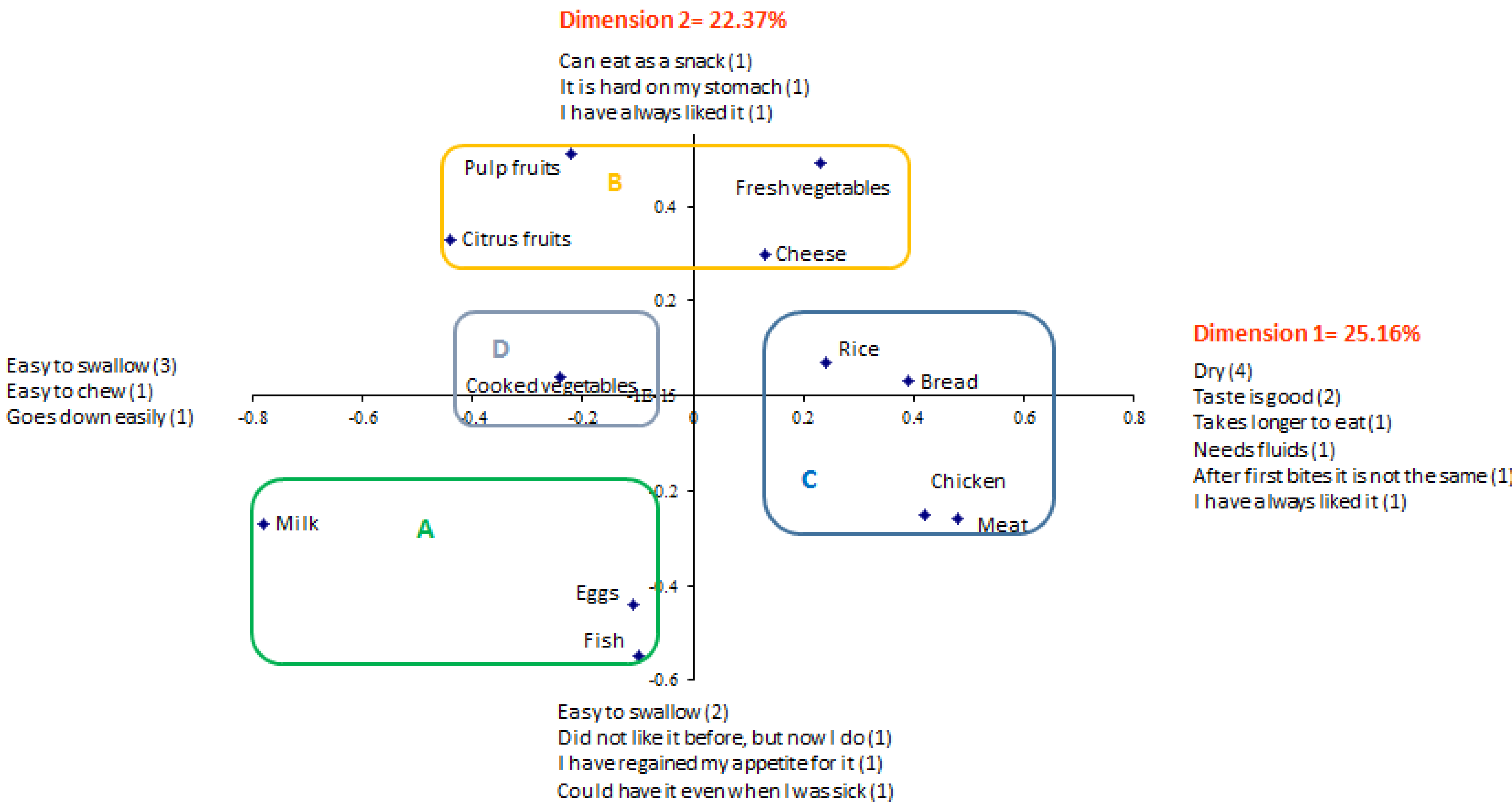

Figure 3-1 Consensus map of the better physical-function patients group (n=11).
The map reflects the location of foods according to constructs of dimension 1 (horizontal) and dimension 2 (vertical).
Note: Frequency (n) of constructs with correlations greater than |0.7| are displayed.

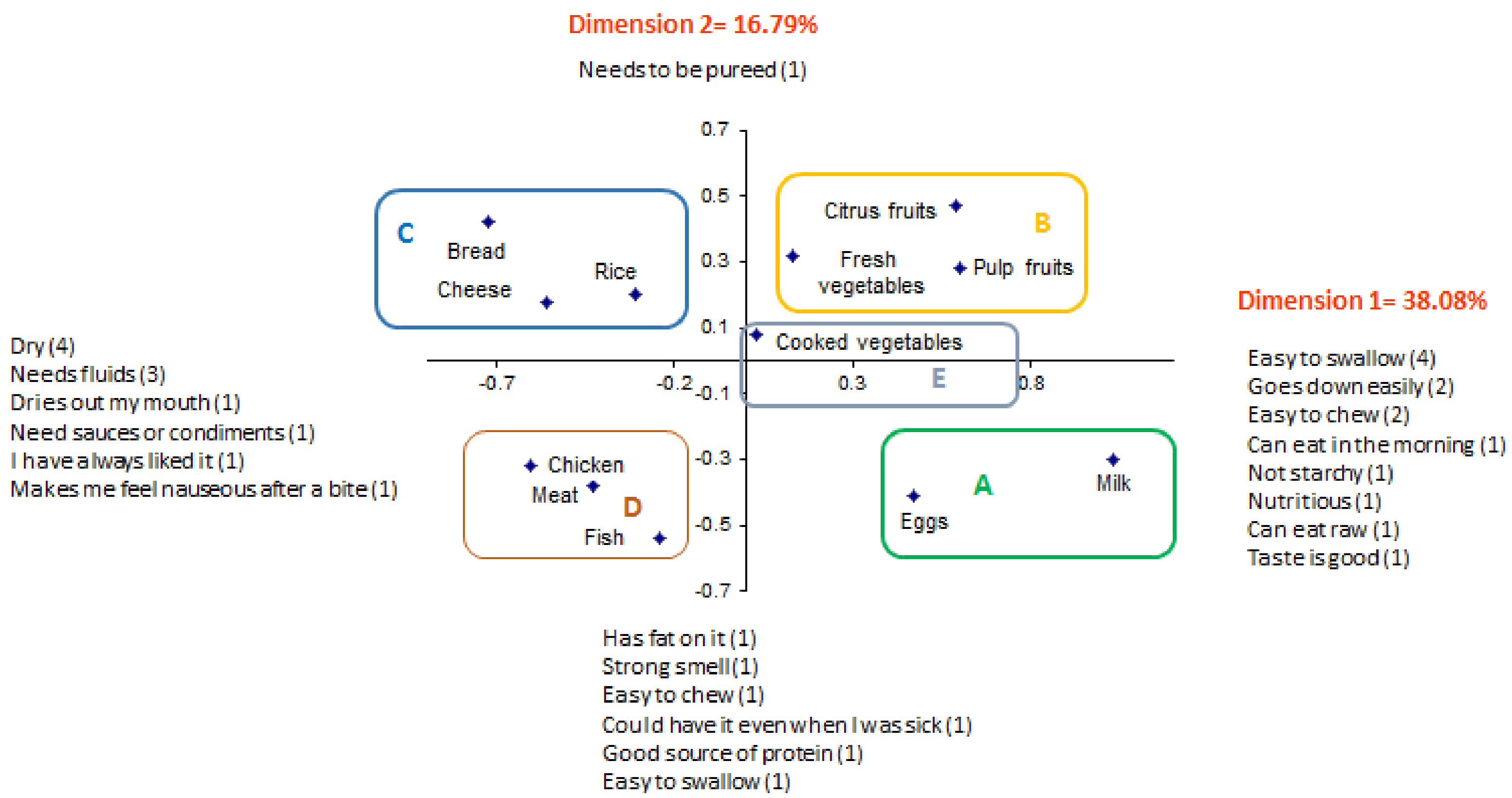

Figure 3-2 Consensus map of the worse physical function patients group (n=8).
The map reflects the location of foods according to constructs of Dimension 1 (horizontal) and Dimension 2 (vertical).
Note: Frequency (n) of constructs with correlations greater than |0.7| are displayed.

CHAPTER 4: The association of taste and smell changes and quality of life in head and neck cancer patients[1]

4.1 Introduction

Multimodal therapy (surgery/Radiotherapy/Chemotherapy) has been used over the last two decades to improve tumor control and survival. However, this treatment approach has significant impact on QoL (1) of head and neck cancer (HNC) patients. Quality of life (QoL) can be defined as the ability of the individual to perform activities related to physical, mental, social and emotional well-being while reporting satisfaction with daily functions (2). QoL has become an outcome as important as overall survival and disease free survival to evaluate the success of the treatment (3, 4). Antineoplastic treatment may alter functionality in activities of daily life (5), and treatment side effects such as mucositis, taste and smell changes, dry mouth, mouth sores, nausea and loss of appetite reduce physical, emotional and social well-being (6-9) and have generally been shown to reduce QoL (10).

Taste and smell changes (TSAs) are one of the most frequent and troublesome side effects reported by cancer patients (11, 12). TSAs vary in nature and severity, and can be characterized as the total absence of taste or smell, reduced or increased sensitivity, distortion of normal taste and smell, presence of phantom tastes or odors and lingering bitter or metallic sensations (13). Due to the close relationship between taste and smell perception and their joint role in flavor perception, it is not uncommon for patients with smell impairments to report taste impairments (14).

A recent systematic review (15) showed that antineoplastic treatment modalities affect the prevalence of taste alterations as evaluated by both self-reports and clinical tests. Approximately half of the patients treated with chemotherapy (Chemo) alone experienced taste alterations, while two thirds of the patients treated with radiotherapy (RT) and three quarters of the patients treated

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[1] A version of this chapter was submitted to the Quality of Life Research Journal as: Alvarez-Camacho M., Gonella S., Ghosh S., Kubrak C., Scrimger R.A., Chu K.P., Wismer W.V. The impact of taste and smell alterations on quality of life in head and neck cancer patients.

with combined RT-Chemo experienced taste alterations (15). Furthermore, high radiation dose and RT to the head and neck area specifically increase the risk of TSAs. During a course of curative RT (60-70 Gy/6-7 weeks) for HNC, over 90% of patients developed taste loss. Although taste loss improves 20-60 days upon completing RT treatment, it has been reported that taste perception generally does not return to normal or near normal levels even a year after RT therapy (15). TSAs may persist up to seven years and a chronic reduced ability to taste may establish in one third of patients (16, 17).

In the advanced cancer population, self-reported TSAs have been associated with reduced energy (8) and protein intake (6) and lower scores in QoL questionnaires (8). In addition, self-reported taste alterations have been associated with shorter survival in advanced cancer (18). Among head and neck cancer (HNC) patients TSAs are established as a nutrition impact symptom associated with reduced dietary intake, restricted food choice and weight loss (19).

Baharvand and colleagues (20) in their cohort study of 22 HN cancer patients found that all patients developed clinically-diagnosed taste loss after RT, and six had total taste loss; QoL significantly deteriorated for those with total or partial taste loss. Similarly, Kubrak et al. (19) found a trend for self-reported taste and smell alterations as a predictor for reduced QoL at a multivariate level (β=-5.0, 95% Confidence Interval [CI] = -10.3; 0.2, p=0.06) among RT-treated orally-fed patients that were followed for 2.5 months end of treatment. Finally, in-depth interviews with 33 RT-treated HNC patients found that 90% of patients reported changes in taste and attributed feelings of depression to the changes in their oral cavity (9). In their study of HNC patient treated with Chemo, Wickham et al. (21) also concluded that patients reporting taste changes are more likely to experience depression than those without taste changes.

TSAs can be evaluated by self-reports or clinical tests, however, clinical tests are not able to capture dimensions such as flavour, food enjoyment, or distortions of normal perception (6). Some studies exploring the impact of TSAs on QoL have assessed taste and smell alterations as individual items on QoL tools (1, 4, 22-25) rather than using a comprehensive self-report taste and smell assessment tool, while others defined QoL as the average of symptoms rather than use a health-related approach (19). In addition, there are no published studies about TSAs among tube-fed patients.

The aims of this study were to investigate the effect of TSAs on overall QoL, to describe the overall QoL and the most important issues over time, in tube fed and orally-fed HNC patients.

4.2 Methods

4.2.1 Study design and clinical setting

This longitudinal study was conducted at the Cross Cancer Institute, the comprehensive treatment centre for northern Alberta. Data were collected in two phases, between February 2007 and August 2009 and between February 2012 and June 2014. This paper presents the pooled data.

Research procedures were in accord with the Alberta Cancer Research Ethics Committee. All patients provided written informed consent.

4.2.2 Sample size

At the baseline, a sample of 116 patients was required to achieve a power of 80% with an effect size of 0.25 (small to medium) to study the association between QoL and taste and smell alterations as measured by the Chemosensory Complaint Score (CCS). The level of significance was at a two-sided α level of 0.05.

4.2.3 Study population

Inclusion criteria were as follows: older than 18 years, diagnosis of HNC (oral cavity, salivary glands, paranasal sinuses, oropharynx, nasopharynx, hypopharynx and larynx) with any histology and at any stage, scheduled to receive curative-intent RT with or without concurrent Chemo or cetuximab. Patients with tumors of the lip and thyroid were excluded.

Patients received treatment according to the standard of care. The median total dose of radiotherapy was 60 Gy. Forty-two (26.2%) participants were treated with surgery prior to Chemo-RT. Planned chemotherapy included high dose cisplatin (n=48) or weekly carboplatin (n=28); six patients were switched to carboplatin due to toxicity and eight patients received cetuximab (Table 4-1).

4.2.4 Data collection

Data were collected prior to any treatment (baseline), on completion of RT or chemo-RT (end of treatment) and at 2.5 months follow-up. Patients entered the study at any time point and were invited to participate in as many time point evaluations as possible.

The mean timeframe between baseline and end of treatment assessments was 14.4 ± 5.8 weeks and 16.5 ± 5.5 weeks for orally fed and tube fed patients, respectively, whereas the mean time between end of treatment and 2.5 months follow-up was 8.4 ± 4.1 weeks and 8.3 ± 3.3 weeks for orally-fed and tube-fed patients, respectively. Variations in assessment time were due to travel constraints, holidays and patients' convenience.

4.2.4.1 Individual characteristics and treatment

Patients' main demographic characteristics, smoking status, alcohol consumption, presence of feeding tube, tumor site and tumor stage, as well as treatment (RT doses and schedule, and antineoplastic drugs administered) were extracted from medical records.

4.2.4.2 Energy and protein intake

Patients' intake was recorded by a self-reported 3-day dietary record (26), a method that provides a valid and reliable estimate of cancer patients (27). Food Processor II Nutrient Analysis Program™ (Esha Research, Salem, OR) was used to determine caloric and protein intake from the food records.

4.2.4.3 Taste and smell functions

Self-perceived taste and smell functions were assessed through the Taste and Smell Survey (TSS) that quantifies the nature and severity of TSAs. Eight items of the TSS assess taste and six evaluate smell perception. The final score, the Chemosensory Complaint Score (CCS) (range 0 - 16, higher score indicates more severity of complaint), is the sum of the Taste Complaint Score (Taste-CS, range 0-10) and the Smell Complaint Score (Smell-CS, range 0-6) (28).

4.2.4.4. Quality of life

QoL was assessed by the University of Washington Quality of Life version 3 (UW-QoL v3), one of the most commonly used questionnaires in HNC (29). It contains 10 domains exploring pain, appearance, activity, recreation, swallowing, chewing, speech, shoulder, taste and saliva with scoring scaled in equal stages from 0 to 100 (higher scores indicate better status). The questionnaire is brief, self-administered, detailed-enough to identify small changes, and HNC-specific (30). It has an internal consistency score of 0.85 (29). Factor analysis from Rogers et al. indicate that two composite scores can be calculated to represent the Physical Function and the Social-Emotional Function (29). The UW-QoL also asks patients to identify the three most important domains during the past seven days and to rate their "Overall QoL during the past 7 days" as 0 (very poor), 20 (poor), 40 (fair), 60 (good), 80 (very good) or 100 (outstanding) (29).

Composite scores were computed for this study as follows: Physical Function as the average of chewing, swallowing, speech, saliva and appearance domain scores (excluding taste); Social-Emotional Function as the average of pain, activity, recreation and shoulder domain scores; and Overall Function as the average of all domains scores (pain, appearance, activity, recreation, swallowing, chewing, speech, shoulder and saliva), except taste. Scores for Physical, Social-Emotional and Overall Function range from 0-100, with higher scores indicating better condition.

The taste domain has four possible responses scored as 0 ("I cannot taste any foods"), 30 ("I can taste some foods"), 70 ("I can taste most food normally") or 100 ("I can taste food normally"). Patient perceived clinical distress for taste and the need for intervention was evaluated through the identification of 'trigger criteria', which occurs when a patient's response is "I cannot taste any food" or "I can taste some food" and indicates taste as an important symptom during the past seven days. (29).

4.2.5 Statistical analysis

Descriptive statistics were adopted: continuous variables were expressed as averages and Confidence Intervals (CI) at 95%, mean and standard deviation or median and Inter Quartile Range (IQR) while categorical variables were summarized as sums and percentages. The χ^2 test with Yates' correction (or Fisher's exact test) and t-test or Mann Whitney U-test were used for comparisons between categorical variables. Descriptive data were presented for all patients included in the study (n=160), those tube-fed (n=44) and those orally-fed (n=116).

Data presentation of overall QoL was stratified into tube-fed and orally-fed groups since significant differences were found between the two groups in tumor site, tumor stage and treatment. In addition, Terrell and colleagues (31) showed the feeding tube to have the most negative impact on QoL compared to 13 different demographic and clinical characteristics.

Generalized Estimated Equation (GEE) modeling was used to estimate the effects of CCS on overall QoL, Social-Emotional Function, Physical Function and Overall Function to allow simultaneous modeling of data that are correlated (32) and provide unbiased standard errors (33, 34). For GEE analysis of Physical and Overall Function we excluded the taste domain of the UW-QOL instrument because CCS was included as an independent variable.

4.3 Results

4.3.1 Study population

One-hundred and sixty patients consented to participate and about a quarter were tube-fed. Data at baseline, end of treatment and at 2.5 months follow-up were available for 126, 100 and 85 patients, respectively (Supplemental Table 4-1).

Most patients were male (n=126, 78.8%) and the mean age was 58.9 years. Half of the patients were current or former smokers and almost 70% (n=107) consumed alcohol at baseline (Table 4-1). Eighty-four patients (52.5%) had a pharynx neoplasm. One-hundred and twenty-four (80%) patients had an advanced tumor stage (T3/T4). RT ± surgery (n=57, 49.1%) was the main therapy in orally-fed patients, whereas the majority of tube-fed patients (n=37, 84.1%) Chemo-RT ± surgery (Table 4-1).

All tube-fed patients continued to have oral intake in the form of clear liquids and supplements during the three study time points. There were no differences in caloric or protein intake, standardized by body weight, between orally-fed and tube-fed patients at any time point (Table 4-1).

4.3.2 Most important issues in tube-fed and orally-fed patients over the time

Patients attributed a different importance to the symptoms evaluated through the UW-QoL over time (Table 4-2). At baseline, swallowing (n=51.6%) and pain (n=36, 37.9%) were reported as the most important symptom during the past 7 days by tube-fed and orally-fed patients, respectively. In both groups taste was ranked as the least relevant problem; only five orally-fed and one tube-fed patient reported taste alterations among the three most important symptoms during the past seven days.

At end of treatment, swallowing became the most important symptom both for tube-fed (n=24, 82.7%) and orally-fed patients (n=49, 69%). Similarly, taste increased in importance in both groups and was ranked as the third and fourth most important symptom by tube-fed (n=12, 41.4%) and orally-fed (n=23, 32.4%) patients, respectively. Overall, 10 patients (4 tube-fed and 6 orally-fed) chose more than 3 symptoms as important at this time point.

At 2.5 months follow-up, the most distressing symptom for tube fed patients continued to be swallowing (n=14, 58.3%) whereas orally-fed patients ranked saliva (n=35, 57.4%) as the most distressing symptom. Taste continued to be the third and fourth most important symptom for tube-fed and orally-fed patients, respectively.

4.3.3 Overall quality of life, Chemosensory Complaint Score and taste trigger criteria for tube-fed and orally-fed patients over time

No significant differences between orally-fed and tube-fed groups were observed for overall QoL and CCS mean scores at any of the study time points. Overall QoL scores declined from baseline to end of treatment for both tube-fed and orally-fed patients and were improved at 2.5 months follow-up but not to pre-treatment levels (Table 4-3). At baseline, 75% of patients (20/31 tube-fed and 74/95 orally-fed) reported a good or higher (score $\geq$ 60) QoL and only 9 patients (3 tube-fed and 6 orally-fed) reported a poor or lower (score $\leq$ 20) QoL. At end of treatment less than half of patients rated their QoL as good or higher while one in five (5 tube-fed and 15 orally-fed) reported a poor or lower QoL. At 2.5 months follow-up, 54 (63.5%) patients (12/24 tube-fed and 42/61 orally-fed) reported a good or higher QoL but 10 (12%) patients continued to report a poor (score = 20) QoL. However, none reported a very poor (score = 0) QoL.

At end of treatment no patients rated their QoL as outstanding (score = 100) and none of the tube-fed patients rated their QoL as outstanding at any time point. The proportion of tube-fed patients with a good or higher QoL was always lower than orally-fed patients at any time point (64.5% vs 77.9% (20/31 vs 74/95) at baseline, 44.8% vs 49.2% (13/23 vs 35/71) at end of treatment, 50.0% vs 69.4% (12/24 vs 42/61) at 2.5 months follow-up).

The pattern for CCS was similar to QoL scores. CCS increased from baseline after the completion of treatment both in the tube-fed group (8.0 ± 2.3 vs 0.2 ± 0.2 at baseline) and orally-fed group (8.7 ± 0.7 vs 1.5 ± 0.5 at baseline) with a reduction in complaints at 2.5 months follow-up (6.4 ± 1.6 in tube-fed and 6.0 ± 0.7 in orally-fed) but not to baseline levels.

At the end of treatment, 35 (49.3%) orally-fed patients reached trigger criteria in the UW-QoL taste domain. These patients also had higher Taste-CS than orally-fed patients without trigger criteria (8.4 ± 1.4 vs 6.2 ± 2.8, $p=.003$). Similarly, 18 (62.1%) tube-fed patients had trigger criteria for the taste domain and higher Taste-CS and CCS scores compared to tube-fed patients without trigger criteria (8.3 ± 1.6 vs 4.1 ± 3.5, $p=.005$ and 10.2 ± 2.4 vs 5.7 ± 4.5, $p=.022$, respectively). No differences were found in Smell-CS at the end of treatment or in any of the scores at baseline and at 2.5 months follow-up between patients with trigger criteria compared to patients without, both for orally-fed and tube-fed patients.

4.3.4 Factors affecting quality of life

GEE was used to estimate the association among self-perceived taste and smell functions, treatment, tube-feeding and six clinical and demographic variables on overall QoL. Table 4-4 presents multivariate results for overall QoL for both tube-fed and orally-fed patients. CCS was a significant predictor of overall QoL in the univariate analysis (β= -1.685, CI: -2.25;-1.12, $p<0.0001$). The β coefficient from multivariate analysis reveal that each unit increase in CCS resulted in a decrease in overall QoL of 1.80.

Tumor characteristics such as site and stage were associated with QoL (Table 4-4). Age was an independent predictor of overall QoL. Compared to current smokers, patients who had never smoked had a significantly better overall QoL

Table 4-5 shows the GEE results for Social-Emotional Function, Physical Function and Overall Function. After adjusting for age, gender, smoking status, alcohol consumption, tumor site, treatment and tube-feeding, CCS was a significant independent predictor of Social-Emotional Function (β=-1.75, $p<0.0001$), Physical Function (β=-1.15, p= <0.0001) and Overall Function (β=-1.17, p=<0.0001).

4.4. Discussion

This is the first study to determine the association of TSAs on overall QoL among HNC patients using comprehensive self-report measures of both. We found TSAs to be a significant independent predictor of overall QoL, Social-Emotional Function, Physical Function and Overall Function after adjusting for age, gender, tumor stage, tumor site, treatment, smoking, alcohol consumption and tube-feeding. These findings add new evidence to the field of QoL in two ways. First, we illustrate an association between self-reported TSAs in HNC patients and their overall QoL. Baharvand and colleagues reported a significant deterioration in QoL at post-treatment among total and partial "taste losers" when assessed by clinical taste evaluations (20). Second, we found that TSAs were an independent predictor of QoL and an important symptom for tube-fed patients as well as for patients capable of oral intake at both end of treatment and at 2.5 months follow-up.

We observed that greater TSAs were associated with reduced Social-Emotional Function, Physical Function and Overall Function. Although the precise mechanism by which TSAs affect QoL is likely multi-factorial, our data is consistent with previous studies in which frustration and disappointment with eating experiences were found to be common among HNC patients as they limit participation in social and recreational activities with friends and family (35, 36).

Overall QoL changed over the three study time points as previously shown by a prospective study (37). The end of treatment time-point was the worst period with the lowest QoL scores reported by both tube-fed and orally-fed groups, and with 20% of all patients reporting a poor or lower QoL. However, QoL was poorer for tube-fed patients compared to orally-fed as the proportion of tube-fed patients with a good or higher QoL was always lower than orally-fed patients at any time point. Moreover, we found that none of tube-fed patients rated their QoL as outstanding at any time points. Although different treatments were given to orally-fed and tube-fed patients, we adjusted for type of treatment in our analyses and the proportion of surgery-treated patients was similar in tube-fed and orally-fed groups. Future studies with larger sample sizes will facilitate evaluation of type of surgery on QoL. We observed a significant association between early stage disease and better QoL that is consistent with other studies (38).

CCS trended similarly with Qol scores. Taste and smell perception were significantly impaired after the completion of the treatment with only a partial recovery at 2.5 months follow-up as highlighted in previous papers (4, 39) that show taste pre-treatment levels not yet recovered one year after treatment. This trend is confirmed by the issues reported by patients as the most important during the past seven days. At baseline, the taste domain was ranked as the least important issue by all patients, but at end of treatment it was ranked third and fourth most important by tube-fed and orally-fed patients, respectively, and this ranking was maintained at 2.5 month follow-up.

Our results showed a different effect for the main demographic and clinical variables on QoL. Having never smoked was associated with a better QoL. These findings confirm Duffy and colleagues' pilot study results (40) that found smoking negatively associated with five scales of the QoL Short Form Health Survey (SF-36V), including General Health among HNC patients. Improved QoL due to smoking in HNC may be explained by its effect on physical function and fatigue (41). Comorbidity was not adjusted in the GEE modeling, however, comorbidity alone has been shown not to affect QoL indices (42). Further studies are warranted to explore the different predictors of QoL in these two populations.

4.4.1 Strengths and limitations

We used two self-report tools for data collection; the best method to capture subjective and individual dimensions such as food enjoyment (6). Consistent with a recent recommendation that identified taste alterations as a patient-reported HN-specific core symptom (43), we believe that self-report tools are the method of choice to assess TSAs and their association with QoL.

Similar to other studies of HNC populations (39, 44), participants of this study were predominantly male. In North America the ratio of HNC of males to females can be greater than 2:1 (45, 46). We observed that gender was not a significant predictor of overall QoL. Females may respond differently to symptoms (38), however, the effect of treatment should not differentially affect taste function (20). Patient recruitment and retention can be challenging in oncology studies. To reduce burden, patients were invited to take part in all time points, and were allowed to enter the study at any time point. This strategy contributed to increase recruitment rate, but had the disadvantage of dealing with some missing data at baseline.

In summary, we found TSAs to be a significant independent predictor of overall QoL, Social-Emotional Function, Physical Function and Overall Function regardless of use of tube-feeding. TSAs are one of a cluster of nutrition impact symptoms with clinical consequences, such as restricted food choice and decreased dietary intake, nutritional status and food enjoyment (39). Our aim was to determine the association of TSAs and QoL among HNC patients and we found that they are an independent predictor of QoL also when oral intake is restricted. As reported by Farhangfar et al. a higher frequency of symptoms does not necessarily predict nutritional or clinical outcomes (47). Therefore, further studies could include additional nutrition impact symptoms to evaluate their combined effect on overall QoL using a multivariate analysis.

These findings highlight the importance of screening all HNC patients for self-reported TSAs (43) even when they are not exclusively dependent on oral food intake (21). Moreover, new treatment-support pathways must be developed for tube-fed patients; current TSAs symptom management is focused on the provision of food choice and eating suggestions to orally-fed patients, while a different approach is required to fully address TSAs experienced by tube-fed patients. A comprehensive self-report tool for TSAs in addition to a routine QoL questionnaire can help health care professionals identify the nature and severity of the taste and smell alterations, and to choose the best strategy for reducing their impact on QoL.

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Table 4-1 Demographics and patient characteristics

	All patients (n=160)	Orally-fed (n=116)	Tube-fed (n=44)	p[e]
Gender (N,%)				.309
M	126 (78.8)	89 (76.7)	37 (84.1)	
Age, year (mean ± SD)	58.9 (11.9)	59.7 (12.5)	56.8 (9.9)	.170
Smoking status[a] (N,%)				.640
Never smoker	40 (25.3)	31 (27.2)	9 (20.5)	
Former smoker	77 (48.7)	55 (48.2)	22 (50)	
Current smoker	41 (26.0)	28 (24.6)	13 (29.5)	
Alcohol consumption[b] (N,%)	107 (69.0)	74 (66.7)	33 (75)	.229
Tumor site (N,%)				.015
Pharynx	84 (52.5)	52 (44.8)	32 (72.7)	
Larynx	36 (22.5)	31 (26.7)	5 (11.4)	
Oral cavity	18 (11.2)	14 (12.1)	4 (9.1)	
Other[c]	22 (13.8)	19 (16.4)	3 (6.8)	
Tumor stage[b] (N,%)				0.002
Tis / T1 / T2	31 (20.0)	29 (25.7)	2 (4.8)	
T3 / T4	124 (80.0)	84 (74.3)	40 (95.2)	
Treatment (N,%)				<.0001
RTchemo ± surgery	86 (53.8)	49 (42.2)	37 (84.1)	
RT ± surgery	59 (36.9)	57 (49.1)	2 (4.5)	
RTcetuximab ± surgery	8 (5.0)	4 (3.4)	4 (9.1)	
Surgery only	7 (4.4)	6 (5.2)	1 (2.3)	
Caloric intake[d], Kcal/KgBW/day (median [IQR])				
Baseline	27.2 [21.6-34.4]	28.9 [21.8-34.5]	24.2 [18.5-27.2]	.08
End of treatment	23.0 [15.1-31.6]	21.1 [11.5-30.7]	26.7 [20.9-38.5]	.075
2.5 months follow-up	31.8 [23.9-36.8]	31.8 [24.4-36.7]	30.5 [23.0-39.3]	.687
Protein intake[d], g/KgBW/day (median [IQR])				
Baseline	1.1 [0.9-1.5]	1.2 [0.9-1.5]	1.1 [0.6-1.3]	.102
End treatment	1.0 [0.5-1.3]	0.9 [0.4-1.2]	1.1 [0.8-1.6]	.086
2.5 months follow-up	1.3 [1.0-1.6]	1.3 [1.0-1.6]	1.2 [0.9-1.7]	.945

Abbreviations: IQR, Inter Quartile Range; RT, Radiation Therapy; SD, Standard Deviation; Tis, Tumor in situ.

[a] Data available on 114/116 orally-fed patients. [b] Data available on 111/116 orally-fed patients

[c] Includes salivary glands (n=11), nasal cavity and paranasal sinuses (n=6), primary unknown (n=4) and soft tissue (n=1).

[d] Data available on 111/126 patients at baseline, 79/100 at end of treatment and 71/86 at 2.5 months follow-up

[e] Comparison between orally-fed and tube-fed patients

Table 4-2 Ranking of the most important issues during the past seven days, as perceived by tube-fed and orally-fed patients at each study time point

Symptom[a]	Baseline (n=126)				End treatment (n=100)				2.5 months follow-up (n=86)			
	Tube-fed (n=31)		Orally-fed (n=95)		Tube-fed (n=29)		Orally-fed (n=71)		Tube-fed (n=24)		Orally-fed (n=61)	
	n (%)	Rank	n (%)	Rank	n (%)	Rank	n (%)	Rank	n (%)	Rank	n (%)	Rank
Pain	15 (48.4)	2	36 (37.9)	1	16 (55.2)	2	34 (47.9)	2	7 (29.2)	3	11 (18.0)	6
Appearance	4 (12.9)	5	7 (7.4)	8	3 (10.3)	6	4 (5.6)	9	1 (4.2)	8	6 (9.8)	8
Activity	8 (25.8)	4	23 (24.2)	4	6 (20.7)	5	18 (25.4)	5	6 (25.0)	4	22 (36.1)	3
Recreation	2 (6.5)	7	6 (6.3)	9	1 (3.4)	8	2 (2.8)	10	2 (8.3)	7	2 (3.3)	9
Swallowing	16 (51.6)	1	28 (29.5)	2	24 (82.8)	1	49 (69.0)	1	14 (58)	1	29 (47.5)	2
Chewing	3 (9.7)	6	16 (16.8)	6	2 (6.9)	7	13 (18.3)	7	4 (16.7)	6	16 (26.2)	5
Speech	9 (29.0)	3	26 (27.4)	3	10 (34.5)	4	16 (22.5)	6	6 (25.0)	4	11 (18.0)	6
Shoulder	1 (3.2)	8	12 (12.6)	7	3 (10.3)	6	6 (8.5)	8	5 (20.8)	5	10 (16.4)	7
Taste	1 (3.2)	8	5 (5.3)	10	12 (41.4)	3	23 (32.4)	4	7 (29.2)	3	21 (34.4)	4
Saliva	2 (6.5)	7	17 (17.9)	5	16 (55.2)	2	28 (39.4)	3	11 (45.8)	2	35 (57.4)	1

Totals are greater than the number of patients since up to three items could be chosen. Ranks may be tied for some domains.

[a] University of Washington Quality of Life questionnaire version 3

Table 4-3 Overall quality of life for tube-fed and orally-fed patients at each study time point

Overall quality of life[a]	Baseline			End treatment			2.5 months follow-up		
	All patients (n=126) N,%	Tube-fed (n=31) N,%	Orally-fed (n=95) N,%	All patients (n=100) N,%	Tube-fed (n=29) N,%	Orally-fed (n=71) N,%	All patients (n=85) N,%	Tube-fed (n=24) N,%	Orally-fed (n=61) N,%
Mean ± SD	60.9 (2.5)	56.1 (3.8)	62.5 (2.0)	47.4 (2.1)	46.9 (4.0)	47.6 (2.4)	55.4 (2.1)	50.8 (4.5)	57.1 (2.3)
Outstanding	4 (3.2)	-	4 (4.2)	-	-	-	1 (1.2)	-	1 (1.6)
Very good	40 (31.7)	9 (29.0)	31 (32.6)	13 (13.0)	4 (13.8)	9 (12.7)	19 (22.3)	6 (25.0)	13 (21.3)
Good	50 (39.7)	11 (35.5)	39 (41.1)	35 (35.0)	9 (31.0)	26 (36.6)	34 (40.0)	6 (25.0)	28 (45.9)
Fair	23 (18.3)	8 (25.8)	15 (15.8)	32 (32.0)	11 (37.9)	21 (29.6)	21 (24.7)	7 (29.2)	14 (23.0)
Poor	8 (6.3)	2 (6.5)	6 (6.3)	16 (16.0)	3 (10.3)	13 (18.3)	10 (11.8)	5 (20.8)	5 (8.2)
Very poor	1 (0.8)	1 (3.2)	-	4 (4.0)	2 (7.0)	2 (2.8)	-	-	-

Abbreviations: SD, Standard Deviation

[a] University of Washington Quality of Life questionnaire version 3

Table 4-4 Generalized estimated equation (GEE) multivariate model: factors affecting overall quality of life

Variable	All patients			
	β	SE	P value	95% CI
CCS (0-16)	-1.80	0.30	<0.0001	-2.38; -1.23
Male gender	-0.44	3.32	0.895	-6.95; 6.07
Tumor stage (ref = Tis /T1 / T2)				
T3/ T4	-9.56	3.80	0.012	-17.00; -2.12
Tumor site (ref = Pharynx)				
Larynx	-0.46	4.79	0.924	-9.85; 8.93
Oral cavity	10.96	4.75	0.021	1.65; 20.27
Other [a]	16.74	5.08	0.001	6.80; 26.70
Treatment (ref = RT ± surgery)				
RTchemo ± surgery	6.50	4.11	0.113	-1.55;14.56
RTcetuximab ± surgery	10.01	8.39	0.233	-6.44; 26.45
Surgery only	-2.59	9.34	0.782	-20.90; 15.71
Smoking status (ref = current)				
Never	6.84	3.29	0.038	0.38; 13.29
Former	3.49	4.01	0.385	-4.38; 11.36
Alcohol consumption (ref=no)	-1.52	3.27	0.643	-7.93; 4.90
Age, years	0.27	0.12	0.022	-0.04;0.49
Tube-fed (ref=orally fed)	-1.11	3.82	0.772	-8.60; 6.38

Abbreviations: CCS, Chemosensory Complaint Score; CI, Confidence Interval; RT, Radiation Therapy; SE, Standard Error; Tis, Tumor in situ

[a] Includes salivary glands (n=11), nasal cavity and paranasal sinuses (n=6), primary unknown (n=4) and soft tissue (n=1).

Table 4-5. Generalized estimated equation multivariate models: effects of CCS on social-emotional, physical and overall functions

Scale		All participants		
		β (SE)	p-value	95% CI
Social-emotional function	a.	-1.75 (0.25)	<0.0001	-2.24; -1.26
	b.	-1.75 (0.25)	<0.0001	-2.25; -1.26
Physical function	a.	-1.03 (0.32)	0.001	-1.66; -0.41
	b.	-1.15 (0.31)	<0.0001	-1.75; -0.54
Overall function	a.	-1.06 (0.31)	0.001	-1.67; -0.46
	b.	-1.17 (0.30)	<0.0001	-1.76; -0.59

Abbreviation: CCS, Chemosensory Complaint Score; CI, Confidence Interval; SE, Standard Error

a. Adjusted for age, gender, tumor stage, tumor site, treatment, smoking status, alcohol consumption.
b. Adjusted for age, gender, tumor stage, tumor site, treatment, smoking status, alcohol consumption and tube-feeding.

Supplemental Table 4-1 Patients' participation according to the three time points of the study

Baseline	End treatment	2.5 months follow-up	All patients (n)	Tube-fed patients (n)	Orally-fed patients (n)
+	+	+	71	14	57
+	-	-	38	13	25
-	+	-	20	9	11
+	+	-	11	4	7
-	-	+	11	2	9
+	-	+	9	2	7
-	+	+	0	0	0

Abbreviation: (+) Patients participated in the study at this time point; (-) Patients did not participate in the study at this time point.

CHAPTER 5: Summary and final discussion

5.1 Summary

The three objectives of this research were to describe perceived intensity and liking dimensions of taste and smell alterations experienced by head and neck cancer (HNC) patients, determine the association of taste and smell alterations and quality of life (QoL), and to ascertain the association between patient Physical-Function (PF) and food characterization with respect to ease of eating. This chapter presents the key points of the research studies presented in Chapters 2-4 with recommendations for future research.

In Chapter 2, intensity and liking for the basic tastes, creaminess and common odors were evaluated before, upon completion of, and 6 weeks and 3-6 months after treatment for HNC. Taste intensity perception was impaired after treatment for all basic tastes, especially salty and umami. Liking scores did not respond to changes in tastants' concentrations after treatment. At 6 weeks and 3-6 months post-treatment, participants disliked the most concentrated solutions of salty, sour and bitter. Creaminess intensity perception increased with the rising concentrations of M.F. in milk and cream at all time points, with the middle concentrations of M.F. being the most liked before treatment. Participants were able to perceive ortho- and retronasal aromas at all time points.

In Chapter 3, the association of PF on food characterization was determined through repertory grid interviews with 19 orally-fed HNC patients between 4-10 months post-treatment. All patients characterized foods using descriptors of taste, ease of eating, convenience, texture, liking and "potential to worsen symptoms." Descriptors of nutrition and smell, on the other hand, were significant only for patients with worse PF.

In Chapter 4, the association between taste and smell alterations and overall QoL of HNC patients was evaluated in a longitudinal study that included assessments before, upon completion and at 2.5 months after treatment. Taste and smell alterations, as measured by the Chemosensory Complaint Score, were a significant predictor of overall QoL, social-emotional-QoL, physical-function-QoL and overall function-QoL even after adjusting for age, gender, tumor site, tumor stage, treatment, alcohol consumption, smoking and tube-feeding. In addition, taste was reported as an important symptom for tube-fed and orally-fed patients at end-treatment and 2.5 months after treatment.

5.2 Interpretation and application of results

5.2.1 Intensity and liking perception

Results from Chapter 2 revealed that intensity perception is impaired at the end of treatment for the basic tastes, with salty and umami the most affected. There are specific receptors for each of these basic tastes but, unfortunately, we lack knowledge of how specific receptors are affected to understand increased impairment of some tastes over others as the result of cancer treatment. Treatment with radiotherapy and/or chemotherapy produces direct changes in the gustatory papillae (1, 2) and radiation affects salivary glands, leading to reduced saliva production (3), while chemotherapy inhibits the renewal of taste cells (4). Results of this study also indicate that taste perception recovers by 6 weeks post-treatment, which agrees with the results reported by Zheng et al.(5)

As oral factors influence texture and viscosity perception (e.g. saliva, swallowing, mouth sensitivity) (6) an item to evaluate creaminess perception and liking was included in the study. Density of fungiform papillae is related to oral touch sensations (7). Viscosity plays an important role in perception of flavor (8) and food intake (9) and can be affected by some of the symptoms experienced by HNC patients as a result of their disease or their treatment. In this study, viscosity measured through intensity perception of creaminess was not impaired as patients were able to discriminate among low and high percentages of milk fat. While 10% and 18% milk fat beverages received higher scores for liking before treatment, there was high variability in the perception of liking at 6 weeks, and 3-6 months post-treatment. Creaminess perception is related to the fat content and creaminess liking and differs across different age groups, gender and income (10).

Although smell provides 80% of the information that comprises flavor perception, smell alterations are often not the focus of attention in the scientific literature (11) or the focus of attention when assessing flavor perception among cancer patients. Smell is important to many different aspects of food consumption and plays an important role in appetite and food intake

(12). In this study, the proportion of patients with normal vs. abnormal orthonasal smell perception remained the same between the time points investigated. We did not, however, quantify the amount of radiation reaching the olfactory epithelium, which is known to impact smell perception as reported by Bramerson et al., especially with doses greater after 10 Gy (13).

The study of taste and smell liking can help shortlist the most accepted tastes and odors and the intensity at which they are highly accepted before and after treatment. Perception of creaminess can help to set the foundation for the quest for the ideal texture that is not only safe, but liked by HNC patients. Results from this study can be used in three ways. First, patients and caregivers can be informed about taste and smell changes after treatment. Second, food preparation intended for intake of HNC patients can be customized at post-treatment. Third, food products can be developed or improved for HNC patients using this information.

5.2.2 Food characterization after treatment

Ours is the first study to investigate patient characterization of foods as a consequence of the Physical-Function symptom experience of HNC patients. Nutrition and smell constructs were only significant among worse PF patients, indicating that their needs and priorities for food selection are different and should be considered when creating a plan to promote food intake. Effective nutritional counselling should consider the social, emotional and physical circumstances of patients as well as their nutritional needs. Our results agree with the observations of Sorensen et al. and Shragge et al. who reported that during severe illnesses, motivations to eat shift from pleasure to survival, leading to selection of foods that are simple and easy to eat (14, 15). Individual nutritional counselling has been shown to be more effective than standard nutritional advice or no nutritional advice amongst HNC patients to improve energy and protein intake, increase quality of life and physical function, and reduce malnutrition (16). Our results can be used as a foundation to customize nutrition education and provide guidance about appropriate and acceptable foods for HNC patients.

The knowledge of food characteristics as perceived by HNC patients can help health professionals identify the reasons for avoidance (e.g. texture that can be modifiable) of nutritious foods and address misconceptions around certain food or food components (e.g. sugar) and risk of cancer. Results from this study can be translated into strategies for food preparation, modification or target messages for patients.

5.2.3. Taste and smell alterations and Quality of Life

With the increasing survival rate of HNC patients in Canada (17), more patients need resources to adjust to their new functional, social, and emotional needs, while health care support teams need to be prepared to face challenges in these areas.

Our study links taste and smell alteration to overall QoL, social-emotional-QoL, physical-function-QoL and overall function-QoL. That is, taste and smell alterations keep patients from activities that are important for their health and their sense of well-being. Results from Chapter 4 indicate that taste and smell changes are among the top 3 and 4 most important symptoms reported by tube-fed and orally-fed HNC patients, respectively, at end of treatment and 2.5 months follow-up. While other symptoms are routinely assessed for follow-up, it is not yet a common practice to screen for details on taste and smell alterations. While priorities from patients and the clinical team can differ at times, it is important to screen HNC patients for the presence and severity of taste and smell alterations in order to address them accordingly.

5.3 Methodological considerations

While we tried to reduce possible confounding factors in all the studies, such as including patients at defined time points and excluding patients with thyroid or lip cancer, there were some factors that may have influenced our results.

A cross-sectional study design (Chapter 2) was selected to reduce patient burden by arranging assessments according to medical follow-up visits. While this study design can reduce the problem of low enrollment and high withdrawal rates, variation in individual preferences due to genetic (7) and cultural differences (18) among patients of each group could have affected our results and therefore a longitudinal study would have been the ideal design. Moreover, due to sample size, we are not able to draw conclusions about the differences in intensity perception associated with different oncologic therapies, such as minor and major oral cavity surgeries (e.g. tonsillectomy vs. total glossectomy) or among patients with chemotherapy vs. no chemotherapy, each of which may affect results and should be explored future studies with a larger sample size.

At our institution, HNC patients have access to a registered dietitian and speech and language pathologist who provide routine follow-ups with the goal of maintaining energy and protein requirements, which may have influenced our results and therefore be different from patients with less access to information.

In Chapter 4 we evaluated the association of CCS on overall QoL. As in other studies of HNC populations and as is characteristic of the disease (19, 20), participants of this study were predominantly male. While gender was not a significant predictor of overall QoL for either tube-fed or orally-fed patients (Chapter 4), females may have responded differently to the interviews based on different priorities and roles (Chapter 3). Finally, dental health is a variable that might have affected taste and smell perception and should be studied further (e.g. infectious causing foul odors or use of dentures) (21, 22).

5.4 Considerations for nutrition and oncology practitioners and future research

There is no remedy or solution for taste and smell alterations, despite the numerous strategies that have been tested, such as the use of condiments on food (23) or zinc supplementation (24, 25). Taste and smell alterations are linked to important nutritional outcomes and quality of life. However, in clinical practice, there are limited routine assessments or follow-ups about taste and smell alterations.

These findings add to our knowledge of taste and smell alterations in three areas. First, the importance of continuously screening for taste and smell alterations among HNC patients, whether orally or tube-fed, with the purpose to identify the leading causes of taste and smell alterations that are treatable (e.g. lack of oral hygiene leading to foul-smell) vs. those that are not modifiable (e.g. previous exposure to toxic substances or RT effect). For instance, the use of a screening tool for taste and smell alterations such as the 16-item Taste and Smell survey (26) could help identify patients with severe alterations and direct them for further assessment using tests of intensity and liking (Chapter 2) that draw information that cannot be obtained through traditional tests of detection and recognition (e.g. identification of taste and aromas that can be used with daily food preparation). Second, the opportunity to explore the use of different aromas and taste concentrations in food or food products to promote intake of enjoyable foods, for instance, the use of flavor extracts to increase flavor and liking without adding sugar or salt (27).

Third, the need to incorporate a discussion and the creation of workshops on taste and smell alterations as part of the nutrition education programs that include expected changes, estimated time to recovery and suggestions for food preparation.

Future studies should investigate the reasons behind liking variability for sweet and umami at post-treatment (e.g. treatment effect, cultural effect or personal preference) and continue to study liking perception using a combination of basic tastes and texture (e.g. sour-sweet, sweet-salty, creamy-sweet) as would appear in foods. Repertory grid method could be used to explore perceptions of other foods and time points to understand the changing needs of the HNC patients beyond 6 months post-treatment.

5.5 Conclusions

This research shows that intensity perception for salty and umami is impaired after treatment, while smell intensity perception is affected less severely than taste. Taste and smell alterations are perceived as an important symptom at the end of treatment and 2.5 months post-treatment, and are an independent predictor of overall QoL, social-emotional-QoL, physical-function-QoL and overall function-QoL whether patients are tube-fed or orally-fed. Food characterization differs among post-treatment HNC patients with better and worse physical function. Descriptors of nutrition and smell are especially important for patients with worse physical function. Findings from this research highlight first, the need to incorporate assessment and management of taste and smell alterations within HNC patient nutrition education programs. Second, to customize nutrition education according to the level of physical function. Third, to explore the use of different aromas and taste concentrations in food or food products to promote intake of enjoyable foods.

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