REVIEW ARTICLE

Impaired Taste Acuity As A Complication of Head And Neck Radiotherapy: A Review

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ABSTRACT

Radiation act as a double edge sword. On one hand, radiation itself is a powerful tool for research, medical diagnosis and therapy etc. On the other hand, radiation exposures, especially at high levels can lead to various adverse health effects. Impaired taste acuity secondary to radiotherapy is a major cause of morbidity in patients undergoing head and neck irradiation and unfortunately most neglected. It affects the quality of life and impairs oral intake, which may have serious implications on the general health consisting of weight loss and nutritional compromise. Thus, it is important to prevent its occurrence, identify and manage the condition to improve the quality of life. Current practice and recommendations are based on limited evidence. The article highlights on the pathogenesis, numerous studies and various management and prevention strategies.

Keywords: Radiotherapy, Taste, Dysguesia, Hypergeusia, Hypogeusia

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INTRODUCTION

Taste perception is an important factor in sustaining human life. Although commonly recognized as important for epicurean pleasure, it is required for motivating food intake, to obtain energy and nutrients which are needed to maintain the body's functions. In addition, it provides warning messages and protection from food-borne and environmental toxins. Therefore it is essential for maintaining our health.[1] Sweet, bitter, salty, sour and umami tastes are generally regarded as five basic taste qualities in humans.[2]
Taste is an important and most neglected alteration caused by ionizing radiation in patients submitted to radiotherapy. Radiotherapy is the therapeutic modality that utilizes ionizing radiation to treat various types of cancers. Like in other structures, the biological effects of ionizing radiations on structures of the oral cavity vary according to the size of the irradiated area, the dose, the type and rhythm of irradiation, as well as the developmental stage of the irradiated tissue. In the development of the taste buds, such effects range from mild growth retardation to total destruction.[2]
Taste disorders occur rapidly and many times precedes the occurrence of mucositis. Patients may experience taste loss (ageusia), alteration (dysgeusia),decreased sensitivity (hypogeusia) or increased sensitivity (hypergeusia), all of which resulting in reduced interest in food intake leading to nutritional compromise and weight loss and most importantly impairs the quality of life.[3]

Taste buds and its function

Taste buds are the anatomical structures which contain the receptor cells that mediate the sense of taste. Most of the taste buds are present on the papillae of tongue and are situated in the mucosa

of epiglottis, palate, pharynx and proximal part of oesophagus. Four types of papillae are located on the tongue (Table 1)

Each taste bud is oval in shape, which has a diameter of about 1/30mm, a length of about 1/16mm. Microvilli present provide the receptor surface for taste. Each taste bud contains 50–100 taste receptor cells and support cells. Taste cells are described as basal, dark, intermediate, and light, based on electron microscopic characteristics (Fig. 1)[3]. The basal cells are at the base of the taste bud and constitute a proliferative population of cells. They divide to produce postmitotic light, intermediate, and dark taste cells with a life span of 10–11 days. Dark cells are defined by a dark cytoplasm (electron-dense), dense-core granules (small vesicles with a dark center) at the tip of the cell, indentations in the nuclear membrane, and collections of heterochromatin (the DNA) along the inner edge of the nucleus. Light cells are characterized by a light cytoplasm (electron-lucent), clear vesicles and mitochondria in the tip of the cell, and a round to oval nucleus with less heterochromatin (DNA) along the inner edge. Intermediate cells have characteristics that are intermediate between the light and dark cells.

Interwoven around the bodies of the taste cells is a branching terminal network of taste nerve fibres that are stimulated by the taste receptor cells. Some of these fibres invaginate into folds of the taste the taste cell membranes near the fibres. It is believed that these vesicles contain a neurotransmitter substance that is released through the cell membrane to excite the nerve fibre endings in response to taste stimulation.[3]

Each taste bud contains 50 to 100 taste receptor cells, which are in a constant rate of turnover, having a life span of approximately 10-11 days.

Mechanism of stimulation of taste buds and transmission of signals to the Central Nervous system

The membrane of the taste cell is negatively charged on the inside when compared to outside. Application of the taste substance to the taste hairs causes depolarization.This change in the electric potential in the taste cell is called the receptor potential for the taste. When a taste chemical binds to a receptor cell near to or protruding through a villus membrane, it opens the ion channel and allows sodium ions or hydrogen ions to enter and depolarize the normal negativity of the cell.

The receptor potential ultimately results in a rise in intracellular Ca^{2+} that triggers transmitter release onto the gustatory nerve fibers (Figure 2).[4] These fibers from the VIIth, IXth, and Xth cranial nerves converge on second-order brainstem gustatory neurons in the nucleus of the solitary tract (NST).[4] Although a family of taste receptors has not yet been cloned, according to the study done by Chandrashekar J et al in 2006, stimula- tion of taste receptor leads to activation of G proteins (gustducin, phospholipase C and hydrol- ysis of phosphatidylinositol- 4,5-biphsophonate), generating second messengers (inositol- 1,4,5 triphosphate and diacylglycerol) and gating of transient receptor protein M5 (TRPM5) ion channels which leads to nerve depolarization.[5]

Factors responsible for gustatory dysfunction

Gustatory dysfunctions such as ageusia hypogeusia and dysgeusia are widespread and associated with a variety of illnesses, from common to obscure. Numerous causes include:

- Aging
- Response to hormonal changes in pregnancy and menopause
- Poor dentition and hygiene
- Use of alcohol and tobacco
- Dental materials
- Xerostomia
- Zinc deficiency
- Liver and kidney disorders
- Diabetes mellitus
- Depression
- Surgical procedures around the chorda tympani nerve or glossopharyngeal nerve
- Radiotherapy
- Drugs: Methotrexate, dexamethasone, antihypertensives, antimicrobial agents, and antiproliferative agents

Radiotherapy and taste dysfunction

Radiotherpy is one of the treatment modality for the treatment of head and neck cancer and the dosage delivered to the tissues depends on numerous factors like location, size of the tumor and the type of therapy used such as teletherapy or brachytherapy.[6,7] Usualy a dose of 2 Gy per day with a total of 50-70 Gy is delivered over a period of of 5-7 weeks.[7] An important alteration caused by ionizing radiation in patients submitted to radiotherapy is the change in taste. Taste deficits as a consequence of head and neck radiation were first described as "taste hallucinations" or "blindness of the mouth" (MacCarthy-Leventhal, 1959).[8]

Three models have been proposed to explain irradiation triggered taste dysfunction[9]:

1. Neurites that innervate sensory organs are radiosensitive, thus disruption of the contact
2. between taste cells and nerves leads to taste cell death
3. Irradiation directly damages differentiated taste cells; and/or
4. Irradiation targets proliferating progenitors, interrupting production of new taste cells.

When radiation affects the nerve fibres there could be a significant physical loss in the population of postsynaptic intragemmal nerve fibers. Since the neurons are nondividing population of cells, they are thought to be generally radioresistant. However, disruption of the functional integrity of the neuron could lead to the symptom of taste loss. Synaptic uncoupling or disruption of membrane integrity leading to a disruption in the contact between the taste cells and nerve fibers, resulting in the inability to conduct action potentials, is a possibility. This was supported by studies conducted by Conger and Well in 1969, where humans treated with fractionated therapeutic irradiation (of about 6kR total exposure) to the head and neck suffered a 77% to 99% decrease in their taste acuity to sugar, acid and quinine.[10] A similar finding was demonstrated on animal models in the study conducted by Essess Ba et al[11] in 1988 and Gorodetsky R at al[12] in 1992.

Second possible site of damage is the taste cells. Previously study by Esses BA et al demonstrated that following irradiation the cells within the taste bud lose their characteristic histological appearances (Figure.3)[3] and all appear as intermediate cells. The disruption of the proliferative capacity of the taste cells would cause stem cells to stop dividing, and, once the current receptors die off, no new ones would be there to replace them. This would be experienced as a loss of taste.[3,11] However this did not gave an explanation for the changes in taste measured at 2–3 days following irradiation in both animals and humans. This is more likely to be a disruption of the current receptor cells, possibly via membrane damage causing loss of structural integrity, or loss of the synaptic contacts. Yamazaki M et al in 2010, investigated histopathological change of taste bud structure and the taste cell population in a mice exposed to a single 15 Gy dose of X-ray irradiation and the findings suggest that X-ray irradiation disrupts the basal cells, resulting in a decrease of the number of taste cells, particularly type II taste cells, which may be the cause of radiotherapy-induced taste dysfunction.[13]

STUDIES

Studies evaluating the effect of radiation dose, irradiated field and duration on gustatory function are very few. Mossman and Henkin[14] studied radiation effect on eight patients for all taste modalities over a period of 7 weeks, and observed a increased threshold values for all taste modalities after 3 weeks of radiotherapy. In 1986 Mossman et al evaluated direct radiation injury to gustatory tissues in their study. During the course of therapy, no taste loss was observed upto 2000cGy and increase gustatory tissue damage between 2000 cGy and 4000 cGy. At 6000cGy dose level, over 90% relative taste loss was observed.[15] In a study developed by Kamprad et al.[16] decreased taste function was observed in patients receiving radiotherapy doses ≥ 40 Gy. However Silva AIV et al.[17] in 2007 demonstrated loss of taste in patients receiving doses >35 Gy suggesting that lower doses can cause deleterious effects on tissues, depending on the irradiation field. Also in their study they observed that loss of taste for the salty flavor was greater on the first week of

radiotherapy. On the second week, only the bitter flavor was significantly perceived. And on the last week, the loss of taste was generalized with all the solutions at low concentration.

In contrast, Maes et al studied a prevalence and distress of taste loss at different intervals after radiotherapy (RT) for head and neck cancer, wherein, loss of taste after RT was found to be most pronounced after 2 months. Bitter and salt qualities were most impaired. Gradual recovery was seen during the first year after treatment. Partial taste loss still persisted 1-2 years after treatment.[18]

In another study by Yamashita et al,[19] observed decline of all the taste on the fifth week after the start of RT and improvement on the 11th week. All patients received a mean dose of 13.7 Gy and 65.3 Gy for the tip and posterior part of the tongue respectively.

All the four basic tastes including umami are affected during RT to the oral cavity and sweet sensation is typically lost first.[18] Loss of umami taste is of atmost importance because it affects pleasure or enjoyement associated with eating. In a prospective study by Yamashita H et al, umami taste declined 3rd week after the start of radiotherapy and was improved by the 8th week.[20] Further, it has been suggested that post-radiation deficits in taste functioning may be related to radiation damage to the salivary glands and associated xerostomia, because saliva is the solvent for gustatory stimuli.[21] However Mossman et al[15] concluded that there is no strong relationship existing between salivary and taste dysfunction after evaluating the effects of radiation therapy on taste and salivary function in man.

Among other factors, the age of the patients plays a significant role in the loss of taste function. Patients under the age of 20 are more prone to more severe loss of taste function because of the presence of a higher number of taste buds.[16]

However during the course of radiation therapy numerous other factors also will contribute to taste alteration along radiation dosage like chemotherapy, antibiotics as well as other systemic conditions like ageing Diabetes Mellitus, hormonal changes and kidney and liver diseases. Hiroo Imai et al. in 2013 studied the prevalence of chemotherapy induced dysguesia in Japanese cancer patients and found that dysgeusia developed in 38.8% of chemotherapy patients, and was most prevalent in patients receiving 5-fluorouracil (5-FU) or its oral analogs.[22]

Table-1: Types of papillae

Papillae	Features
Filiform papillae	These are the most numerous and appear as short, rough structures covered with thick keratinized epithelium. They do not contain taste buds.
Fungiform papillae	These are dispersed across the surface of the tongue. They are more box-like, with a connective tissue core and a thin covering of epithelium. Most of the fungiform papillae contain a single taste bud on the tip.
Circumvallate papille	These are located on the posterior aspect of the dorsal surface, appearing as pin-cushions with a surrounding trough, called a crypt. The crypt is lined by an epithelium, called the gustatory epithelium, which contains several taste buds.

TASTE TESTING METHODS

Whole mouth testing, spatial taste testing, taste threshold or suprathreshold testing and electrogustometry can be conducted. Whole mouth testing is performed by applying the tastant as an oral rinse followed by thorough water rinsing. Spatial testing is conducted by localized application of specific testant to various areas of the mouth. Tastant can be delivered by filter paper of standard size soaked with stimulus, cotton tipped applicators, eye droppers or impregnated strips.[23] Taste threshold or suprathreshold testing uses recommended concentrations of tastants are sucrose 300 mg/ml; citric acid 60 mg/ml; sodium chloride 80 mg/ml; guanine 20 mg/ml. Umami is typically assessed by taste recognition threshold using 10 ml monosodium glutamate whole-mouth rinses (25, 50, 75 and 100 mM). The five funda-

mental taste sensations can be tested: sour (citric acid), sweet (glucose), salt (sodium chloride), bitter (guanine or local anesthetic) and umami (monosodium glutamate).[18] Electrogusto- metry consists of application of a weak electric oral stimulus which measures a function of taste perception, which is different from that induced by chemical stimuli.[24]

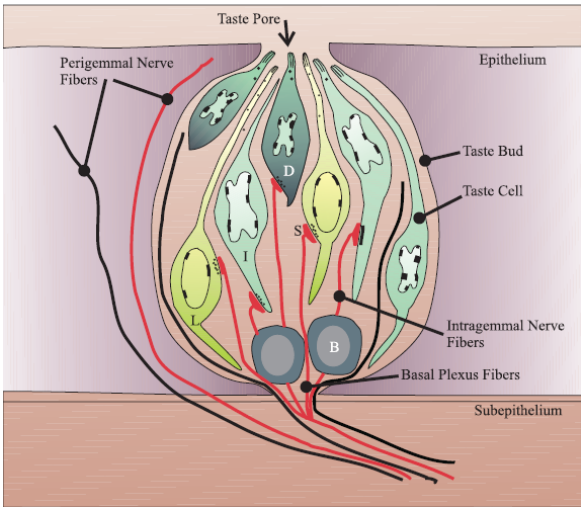

Figure-1 : Schematic of a normal taste bud. All of the elements of a taste bud are illustrated. The taste bud contains basal cells (B) in the lower portion of the bud and all three types of taste cells extending upward to the opening at the top, the taste pore. The light cells (L), intermediate cells (I), and dark cells (D) are pictured with some of the features that characterize each cell type. In addition, the intragemmal and perigemmal nerve fibers are seen. The nerve fibers are present in the subepithelial connective tissue and enter each bud from the base. The red fibers represent the nerve fibers which contain synaptic vesicle proteins, and the black fibers represent nerve fibers which contain peptides. S, synapse.

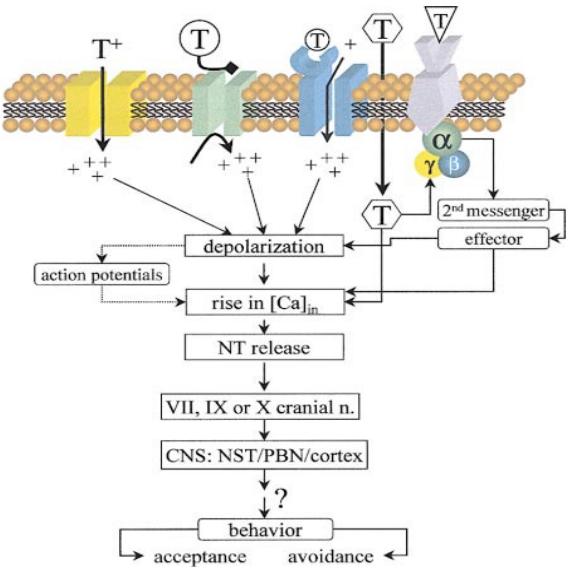

Figure-2: General taste transduction pathway

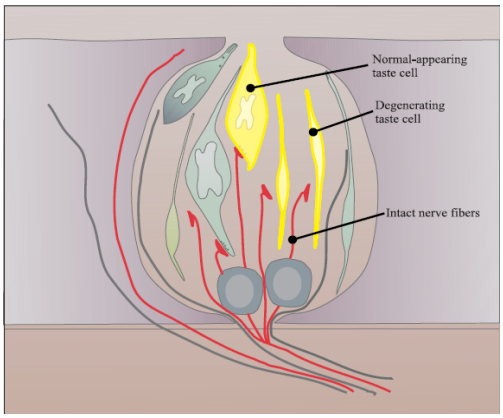

Figure 3. The effects of radiation on taste buds. At the peak of radiation damage (approximately 7 days), some of the light to intermediate taste cells are degenerating, but the dark cells and all subtypes of nerve fibers remain intact. The nerve fibers containing synaptic vesicle proteins (red) and the nerve fibers containing peptides (black) remain as they were in the normal taste bud.

Recovery of taste acuity

Patients recognize impairement of taste 20-60 days after the radiation therapy and is usually recovered in 60-120 days.[25]
Study by P.L. Sandow demonstrated that radiation induced taste deficits can be recovered by 6 months period.[8] However, Maes et al noticed persistence of partial taste loss upto1-2 years after the treatment.[18]

Prevention and management of radiotherapy induced gustatory dysfunction

Cancer and its treatment leads to malnutrition in 40% or more of hospitalized patients. Thus, prevention or management of gustatory dysfunction in patients receiving radiation therapy has two important aspects: to improve the quality of life and to improve the outcome of therapy by maximizing the patient's ability to eat.
Specific conditions related to taste dysfunction such as hyposalivation, poor oral hygiene, use of tobacco products and/or alcohol has relatively simple solutions. Discontinuing the etiologic habit, chewing sugarless gum or candy for taste and salivary stimulation or prescribing sialogogue can be used for individuals with residual salivary gland function. Chewing gum or candy may also cover unpleasant taste and provide symptomatic relief.[26]
After evaluating the patient for taste acuity, indi-

vidual diet management can be done, resulting in the most palatable diet available to the patient. This would require individual diet management, depending on the thresholds that can change for the patient.

In selected cases, modification of cancer therapy may be possible. In HNC patients, radiation fields that avoid exposure to critical sites for taste can be chosen when not detrimental to tumor management. Advances in radiation therapy, including intensity modulated radiotherapy (IMRT) and image guided radiotherapy (IGRT-tomotherapy) can spare high dose exposure of salivary glands and taste-receptors in part of the oropharynx,[27] although wider regions of low dose RT exposure occur. The impact of IMRT or IGR- T upon taste function has not been adequately studied. Radioprotectors such as amifostine can also contribute to taste maintenance, either directly through taste bud protection or indirectly by salivary gland protection.[28]

Zinc suppliments have been tried in the treatment of taste abnormalities with a dose of 45 mg tablet given thrice daily during and upto 1 month post radiotherapy and has shown effective results.[29]

In another study Zinc sulfate capsule 50 was given thrice daily . Medication was started with beginning of radiotherapy and continued one month after completion of irradiation. Taste perception threshold did not change significantly at the end of radiation, except the sour taste perception suggesting that a short course of supplementation with zinc sulfate in head and neck cancer patients under radiotherapy can prevent radiation-induced taste alterations.[30-32]

CONCLUSION

Taste alterations are neglected most often by the clinician as well as the patient during the course of radiation therapy. Ionizing radiation utilized in radiotherapy for head and neck tumors causes deleterious effects on the taste buds and thus taste function. Taste abnormalities in patients undergoing cancer therapy may be due to numerous reasons, however identification of the same, and prevention and management is most important as it can decrease appetite and dietary intake, leading to malnutrition and weight loss, and thus affecting the quality of life and even survival. Patients should be educated about the taste alterations and diet modifications can be done by altering the flavours of the food. Also taste testing methods should be performed in all the patients before, during and after the therapy as taste alterations are manifested even with a dosage of 35 Gy and within 1 week of radiotherapy depending on the irradiated field. Recovery of taste acuity occurs within 3-4 months in most of the patients, but may persist for 1-2 years. Thus taste testing should be performed even after the therapy as it helps in evaluating the prognosis to improve the general health of the patient.

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