



## Gustatory disturbances occur in patients with head and neck cancer who undergo radiotherapy not directed to the oral cavity

José Lucas Barbosa da Silva<sup>a</sup>, Richard L. Doty<sup>b</sup>, João Victor Massamitsu Katayama Miyazaki<sup>c</sup>, Ricardo Borges<sup>d</sup>, Fábio de Rezende Pinna<sup>d</sup>, Richard Louis Voegels<sup>d</sup>, Marco Aurélio Fornazieri<sup>e,\*</sup>

<sup>a</sup> University of Sao Paulo, Londrina State University, Brazil

<sup>b</sup> Smell and Taste Center, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, United States

<sup>c</sup> Londrina State University, Brazil

<sup>d</sup> Division of Otorhinolaryngology, University of Sao Paulo, Brazil

<sup>e</sup> Department of Surgery, Londrina State University and Pontifical Catholic University of Parana, Brazil

### ARTICLE INFO

#### Keywords:

Taste dysfunction  
Radiotherapy  
Dysgeusia  
Head and neck  
Cancer

### ABSTRACT

**Introduction:** Even the most modern radiation techniques still result in some degree of toxicity to adjacent normal tissues. Consequently, the radiotherapy treatment in head and neck neoplasms potentially leads to gustatory dysfunction even in cases when the treatment area is outside or adjacent to the oral cavity. In this study we quantitatively and qualitatively assessed gustatory function in patients with head and neck cancers who underwent radiotherapy inside and outside of the oral cavity.

**Methods:** Fifty-six patients with head and neck cancer responded to a specific questionnaire and had their gustatory function tested before, immediately after, and at 3 and 6 months following radiotherapy treatment. The irradiation field did not include the oral cavity in 29 patients and included it in 27 patients.

**Results:** All patients suffered a severe loss of taste immediately after radiotherapy. The identification of sweet and bitter tastes decreased in both groups, but the sour decrement was exclusive to those who had the oral cavity irradiated. Fourteen percent of patients complained of qualitative changes of taste, namely taste distortions. No impact of xerostomia on the taste measures was apparent.

**Conclusion:** We found that patients with head and neck neoplasms submitted to radiotherapy have disturbed taste even when irradiation does not include the oral cavity. This deficit is worse immediately after the end of radiotherapy. Our findings do not support the hypothesis that decreased salivary flow is the major cause for radiation-induced changes in taste function.

### Introduction

Radiotherapy in patients with head and neck cancer can lead to taste disturbances when the focus of the radiation includes the oral cavity [1–10]. Among symptoms are partial or total loss [1–2], dysgeusia (distortion of gustatory sensation), and phantogeusia (gustatory sensations in the absence of stimuli) [11] – symptoms that can lead to nutritional deficits, reduced quality of life, and depression [12–19]. Presently the degree of reversibility of gustatory loss after completion of radiotherapy is not entirely clear and heterogeneous findings abound [1,6,8,10,20–23]. This suggests that there is considerable individual variation in susceptibility to taste dysfunction from radiotherapy of the head and neck region.

Despite the strong evidence that *direct irradiation* of the oral cavity

can impair taste [1,2,4], whether or to what degree head and neck radiation outside the oral cavity impacts taste is not known. Even though improvements in limiting the field of radiation have been made, current radiotherapy techniques, such as three-dimensional conformal radiotherapy (3DCRT), intensity modulated radiotherapy (IMRT), stereotactic radiotherapy, and volumetric arc therapy, still produce some degree of toxicity in normal surrounding tissues [20–23]. Therefore, gustatory function may potentially be compromised in head and neck radiotherapy patients even when the irradiation field does not directly focus on the oral cavity.

In this study, we quantitatively assessed gustatory function in patients with malignant tumors of the head and neck whose oral cavities had been exposed directly or indirectly to the field of radiotherapy. To assess changes over time, testing was performed before, immediately

\* Corresponding author at: Department of Surgery, Londrina State University, 60 Robert Koch Avenue, Londrina 86038350, PR, Brazil.

E-mail address: [marcofornazieri@uel.br](mailto:marcofornazieri@uel.br) (M.A. Fornazieri).

<https://doi.org/10.1016/j.oraloncology.2019.06.008>

Received 27 December 2018; Received in revised form 14 May 2019; Accepted 7 June 2019

Available online 18 June 2019

1368-8375/ © 2019 Elsevier Ltd. All rights reserved.

after, and at 3 and 6 month intervals following the completion of radiotherapy treatment. Our objectives were to verify and compare the degree of recovery of the gustatory function after direct and indirect irradiation of the oral cavity, calculate the prevalence of qualitative disturbances of such treatments, assess whether each of the four basic taste qualities were impacted differentially, and determine the association of radiotherapy-induced xerostomia with the taste test measures.

**Methods**

*Design*

Fifty-six patients with head and neck malignant neoplasms were examined before, immediately after, and at 3- and 6-month intervals following the completion of radiotherapy treatment. Data were collected at a tertiary hospital between December 2012 and November 2015. Individuals with previous gustatory complaints, upper airway infections, history of head trauma, chemotherapy introduced after radiotherapy, neurological or psychiatric illnesses (except depression), submitted to glossectomy or surgical excision of the submandibular gland and fewer than 50% of completed test items in the initial gustatory test were excluded. Three patients were tracheostomized, and none had percutaneous endoscopic gastrostomy. Patients were divided into two groups according to the planning target volume (PTV). One included those patients on which PTV included the oral cavity (direct group; Table 1), and the other those whose radiotherapy did not include the oral cavity (indirect group). All patients provided written informed consent and the study was approved by the local ethics committee.

*Radiotherapy*

Patients were treated using conventional radiotherapy with two opposite and lateral irradiation fields and a low anterior cervical field. Each patient received 25 fractions of 1.8 Gy/day in the first treatment phase, totaling 45 Gy. After this period, marrow collimation and three sessions of 1.8 Gy/day - totaling 50.4 Gy - were performed. Finally, a BOOST of 10 more sessions of 2 Gy/day was performed at the lesion site, with the total received of 70.4 Gy. Some individuals were treated differently according to the location of the lesion. Patients with parotid tumors received the radiation in incident fields only on the side of the lesion, forming an angle of 40–50° between them, divided into 35

fractions of 2 Gy/day, totaling 70 Gy. Patients with tumors in the laryngeal region received irradiation in two parallel and opposing fields, with an angle of 180°, at a dose of 2 Gy/day in 30 fractions, totaling 60 Gy.

*Gustatory function and xerostomia*

Gustatory function of the four classic taste qualities was tested using a modified global gustatory test [24]. Solutions used were NaCl 0.31 M (for salt), citric acid 0.015 M (for sour), sucrose 0.49 M (for sweet), and caffeine 0.04 M (for bitter). The solutions were presented as oral sprays. The examiner presented 16 tastes (four of each type) from a pre-determined random order. Patients were asked to perform the test without knowing the taste of each vial. The patients were required to choose, on a given trial, whether the sensation was perceived as sweet, sour, bitter or sour. An answer was required even if no taste sensation was evident (i.e., the test was forced-choice). The test score was the total number of correct answers (0 to 16 points). Gustatory function was classified as normogeusia (13–16 correct answers), mild hypogeusia (10–12), moderate hypogeusia (7–9), severe hypogeusia (4–6), and ageusia (< 4).

The evaluation of the qualitative taste disorders (dysgeusia and phantogeusia) of the taste was carried out through a questionnaire. All patients were questioned, at each evaluation, about the occurrence of taste distortions in the presence or not of a gustatory stimulus. If so, the participant was invited to describe the event that occurred. Dysgeusia was defined as a distorted perception of the taste and phantogeusia as a gustatory perception in the absence of external stimulus [11]. Hypogeusia complaints were not considered among qualitative disorders. All patients were questioned about the occurrence of salivation disorders, such as tongue or oral mucosal dryness before the start of radiotherapy, in the end, 3 and 6 months after radiotherapy.

*Statistical analysis*

After verification of normality by the Shapiro-Wilk test, we compared age, irradiation dose focused on the tumor, and global gustatory test scores using the Student's *t*-test among the two groups. Gender, chemotherapy, smoking, prevalence of qualitative alterations of palate and staging were compared using the Fisher's Exact Test. The global gustatory test scores were compared among groups using a random-effect mixed model with repeated measures, with the factors of the time

**Table 1**

Patient characteristics of the direct or indirect oral cavity radiation groups.

	Direct group	Indirect group	P value ****
Subjects (n)	29	27	
Local	Oropharynx (3), oral cavity* (13), hypopharynx(1)**	Larynx *** (20), hypopharynx (2), cervical nodes (4), medulloblastoma (1);	
Age (mean, range)	54.8(20–76)	59.7(29–80)	0.11
Sex (m = male, f = female)	23 m, 4f	25 m, 4f	1.0
Radiotherapy to primary site (Gy)	69.2	64.3	0.003
Chemotherapy	58.6%	62.9%	0.78
Previous chemotherapy	51.7%	44.4%	0.60
Concomitant chemotherapy	43.7%	57.1%	0.51
Smoking	79.3%	70.3%	0.54
Xerostomia after radiotherapy	85.7%	60.8%	0.06
TNM classification	I 1 II 9 III 8 IV 11 na 0	I 3 II 8 III 10 IV 5 na 1	0.35

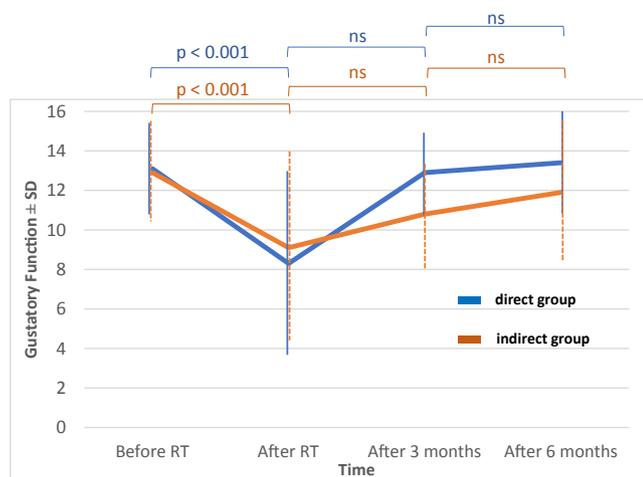
na = not applicable.

\* Oral cavity: base of the tongue, tonsils, palate.

\*\* Although the tumor was located in the hypopharynx, the planning target volume (PTV) included the tongue.

\*\*\* Larynx: supraglottis, infraglottis, glottis.

\*\*\*\* Based on Fisher's Exact and T Tests.



**Fig. 1.** Mean score in the gustatory test before and after radiotherapy between patients who received direct and indirect radiation in the oral cavity for head and neck cancer treatment. There was a significant decrease in gustatory function after radiotherapy in both groups ( $p < 0.001$ ). Three months after the end of the radiotherapy, the direct group returned to normal rates. The indirect group returned to gustatory function baseline only by the sixth month after radiotherapy.

of the visit (pre, immediately post therapy, and 3 and 6 months after therapy), direct or indirect radiotherapy to the tongue, and the interaction between visit with tongue being a radiotherapy target or not. The Wilcoxon Mann-Whitney test was used to compare separately the number of correct answers from each of the 4 flavors throughout the follow-up period in the direct and indirect groups. Multiple linear regression was used to verify the possible effects of gender, age, history of smoking, staging, xerostomia, and previous or concomitant chemotherapy, on the post-radiotherapy taste function. The dependent variable in this model was the initial taste test score minus that of the end of the radiotherapy treatment. Significance level was set at 5% and power at 90%. Considering a mean pre-radiotherapy score of 13, post-radiotherapy of 10, and a standard deviation of 2.0, 11 patients were needed in each group to make the planned comparisons.

## Results

As shown in Fig. 1, both groups showed a decrease in mean gustatory test scores immediately after radiotherapy [direct group =  $-5.4$  points (CI 95%  $-7.5$  to  $-3.4$ ;  $p < 0.001$ ; indirect group =  $-3.4$  points (CI 95%  $-5.3$  to  $-1.5$ ;  $p < 0.001$ )]. Patients' gustatory mean scores returned to baseline values by six months after the end of radiotherapy ( $p = 0.89$ ). Although the group indirectly irradiated in the oral cavity tended to present a slower recovery than that of the direct group three months after radiotherapy, this effect was not statistically significant ( $p = 0.34$ ).

Fourteen percent of patients presented qualitative taste distortions during and after radiotherapy. This phenomenon tended to be more prevalent in the group irradiated directly to the mouth (19% vs 8.7%), although the difference was not statistically significant ( $p = 0.40$ ). Some patients complained of phantogeusia (e.g., presence of a sour taste in the mouth) or dysgeusia (described as changes in food texture, water with bad taste, and a continuous salty taste). One patient had a referred palate paresthesia, an atypical symptom. In one third of the cases, qualitative distortions started 3 months after the end of treatment. The remaining cases occurred during radiotherapy or shortly after its end.

There was a partial taste loss for sweet and bitter immediately after radiotherapy in both groups (Figs. 2 and 3). Also, at this time, only patients in the direct group presented partial loss for the sour tasting

stimulus ( $p = 0.02$ ). All directly irradiated individuals recovered completely their gustation three months after radiotherapy, as measured by our tests ( $p = 0.11$ ). On the other hand, patients in the indirect group only recovered initial capacity of sour identification at 6 months after radiotherapy.

The presence of xerostomia was evaluated in each interview to assess its association with recovery and gustatory loss. All patients in the direct group received radiation in the major salivary glands. After radiotherapy, 87.5% of these patients reported xerostomia versus 61.9% in the indirect group, a difference that was not statistically significant ( $p = 0.09$ ). In the third evaluation, 100% of the patients in the direct group reported xerostomia after their taste function had returned to normal. This contrasts with 60.9% of the patients in the indirect group.

Gustation loss immediately after the end of radiotherapy was not influenced by sex, age, field of radiotherapy, previous or concomitant chemotherapy, xerostomia, staging, or smoking behavior of the patients (Table 2).

## Discussion

In addition to confirming previous findings of the deleterious effect of direct radiotherapy of the oral cavity on taste function [1,4–5,7,25], our study demonstrates, for the first time, the independent negative effect of indirect irradiation to the oral cavity on such function. This effect was present after controlling for age, previous or concomitant chemotherapy, smoking, tumor stage, and xerostomia. Intensity-modulated radiotherapy and inferior radiotherapy techniques, due to the intrinsic properties of the beam photons, generate a low to moderate dose of irradiation in tissues beyond the immediate focal area and presumably is the basis of our finding [23]. Although some authors have demonstrated harmful effects of radiation on gustatory function when applied in different parts of the tongue [4,21] or in different regions of head and neck [10], none had excluded the oral cavity from the treatment field. Our study is the first to document that damage to gustatory function can occur even when the radiation field does not directly involve the tongue and, consequently, the taste buds.

Regarding qualitative gustatory disturbances, this study is the first to show that dysgeusia and phantogeusia also occur in some patients when irradiation is not directly applied to the oral cavity. As with lessened function, the potential cause is also the spreading of small doses of radiation to the oral cavity. The prevalence of qualitative gustatory distortion in the group directly irradiated to the mouth of our sample was 19%, similar to 15.2% estimated by McLaughlin et al. [10]. As would be expected, we found a higher prevalence of qualitative changes in taste function in the group whose oral cavity was the target of the radiation and who received higher doses of radiotherapy (19% direct group vs. 8.7% indirect group). In regard to the type of changes, previous studies depicted presence of a persistent metallic or bitter taste, tingling sensations, and burning [10,11]. We observed that some subjects perceived a sour taste in the mouth, changes in the perception of food texture and in the taste of water, and persistent salty sensations. Previous research has found that head and neck patients who experience qualitative disturbances of taste from radiotherapy exhibit greater weight loss than those who do not experience such disturbances [10].

We found that the capacity to identify sweet, bitter and sour tastes was affected by radiotherapy. These changes were more pronounced in individuals irradiated directly in the oral cavity. Previous studies have shown that the detection of all four classic tastes (sweet, bitter, sour, and salty) is affected by radiotherapy, being bitter and sweet the most impacted [1,7]. This fact suggests that the sweet and bitter identification capacity is more sensitive to external aggressions or that a smaller number of cells in the gustatory bud are capable to perceive sweet and bitter. Probably, in our sample, salt identification was not compromised because the higher concentration of NaCl in the test employed compared to previous studies. In chemosensory research, standardization of

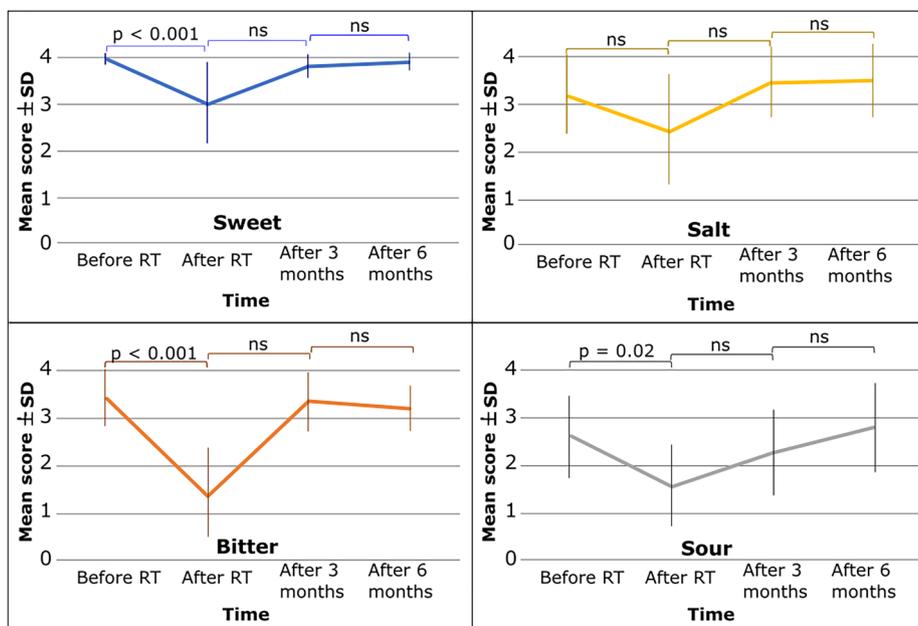


Fig. 2. Mean of the four taste qualities in the direct irradiation group. At the end of radiotherapy there was a statistically significant decrease in the ability to identify sweet, bitter and sour.

the tests in the studies done worldwide is a goal that has yet to be achieved.

The concept that xerostomia, per se, is the direct basis for the decreased taste function of those patients whose major salivary glands were impacted by radiation (100% of cases of direct radiation of the oral cavity) does not receive strong support from our findings. In accord with evidence that xerostomia is commonly difficult to resolve [24,26], the gustatory function of our patients returned to normal three months after radiotherapy even though all of the patients continued to report the presence of xerostomia. While it is possible that at some point xerostomia had some degree of impact on taste function, such an impact did not reverse return of taste function over time. A more likely explanation of our findings is the role of cellular apoptosis within the taste

buds and the reduction and subsequent replacement of the gustatory cells responsible for the dysfunction [8,27].

It is important to note several potential limitations of our study. First, because much of “taste” is really due to smell (via molecules reaching the olfactory epithelium via the nasopharynx during deglutition) [28], a number of our patients’ complaints of taste dysfunction could reflect radiation effects on the olfactory system. Second, to increase the participation and adherence of the patients to the study protocol, we chose a brief whole-mouth test that focused only on the ability to identify classic taste sensations. Hence, threshold sensitivity, which may be more sensitive to taste deficits, was not assessed. Moreover, the ability to taste other agents known to activate taste receptors, such as umami, was also not evaluated. Third, although the

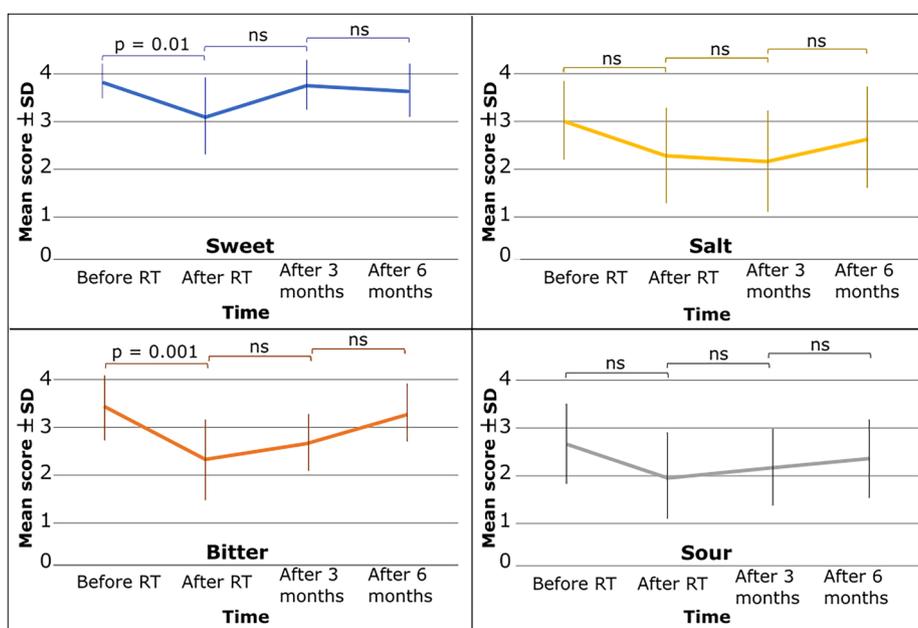


Fig. 3. Mean of the four taste qualities in the indirect group. At the end of radiotherapy there was a statistically significant decrease in the identification capacity of sweet and bitter.

**Table 2**

Multivariate analysis of factors associated with decreased gustatory function at the end of radiotherapy (number of observations = 36; R squared = 0.33).

	Marginal Effect (ME) <sup>a</sup>	95% CI; p value
Age	−0.02	−0.15 to 0.10; 0.74
Sex (female, as reference)	−4.04	−8.06 to −0.01; 0.05
Type of radiotherapy (mouth irradiated, as reference)	−1.56	−4.93 to 1.80; 0.35
Smoking	−1.23	−4.93 to 2.47; 0.50
Previous chemotherapy	−1.41	−5.03 to 2.20; 0.43
Concomitant chemotherapy	+0.59	−2.77 to 3.97; 0.72
Xerostomia	+0.48	−3.02 to 3.90; 0.78
TNM classification (stage I, as reference)		
II	−3.93	−9.47 to 1.59; 0.16
III	+0.17	−5.74 to 6.09; 0.95
IV	−0.84	−6.93 to 5.25; 0.80
Constant (k)	13.75	

<sup>a</sup> Marginal effect = change in the gustatory test score associated with the independent variables.

whole-mouth approach to testing is a direct assessment of a patient’s overall perception of taste, it may have underestimated radiation-induced damage to more specific regions of the tongue given the compensation from redundancy of innervation of the taste buds by multiple cranial nerves [29] (Doty et al., 2015). Finally, due to the gravity of the disease and morbidity of the treatment, many patients did not complete the study protocol as a result of death or indisposition to repeat the tests.

**Conclusion**

Our study indicates that patients undergoing head and neck radiotherapy suffer from severe loss of taste bud-mediated taste sensations. The impairment not only occurs when the oral cavity is direct irradiated, but also the irradiation field is not focused on the oral cavity. The deficit is worse immediately after the end of radiotherapy. Some patients have qualitative taste distortions after radiotherapy, regardless of whether the taste buds were directly or indirectly irradiated. The most affected gustatory bud cells were found to be those responsible for the detection of sweet, bitter and sour sensations. Decrease in salivary flow due to radiotherapy does not appear to be the primary basis for the radiation-induced changes in taste function.

**Declaration of Competing Interest**

Author declares that there is no conflict of interest.

**Appendix A. Supplementary material**

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.oraloncology.2019.06.008>.

**References**

[1] Maes A, et al. De Gustibus: time scale of loss and recovery of tastes caused by radiotherapy. *Radiother Oncol* 2002;63(2):195–201. [https://doi.org/10.1016/S0167-8140\(02\)00025-7](https://doi.org/10.1016/S0167-8140(02)00025-7).

[2] Grazia M, Redda R, Allis S. Radiotherapy-induced taste impairment. *Cancer Treat Rev* 2006;54(1):7. <https://doi.org/10.1016/j.ctrv.2006.06.003>.

[3] Silva AIV, Galante C, Manzi FR. Efeito da radiação ionizante sobre o paladar em pacientes submetidos a radioterapia para a região da cabeça e pescoço. *Radiol Bras* 2011;44(5):297–300. <https://doi.org/10.1590/S0100-39842011000500007>.

[4] Fernando IN, et al. The effect of head and neck irradiation on taste dysfunction: a prospective study. *Clin Oncol Orig Art* 1995;173–8. [https://doi.org/10.1016/S0936-6555\(05\)80511-4](https://doi.org/10.1016/S0936-6555(05)80511-4).

[5] Mossman KL, Henkin RI. Radiation-induced changes in taste acuity in cancer patients. *Int J Radiat Oncol Biol Phys* 1978;4(7–8):663–70. [https://doi.org/10.1016/0360-3016\(78\)90190-6](https://doi.org/10.1016/0360-3016(78)90190-6).

[6] Mirza N, Machtay M, Devine PA, Troxel A, Abboud SK, Doty RL. Gustatory impairment in patients undergoing head and neck irradiation. *Laryngoscope* 2008;24–31. <https://doi.org/10.1097/MLG.0b013e318155a276>.

[7] Sandow PL, Hejrat-Yazdi M, Heft MW. Taste loss and recovery following radiation therapy. *J Dent Res* 2006;85(7):608–11. <https://doi.org/10.1177/154405910608500705>.

[8] Yamashita H, et al. Taste dysfunction in patients receiving radiotherapy. *Head Neck Jun* 2006;28(6):508–16. <https://doi.org/10.1002/hed.20347>.

[9] Baharvand M, Shoalehsaadi N, Barakian R, Jalali Moghaddam E. Taste alteration and impact on quality of life after head and neck radiotherapy. *J Oral Pathol Med* 2013;42(1):106–12. <https://doi.org/10.1111/j.1600-0714.2012.01200.x>.

[10] McLaughlin L. Taste dysfunction in head and neck cancer survivors. *Oncol Nurs Forum* 2013;40(1):E4–13. <https://doi.org/10.1188/13.ONF.E4-E13>.

[11] Ijpm I, Timmermans ER, Renken RJ, Ter Horst GJ, Reyners AKL. Metallic taste in cancer patients treated with systemic therapy: a questionnaire-based study. *Nutr Cancer* 2017;69(1):140–5. <https://doi.org/10.1080/01635581.2017.1250922>.

[12] Braam PM, Roesink JM, Raaijmakers CP, Busschers WB, Terhaard CH. Quality of life and salivary output in patients with head-and-neck cancer five years after radiotherapy. *Radiat Oncol* 2007;2(1):3. <https://doi.org/10.1186/1748-717X-2-3>.

[13] Dirix P, Nuyts S, Vander Poorten V, Delaere P, Van Den Bogaert W. The influence of xerostomia after radiotherapy on quality of life: results of a questionnaire in head and neck cancer. *Support Care Cancer* 2008;16(2):171–9. <https://doi.org/10.1007/s00520-007-0300-5>.

[14] de Graeff A, de Leeuw JR, Ros W, Hordijk G, Blijham G, Winnubst J. Long-term quality of life of patients with head and neck cancer. *Laryngoscope* 2000;110(1):98–106. <https://doi.org/10.1097/00005537-200001000-00018>.

[15] Langendijk JA, Doornaert P, Verdonck-de Leeuw IM, Leemans CR, Aaronson NK, Slotman BJ. Impact of late treatment-related toxicity on quality of life among patients with head and neck cancer treated with radiotherapy. *J Clin Oncol* 2008;26(22):3770–6. <https://doi.org/10.1200/JCO.2007.14.6647>.

[16] de Melo Filho MR, et al. Quality of life of patients with head and neck cancer. *Braz J Otorhinolaryngol* 2013;79(1):82–8. <https://doi.org/10.5935/1808-8694.20130014>.

[17] Ehrsson YT, Langius-Eklöf A, Laurell G. Nutritional surveillance and weight loss in head and neck cancer patients. *Support Care Cancer* 2011;1–9. <https://doi.org/10.1007/s00520-011-1146-4>.

[18] Fazekas Z, Gao D, Saladi RN, Lu Y, Lebwohl M, Wei H. Protective effects of lycopene against ultraviolet B- induced photodamage. *Nutr Cancer* 2009(October 2011):37–41. [https://doi.org/10.1207/s15327914nc4702\\_11](https://doi.org/10.1207/s15327914nc4702_11).

[19] Neilson K, et al. A longitudinal study of distress (depression and anxiety) up to 18 months after radiotherapy for head and neck cancer. *Psychooncology* 2013;22(8):1843–8. <https://doi.org/10.1002/pon.3228>.

[20] Strojjan P, et al. Treatment of late sequelae after radiotherapy for head and neck cancer. *Cancer Treat Rev* 2017. <https://doi.org/10.1016/j.ctrv.2017.07.003>.

[21] Owadally W, Staffurth J. Principles of cancer treatment by radiotherapy. *Surg (United Kingdom)* 2015;33(3):127–30. <https://doi.org/10.1016/j.mpsur.2017.12.006>.

[22] Truong MT, Kovalchuk N. Radiotherapy planning. *PET Clin* 2015;10(2):279–96. <https://doi.org/10.1016/j.cpet.2014.12.010>.

[23] Leeman JE, et al. Proton therapy for head and neck cancer: expanding the therapeutic window. *Lancet Oncol* 2017;18(5):e254–65. [https://doi.org/10.1016/S1470-2045\(17\)30179-1](https://doi.org/10.1016/S1470-2045(17)30179-1).

[24] Soter A, Kim J, Jackman A, Tourbier I, Kaul A, Doty RL. Accuracy of self-report in detecting taste dysfunction. *Laryngoscope* 2008;118(4):611–7. <https://doi.org/10.1097/MLG.0b013e318161e53a>.

[25] Yamashita H, et al. Relation between acute and late irradiation impairment of four basic tastes and irradiated tongue volume in patients with head-and-neck cancer. *Int J Radiat Oncol* 2006;66(5):1422–9. <https://doi.org/10.1016/j.ijrobp.2006.08.037>.

[26] Chencharick J, Mossman K. Nutritional consequences of the radiotherapy of head and neck. *Cancer* 1983;51(5):811–5. [https://doi.org/10.1002/1097-0142\(19830301\)51:5<811::AID-CNCR2820510511>3.0.CO;2-M](https://doi.org/10.1002/1097-0142(19830301)51:5<811::AID-CNCR2820510511>3.0.CO;2-M).

[27] Nguyen HM, Reyland ME, Barlow LA. Mechanisms of taste bud cell loss after head and neck irradiation. *J Neurosci Mar*. 2012;32(10):3474–84. <https://doi.org/10.1523/JNEUROSCI.4167-11.2012>.

[28] Burdach KJ, Doty RL. The effects of mouth movements, swallowing, and spitting on orthonasal odor perception. *Physiol Behav* 1987;41(4):353–6. [https://doi.org/10.1016/0031-9384\(87\)90400-8](https://doi.org/10.1016/0031-9384(87)90400-8).

[29] Doty RL, Heidt JM, MacGillivray MR, Dsouza M, Tracey EH, Mirza N, et al. Influences of age, tongue region, and chorda tympani nerve sectioning on signal detection measures of lingual taste sensitivity. *Physiol Behav* 2016 Mar;1(155):202–7. <https://doi.org/10.1016/j.physbeh.2015.12.014>.