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Research Article

Electrogustometry and Contact Endoscopic Findings in Patients with Squamous Cell Carcinoma of the Oropharynx, Hypopharynx and Larynx after Treatment with Radiochemotherapy

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Abstract

We have studied in parallel changes in electrogustometric thresholds and in morphology of the fungiform papillae as well as in shape and density of the vessels of the tip of the tongue in patients with head and neck malignancy before and after treated with radio chemotherapy . We have also studied whether the observed changes in function and morphology may be reversible. Eighteen patients with head and neck malignancies (hypopharynx, larynx, oropharynx, parotid) treated with radio chemotherapy were prospectively studied. Measurements took place before starting treatment and at the end of each cycle of chemotherapy. Additional measurements were conducted two and four months after the end of the therapy. All patients showed pronounced alterations in fPap form and vascularization. After the end of therapy an improvement in the EGM-thresholds without immediate improvement in the shape and vascularization of fungiform papillae was found. Two months after the end of the therapy a minimally significant difference in the EGM-thresholds measured on the tip of the tongue was shown. By the second measurement we have noticed a little improvement of the EGM-threshold, accompanied only by an improvement in the vascularization of fPap.

Of note, the improvement in taste acquity was not directly accompanied by changes in vascularization of papillae and shape.

Keywords: Contact Endoscopy; Radiochemotherapy; Electrogustometry; Fungiform Papillae; Vascularization; Taste

Introduction

Cancer chemotherapy has a significant impact on cells of both malignant and healthy tissues, not only by interfering with cell division but also through its effect on non-dividing cells. Systemic administration of chemotherapeutic drugs often causes severe acute adverse effects such as bone marrow suppression and alimentary tract mucositis. In the oral cavity, the cytotoxic effects and the immune suppression may predispose patients to oral mucositis and hemorrhage, reduced or impaired salivary gland function and oral infection [1].

Taste disorders are present in the majority of HNC patients undergoing Radiation Therapy (RT) as well in cancer patients receiving Chemotherapy (CT) [2]. Taste complains are often present before treatment due to the malignancy. Up to 89% of patients prior to RCT have some taste disturbance [3]. RT to the head and neck commonly impacts saliva production and taste receptor function, typically after 10-14 days of treatment, consistent with the taste receptor turnover. Following RT, taste may recover within several months after resolution of mucosal damage [4] . However, taste change may remain due to hyposalivation and receptor damage [4].

All four basic tastes and umami are affected during RT to the oral cavity. RT can lead to direct damage to taste-receptors, synaptic uncoupling, and other possible neurologic damage [5,6]. In addition, radiation typically causes hyposalivation, thus reducing delivery of molecules to receptor sites, and reducing exposure of receptors to salivary-delivered growth factors. Post-treatment recovery of taste is variable, in some studies improving in 2-6 months following cancer therapy, but may continue indefinitely [6,7].

The present study was undertaken to evaluate the gustatory function and the accompanying changes in the form and vascularization of the tongue mucosa in patients with head and neck malignancies after treatment with radio chemotherapy. For that purpose, Electrogustometry (EGM) was combined with Contact Endoscopy (CE).

The first hypothesis was the existence of a strong association between elevated EGM-thresholds and morphologic changes on CE during the course of Radio Chemotherapy (RCT) in patients with HNSCC (head and neck squamous cell carcinoma). The studied parameters were the EGM-thresholds, the vascularization of the tip of the tongue and the morphology of fPap. The second hypothesis was that there was a strong association between the above parameters 2 and 4 months after completion of RCT treatment.

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Method

Twenty consecutive patients (age range: 42-78 years, mean age: 57.4 years) with malignant lesions of the head and neck region treated with concurrent RCT (n=20/ Cisplatin 20mg/m2+5-FU 600 mg/m2) were included in the prospective study. Unfortunately, 2 of them have either abandoned the measurements (n=1) or died (n = 1) during the therapy. Two of the remaining patients have participated in previous studies of ours [2,4]. The remaining (n=18) have completed the study. These patients (n=18) were treated for squamous cell carcinoma (n=18) of the hypopharynx (n=9), larynx (n=5), and oropharynx (n=4). A radiation dose ranging between 50,4 Gy to 72 Gy was delivered to the primary tumor. Chemotherapy was given in 2 cycles (of 1 week each). Measurements took place before the beginning of treatment (serving as a reference for each patient) and the end of each cycle of chemotherapy. For the design of the study the first measurements took place before the beginning of the therapy, the second measurements at the end of the first cycle of chemotherapy and the third measurements one week after the end of the second cycle of chemotherapy. We also studied the above functional and morphologic taste parameters 2 and 4 months after completion of RCT.

Patients with severe mucositis and oral bacterial infections present before the beginning of therapy were excluded, as previously suggested [8].

The study was conducted following the guidelines of the Declaration of Helsinki on biomedical research involving human subjects and was approved by the local ethics committee. All study participants provided written consent after they had been extensively informed about the study's procedures and purposes. To minimize variability in technique and interpretation of the findings, all examinations were carried out by the same examiner (PP).

Electrogustometry testing: We have evaluated taste acuity with EGM. Electrical stimuli were delivered with an electrogustometer (TR-06, Rion Co, Tokio, Japan) with a single, flat, circular stainless steel stimulus probe (5mm in diameter). The device produces low-amplitude stimuli of pre-determined duration (0.5, 1, 1.5, and 2 seconds). A feedback circuit controls the output current with an error of < 1%.

All subjects were instructed not to drink or eat an hour before the beginning of the testing session. First, a 30dB-stimulus was administered to test whether the subject was in a position to recognize electrogustometric stimuli. Stimulation started at the lowest stimulus amplitude (-6 dB), and increasingly stronger stimuli were presented until the subject recognized the stimulus. If the threshold for stimulus perception was not clearly determined, the next higher- and lower-strength stimuli were presented to the individual. The electric threshold scores were measured at six locations, namely at the area of the vallate papillae on both sides of the tongue, defined as area A (right) and F (left), innervated by the glossopharyngeal nerve, para-medially on both sides of the tongue apex, defined as area C (right) and D (left), each 2 cm away from the tip, at an area innervated by the chorda tympani and at the soft palate, defined as area B (right) and E (left), innervated by the major petrosal nerve bilaterally (Figure 1).

In healthy subjects, electric gustatory thresholds for the tongue apex, vallate papillae, and soft palate were set at levels up to 8, 14 and 22 dB respectively. A 500-ms electric stimulus was applied, beginning at -6 dB and increasing up to +34 dB (3-400 μA) in 2dB-steps (Pavlidis et al., 2014). Thresholds were measured randomly on both sides of the tongue in order to avoid any possible bias. All six areas were tested with the same stimulus duration before proceeding with the application of a stimulus of different duration. This procedure resulted in a 3–4 minutes' stimulus interval (between the application of stimuli of different duration), thereby decreasing the possibility of the emergence of stimulus adaptation. The subjects had been instructed to discriminate between the perception of a sour/metallic taste (suggesting gustatory function - taste threshold) and the perception of an electrical sensation (suggesting trigeminal stimulation). The subject answered "yes" or "no", if she/he perceived any taste sensation. The subject was kept unaware of whether or not the current was applied (blind test) as previously reported [2]. A two-alternative forced-choice initially ascending single-staircase detection was employed using a two-down, one-up rule [9]. The trial sequence was begun at the 8-mA current level, as in previous studies [9,10]. If the subject missed a trial before reaching this criterion, the subsequent trial was presented at the next higher stimulus level. This latter process was continued until five consecutive correct trials occurred at a given current level. At this point, the subsequent trial was presented at the next lower stimulus level. If the first or the second two successive correct trials was missed at this stimulus level, the subsequent trial was presented at the next higher level, representing a reversal in the staircase. If two successive correct trials occurred at this level, the following trial was given at the next lower level.

Contact Endoscopy: Imaging was performed using a 30° contact endoscope (magnification × 60 and × 150; Karl Storz, Tuttlingen, Germany). Identification of fPap was first performed using a non-contact technique. Subjects were instructed to rinse their mouth with water before contact endoscopy. A contact technique was used first without staining for imaging of subepithelial vessels. After careful suctioning of the saliva, methylene-blue 1% solution was used to stain epithelia and taste pores. A filter paper strip delineating an area of 1 cm^2 was placed in a paramedian position on the tongue tip as proposed in previous studies [10,11]. To address the problem of instability of the tongue during endoscopy, the subjects were advised to hold the tip of their tongue gently between their upper and lower teeth, to avoid venous congestion and hyperemia which could eventually confound contact endoscopic findings. The subjects were asked to seat in the examination chair with their head and neck supported by a pillow. The patients were asked to keep the tongue in a fixed position as much as possible. Examination time by CE was about 30 s. Anesthesia was not necessary. A cold light source was used to minimize any heat at the tip of the endoscope. No change (increase or decrease) in vascularisation has been observed during examination by CE.

The form of the fungiform papillae was classified to one of four types in increasing order of damage as following: Type 1, (egg-shaped or long ellipse type – without surface thickness), Type 2 (slight thicker surface compared to type 1), Type 3 (thick and irregular surface) and Type 4 (remarkably flat and atrophic surface). It should be stressed that the mushroom-shaped papillae with horny tips were counted as filliform (and not as fungiform) papillae (Just et al. 2006). Due to their

very light staining, fungiform papillae could be readily distinguished from filiform papillae, which stained dark [8].

The classification of the blood vessels' morphology at the tip of anterior tongue apex was performed according to a classification by Negoro et al. [11]. Five types of vessels' morphology, classified in increasing order of morphologic alterations were found, namely Type A (clear loop and wooden branch shape), Type B (unclear loop and wooden branch shape), Type C (elongated blood vessels), Type D (granular shape or dotted shape) and Type E (unclear blood vessels).

Eighteen (out of initially 20) participants completed the study.

Patient-Reported Outcomes: We asked the participants for any subjective perception of hypogeusia, ageusia, and phantogeusia before EGM and chemogustometry. The first question was, "do you experience any taste loss?" The three possible answers were: "I have no taste at all" (= ageusia), "I think my sense of taste is reduced" (= hypogeusia), or "I feel no change in taste". The second question was whether they experienced taste sensation(s) without eating or drinking anything (= phantogeusia).

Statistical Analysis: The null hypothesis was that there was no statistical difference in EGM-thresholds between groups. For statistical analysis, if an EGM-threshold could not be measured at all, then it was assigned a numerical value of 36 dB. We used a quantile-quantile test (QQplot) to examine the distribution of our findings. A quantile-quantile plot (QQ plot), a graphical tool for assessing normality, is a plot of the sorted values from the data set against the expected values of the corresponding quantiles from the standard normal distribution. The QQ plot of the data did not show any normal distribution. As a result, non-parametric tests were applied. The level of statistical significance was set at $p < 0.05$. On each occasion, the EGM-thresholds between two groups were compared using Kruskal-Wallis and Mann-Whitney tests. The Bonferroni correction was used when necessary. Tukey's multiple comparison tests were used to detect differences significant at the 0.05-level in mean thresholds for the various age categories. For analysis of the regression between EGM-threshold, form, and vascularisation of fPap, the Kendall rank correlation coefficient was applied. The null hypothesis was that the two variables examined on each occasion were independent.

To examine the effect of age on our results, we have applied Cohen's d Test. Cohen's d-Test is used to analyze the effect size. The sample size is an important feature of any empirical study in which the goal is to make inferences about a population from a sample. In practice, the sample size used in a study is determined based on the expense of data collection, and the need to have sufficient statistical power. In our case, the result of d-Test was d=0,2189, which means that the age distribution (mean and standard deviation) had a small effect on the analysis.

To examine further parameters concerning the population of our study, we have estimated the impact of the sample size. The total number of participants is adequate for a confidence level of 99%. The population (n=8) is also adequate for the above confidence levels (margin of error = 0.0%).

Data were analyzed using IBM® SPSS®Statistics 26.

Results

EGM-Thresholds: There were considerable changes in EGM-thresholds in all patients of te group. At the mid time of the radiotherapy regimen, all the patients showed elevated EGM-thresholds (between 30 and 34 dB, p=0.0208). Some of them (n=13) also reported gustatory hallucinations (phantogeusia) or dysgeusia. During the third measurement, a complete ageusia ($p < 0.001$ for all six recorded loci) was observed. Patients reported an inability to recognize any stimulus. By the second examination, 5 patients reported hallucinations, 7 patients reported dysgeusia and 4 ageusia. By the third examination, 4 patients reported dysgeusia and the rest ageusia. By the 4th examination, all patients reported ageusia and by the fifth measurement 6 reported ageusia, 7 phantogeusia and 5 dysgeusia.

Although there was a significant statistical difference between values before the beginning of therapy and values after one week of therapy (p=0.03 for all six loci), 7 of the patients reported hypogeusia, 7 reported allogeusia and 6 dysgeusia a week after the beginning of treatment. During the third measurement sessions, all patients (n=18) reported hypogeusia, and 6 patients reported dysgeusia. There was a significant difference between the EGM-threshold values recorded during the second and those of the third measurement (p=0.03) and between the ones of the first and the third measurements (p=0.02). We have also found differences between the EGM-thresholds recorded 2 and 4 months later. In both measurements, we have recorded a slight improvement (light decrease) in thresholds compared to those measured the third week of radio chemotherapy.

Despite the fact that there was a significant statistical difference between values before the beginning of therapy and values after one week of therapy (p=0.02 for all six loci, Cohen's d-Test= 0.35), six of the patients reported hypogeusia, one reported allogeusia and one dysgeusia a week after the beginning of treatment. During the third measurement sessions, all patients reported hypogeusia, and 3 patients reported dysgeusia. The statistical analysis revealed a significant difference between the EGM-threshold values recorded during the

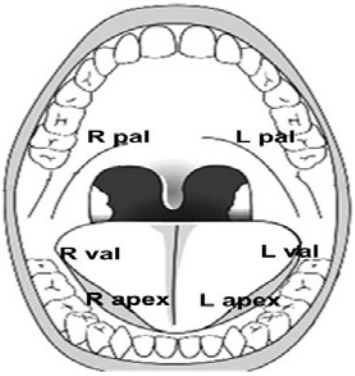

Figure 1: Localisations of EGM-threshold measurements. The sites have been chosen to evaluate the function of the chorda tympani, glossopharyngeal and greter petrosal nerves. Site A in picture correspond to right soft palate (Rpal, innervated by the glossopharyngeal nerve), site B to right vallate papillae (Rval, innervated by the major petrosal nerve) and site C to right tongue apex (Rapex, innervated by the chorda tympani). Sites D, E and F refer to the left-sided tip of the tongue, vallate papillae and soft palate respectively.

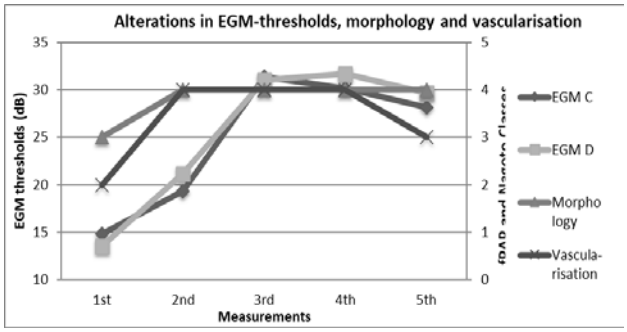

Figure 2: EGM-Thresholds, morphology and vascularization of fPap during 1st, 2nd, 3rd, 4th and 5th measurement in positions C and D. Though EGM-Thresholds seem to improve slightly, we did not find any distinct improvement in form and vascularization. On the contrary, we have noticed that in some patients the above parameters seem to deteriorate further.

second and those of the third measurement (p=0.02, Cohen's d-Test= 0.41) with higher thresholds at the third measurements and between the ones of the first and the third measurements (p=0.001, Cohen's d-Test>0.5) again with higher thresholds at the third measurement.

We have found a significant statistical difference at all six loci (p=0.011) between the first and the fifth measurement. It is obvious that taste acquity deteriorate during and after the therapy.

The EGM-Thresholds at some loci seem to deteriorate further 4 months after the end of the therapy. Compared to those recorded 2 months after the end we have found a significant statistical difference at Loci A (p=0.015), B (p=0.02), E (p=0.015) and F (p=0.023).

Structural changes related to the fungiform papillae: The shape of fPap and vascularisation of the tongue tip worsened significantly during therapy (compared to findings before beginning otreatment) when the Negoro's classification criteria are used. Changes in both structure and vascularization of fPap have been detected. It is interesting that the parameters of fPap (vascularization and form) seem to have a deteriorating tension after the end of the treatment. By the 1st measurement we have found 8 patients with 3/B fPap, 6 patients with 3/C, 2 of them with 2/A and 2 of them 2/C. By the 2nd measurement we have found 2 patients with 4/D fPap, 6 patients with 3/E fPap, 5 patient with 3/C fPap, 4 patient with 4/B fPap and 3 patient with 4/E f Pap. By the 3 rd measurement 3 patients had 4/C fPap, 6 of them 4/E fPap, 5 patients 4/B fPap, 3 patients with 4/D fPap and 1 of them with 4/E fPap. By the 4th measurement we have found 6 patients with 4/C fPap, 5 of them with 4/B fPap, 4 of them had 3/D fPap, 2 patients had 4/C fPap and 1 of them had 4/C fPap. By the 5th measurement 4 patients had 4/C fPap, 6 patients had 4/D fPap,53 patients had 4/B fPap, 2 of them 3/C fPap and the last 1 patients 4/B fPap.Correlation between EGM-Thresholds and the morphology and vascularization of fPap.

We have used the Spearman-test to calculate any correlation between the EGM-thresholds and the morphology and vascularization of fPap. The null hypothesis was that there is no correlation between the above parameters for all 5 measurements of the study.

On the 1st measurement we have found a negative correlation between EGM-thresholds of the right side of the tip of the tongue (point C) and the morphology of fPap (r=0,719). On the contrary, there was no correlation between EGM-thresholds on the rigt side of the tip of the tongue (point D) and the morphology of fPap. Concerning the left side of the tip of the tongue (point D) we have found no correlation between the EGM-thresholds and the morphology of fPap (p=0.130), but there is a strongly positive one between them and the vascularization (r=0.763).

On the 2nd measurement EGM-Thresholds and the morphology of fPap (r=0,094) or their vascularization (r=0.0433) were not correlated on point C. Concerning point D there was a strong correlation between the EGM-Thresholds and the morphology of fPap (r=0.682) and none between D have discovered a strong positive one between the above parameters (r=0.082).

On the 3rd measurement no correlation between EGM-Thresholds and the morphology of fPap or their vascularization was to be found on both sides of the tongue.

Two months after the end of the therapy (4th measurement) on point C was no correlation between EGM-thresholds and the morphology of fPap (r=0,094). We have found a strong one between EGM-thresholds and vascularization of fPap (r=0.738). Concerning point D we have noticed no correlations at all.

Four months after the end of the treatment (5th measurement) on the right side of the tongue's tip (point C) no correlation between EGM-thresholds and the morphology of fPap (r=0,064) or their vascularization (r=0.0200) were detected. On point D we have found a strong correlation between the EGM-thresholds and the morphology of fPap (r=0.25). On the contrary, there is no correlation between the EGM-thresholds and the vascularization of the papillae (p=0.0319).

For better visualization of the changes in EGM-Thresholds, morphology and vascularization of fPap during the study we present the respective results in figure 2 for positions C and D. Though EGM-Thresholds seem to improve slightly, we did not find any distinct improvement in form and vascularization. On the contrary, we have noticed that in some patients the above parameters seem to deteriorate further.

Discussion

Taste dysfunction after radiotherapy for head and neck cancer is a common problem for patients [4,12,13]. During a 6 to 8 week course of daily radiotherapy, taste loss typically occurs by 3-4 weeks and all taste modalities are commonly affected [14,15,16]. In a recent systematic review [14] all tastes decline at 4th to 5th week after radiotherapy and improve on the 11th week.

Deterioration of EGM-Thresholds during RCT in head and neck malignancies has been already reported [4]. The novelty in the present study is the finding that the EGM-thresholds do not improve parallel to the morphology and the vascularization of fPap. The first parameter that seems to improve is vascularization. Another interesting finding is that EGM-Thresholds seem to further deteriorate even after completion of RCT treatment. Our findings may support models which suggest that the regeneration of taste buds depends on the existence of functionally intact nerve fibers. Irradiation may damage nerve fibers that innervate taste buds, causing taste cell death indirectly [5], because maintenance of mature taste cells requires nerve contact [16].

Three models have been proposed to explain irradiation-triggered taste dysfunction [16]. Neurites that innervate sensory organs are radiosensitive. Therefore, disruption of the contact between taste cells and nerves leads to taste cell death; (2) Irradiation directly damages differentiated taste cells; and/or (3) Irradiation targets proliferating progenitors, interrupting the production of new taste cells [5]. It has been proposed [16] that a single, moderate dose of irradiation causes immediate cell cycle arrest in taste progenitors, followed by a disruption in the supply of new cells to taste buds, which results in reduced taste cell number a week after radiation exposure. The same authors proposed that disrupted taste cell renewal is the primary mechanism responsible for functional taste loss in patients receiving radiotherapy. The authors suggest that, if a single 8 Gy dose targets taste cells directly; the number of taste cells would expectedly decrease within the first few days after irradiation exposure. However, if the effect of irradiation on taste receptor cells is indirect, i.e., due to a reduction of newborn cells entering taste buds with continued natural cell death of relatively short-lived taste cells, it would be expected that the number of taste cells would not decrease until later time points following irradiation. Our findings, especially those of the last examination and measurement, are in agreement with the above theory [16]. Although the patients' EGM-thresholds eventually recover, the morphology and vascularization of fPap do not show any further improvement.

In oral mucosa in general [17,18,19], and more specifically in gustatory epithelium, irradiation targets proliferating cells, resulting in an insufficient supply of new cells to the epithelium and taste buds, respectively. Two specific taste cell types are reduced 7 days after irradiation: Type II cells, which transduce sweet, bitter and umami [5] and Type III cells, which mediate sour [20] and synapses with taste afferents [21]. The timing for loss of taste cells is broadly congruent with the onset of functional taste loss in patients, which is first observed after 1 week of radiotherapy [15], with more broad taste dysfunction in patients by the third to fourth weeks [3,22].

The mechanisms by which cytostatic agents cause taste distortions are not entirely understood. They may impair receptor activity [23] and/or affect saliva and mucus production [24]. Besides, cytostatic agents might be secreted in saliva or diffuse from plasma into the oral cavity [25]. One major point seems to be the inhibitory effect of cytostatic agents on mitosis of replicating receptor cells [26]. In many patients, Taste Alterations (TAs) disappear shortly after the end of CT because the cell turnover is restored. Patients with a history of nicotine abuse and older patients reported fewer TAs than did non-smokers and younger patients. It is well documented that both smokers and elderly patients tend to have elevated taste thresholds (hypogeusia) [27]. Accordingly, CT-induced changes in taste are presumably less noticeable by smokers and by the elderly because their thresholds have gradually increased over time. These patients might notice TAs either later or less intensely, and TAs are, therefore, often not reported by the patient even though they are objectively measurable [28]. We have made similar observations in our patients. Chemotherapy may have an immediate effect on taste; some patients will complain of a bitter taste during the intravenous administration of the cytotoxic drugs. Although such gustatory changes may last for a few hours to several days, changes of this kind lasting for weeks or months have also been reported [29].

Early effects of radiation may result through damage to receptors by low-level radiation. During a course of curative radiation therapy for head and neck cancer (e.g., 60-70 Gy given over 6-8 weeks), the salivary function was observed to decrease by the end of the first week, and taste function was measurably impaired by the end of the second week of treatment [15]. Initial assessment of patients' reports of taste changes during radiation therapy has shown that there is considerable change during treatment and that pre-treatment taste sensation does not recover [1, 30,31]. These taste complaints may be due to direct effects upon taste receptors and to reduced saliva production resulting in secondary infection and reduced delivery of tastants to receptor sites.

In the chemotherapy setting, the etiology of taste disorders is not only due to taste receptors' and neurons' damage induced by cytotoxic chemotherapy and/or radiation therapy but is more likely to be multifactorial. The median recognition threshold for salty sensation may be increased after a period of zinc depletion; this phenomenon was reversed after a zinc repletion period. However, zinc supplementation rarely impacts on taste in these patients [32].

Drugs other than chemotherapeutic agents, including some antibiotics, analgesics, biphosphonates, antihypertensives and cardiac medications, bronchodilators, muscle relaxants, antidepressants, and anticonvulsants may also alter taste [33,34,35]. Indeed, many cancer patients may be talking one or a combination of such compounds and this fact must be considered when evaluating taste in such patients. The patients who took part in our study did not receive any medication such as the above Agents that affect hormonal changes, such as tamoxifen, may also affect taste [36,37].

Conclusion

In conclusion, taste disorders in the oncology setting have been understudied and indeed are likely to be underestimated, making recommendations concerning diagnosis, therapy, and prognosis of taste dysfunction difficult [2,38]. To the best of our knowledge, the present study provides for the first time combined data concerning the changes in the structure and vascularisation of fPap in association with the changes in EGM-thresholds in patients with head and neck malignancies both during and after treatment with RCT. The take-home message is that the EGM-thresholds do not improve simultaneously with the morphology and vascularization of fPap. A research step for the future high needs further investigation is the regeneration of nerve-fibers on the tip of the tongue after the treatment with radiotherapy.

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Author Contributions: PP has contributed to the conception and design of the study, acquisition and analysis of data and drafting a significant portion of the manuscript and figures. GAS contributed analysis of data and drafting a significant portion of the manuscript and figures GK contributed to the data acquisition and drafting a significant portion of the manuscript and figures. HG and PP have contributed to the conception and design of the study, acquisition and analysis of data and drafting a significant portion of the manuscript. He has also checked the final arrangements in the manuscript. FG

and MF made the statistical analysis.

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