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Objective and Subjective Hyposalivation after Treatment for Head and Neck Cancer: Long Term Outcomes

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Abstract

Objectives—This study examined saliva weight over time and its association with diet and patient-rated swallowing, dry mouth, sticky saliva, and dysgeusia QoL in HNCA patients treated with surgery (S) plus adjuvant (chemo)radiotherapy (CRT), or primary (C)RT.

Methods—Prospective cohort study in outpatient HNCA Center setting. Patients were seen pre-treatment, 1,3,6,12,24 and 36+ months post-treatment. All had newly diagnosed oral, oropharynx, nasopharynx, larynx/hypopharynx cancer from 2010–2016 who were to undergo S+(C)RT or primary (C)RT. Stimulated saliva weight was assessed with the Saxon test. Diet, eating, dry mouth and dysgeusia QoL were assessed and correlated with saliva weight, treatment modality, and tumor site.

Results—Saliva weight decreased the most within the first 3 months across treatment groups, except for the S+(C)RT group, which continued to decline. Similar trends were seen by tumor site. PSS Normalcy of Diet and all QoL scores declined following treatment. EORTCHN35 QoL EAT-10, MDADI Composite, Global, and subdomain scores and PSS Diet were significantly correlated with saliva weight.

Conclusions—Saliva weight worsened post-treatment across groups and tumor site, with improvement by 36+ months. Saliva weight correlated with diet, eating QoL and perception of dysgeusia across time points. Despite dose-sparing IMRT, newer technologies are needed to preserve saliva production and maintain higher QoL.

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Keywords

hyposalivation; head and neck cancer; quality of life; outcomes

Introduction

Radiation therapy is an effective treatment modality for select patients with head and neck cancer. There is strong evidence that supports its use in the primary and adjuvant setting to improve locoregional control and overall survival^{1,2}. The unfortunate side effects of radiation therapy in the treatment of head and neck malignancies are well recognized^{3–5}. Exposure of the major salivary glands to high doses of radiation impairs saliva production, resulting in xerostomia. Reduced saliva production is the most commonly reported late side effect of irradiation for head-and neck malignancies and is the major cause of decreased quality of life (QOL)^{6,7}. The addition of chemotherapy can exacerbate the symptoms. Surgical ablation of the upper aerodigestive tract can also interfere with saliva production and dry-mouth perception. With reduced saliva production come alterations in speech and taste, malnutrition and difficulty with mastication and deglutition, as well as impairment in eating pleasure and socialization. Patients with dry mouths are predisposed to mucosal ulcerations, fissures, dental caries and infections⁸.

There are a number of strategies for assessing salivary gland function. A well described strategy for objectively documenting saliva production is salivary flow testing. Unstimulated salivary flow rate is assessed by having the patient constantly drain saliva from the lower lip into a container for 15 minutes⁹. Alternatively patients can be asked to spit into a cup for a designated period of time⁹. Other methods have the advantages of measuring the production of each gland independently. Parotid saliva collection can be done by catheterization of Stensen's duct or by using a suction cup such as Lashley cup and Carlson-Crittenden cup attached to the mucosa surrounding the duct opening¹⁰. Stimulated saliva production can be assessed by having the patient chew unflavored gum or paraffin for 1 minute⁹, chewing gauze¹¹, or exposing the tongue to a solution of 2% citric acid at intervals of 30 seconds. Sialometry studies have examined stimulated and unstimulated saliva flow rates^{10,12–14}, as well as stimulated saliva weight^{9,15–20}. Both techniques for measuring stimulated and unstimulated saliva are reliable and validated. However, obtaining unstimulated salivary flow can be problematic in the treated head and neck population, as some may experience difficulty with the requisite rinsing of the mouth prior to the exam, as well as repeatedly spitting into a container. In addition, in our experience, the surgical modifications to the patients' lips or anterior oral cavity can make these collection methods challenging. Further, exposure to citric acid to obtain stimulated salivary flow can be difficult in the early post-treatment period due to oral mucosal sensitivity. The Saxon Test which involves chewing of gauze for 2 minutes, is a reliable, validated assessment of stimulated saliva production¹¹. This test has been found to be a tolerable method for obtaining stimulated saliva production in treated head and neck cancer patients^{15–21}. The Saxon test has been used with patients having undergone primary (chemo)radiotherapy, as well as adjuvant (chemo)radiotherapy, with good patient ability to complete this saliva production task^{15–21}. In addition, this test

has been performed in conjunction with a battery of other vocal tract assessments, as it can easily be completed during a clinic visit^{15–20}.

Patients' perception of dry mouth has been examined in the primary chemoradiotherapy population^{14,15,20–23}, often using the EORTC QLQ-H&N35²⁴ patient-rated QOL scale. Studies have typically examined outcomes within the first 6–12 months^{15,20,25}, however, studies have shown complaints of xerostomia up to three years post-radiotherapy^{14,21}. Studies have also correlated xerostomia with diet and swallowing QOL in the chemoradiotherapy (CRT) population^{15,20,26}, using the Performance Status Scale^{27,28} and the MD Anderson Dysphagia inventory²⁹, respectively. Impairment in taste is a common side effect of radiotherapy and has been found to reduce overall quality of life and oral intake in patients undergoing radiotherapy^{30–34}. No study to date, however, has examined saliva weight and its association with diet, dry mouth, dysphagia and swallowing QOL in both the primary (C)RT and the surgical population with and without adjuvant (C)RT. We present the largest cohort (Level of Evidence: 2b [individual cohort study]) of head and neck cancer patients in which stimulated saliva weight has been tracked over an extended follow-up period and has been correlated with symptoms and function at each time point. This provides a clear, longitudinal representation of the patient experience following head and neck cancer treatment across tumor subsites and treatment modalities. The purpose of this study was to examine saliva weight by treatment across time in treated head and neck cancer patients. We hypothesized that there would be differential effects on salivary production across the treatment groups. We also hypothesized that saliva production would be worst immediately post-treatment and would improve over time.

Methods

This study was approved by the Mount Sinai Institutional Review Board and all subjects provided informed consent. Patients undergoing treatment for new head and neck cancers were included in this study. Treatment sites included oral cavity, oropharynx, nasopharynx, larynx and hypopharynx. Treatments included: 1) surgery only (S); 2) surgery + adjuvant radiotherapy (SRT); 3) surgery + chemoradiotherapy (SCRT); 4) primary radiotherapy (RT) and; 5) primary chemoradiotherapy (CRT). All patients who underwent (C)RT were treated with intensity-modulated radiation therapy (IMRT). Patients were consecutively referred by their surgical, medical, or radiation oncologist for a functional assessment prior to treatment between 2010 and 2017. As part of our usual protocol, the speech-language pathologist (SLP) evaluated patients at the following time points throughout treatment: baseline (before treatment), 1, 3, 6 and 12 months post-treatment¹⁷. In addition, patients were routinely seen yearly after 12 months post-treatment, and time points up to 60 months were obtained. One of two SLPs routinely performed these assessments. No patients received any parasympathomimetics, such as Pilocarpine, to enhance salivary production during or after treatment.

Assessments

Saliva Weight—The subject's stimulated saliva production was quantified using the Saxon test¹¹. This reliable and validated technique relies on taking the difference of the weight of a

4 × 4 inch folded sterile piece of gauze before, and after, chewing for 2 minutes. The chewed gauze is spit into the cup for reweighing. The liquid crystal display (LCD) electronic top-loading scale (Cole-Palmer model# 11320-00) was used for the xerostomia assessment. Saliva production was examined in relation to scores on the PSS and QOL questionnaires. Patients were instructed to take nothing by mouth for one hour prior to the assessment. In addition, they were instructed to chew on the gauze as if they were chewing food. Should they have been experiencing any oral pain due to mucositis, etc., they were instructed to chew as slowly as is comfortable. Time of day varied per patients, depending on time of appointment.

Performance Status—Diet was examined using the “Normalcy of Diet” domain on the Performance Status Scale^{27,28}. This domain is scaled from 0–100, with a higher score indicating better functioning. This scale was chosen because it has been validated in the head and neck population^{27,28}. The PSS is administered by the clinician, who queries the patient regarding what foods are eaten, targeting the food categories on the scale.

QOL Questionnaires—Patients completed quality of life questionnaires at each time point. The EORTC QOL scale, a 30 item questionnaire that assesses head and neck-related QOL²⁴, was used to examine patient-perceived issues related to their treatment. Specifically, dry mouth, sticky saliva, and altered intra-oral sensation/dysgeusia, as per the “dry mouth”, “sticky saliva”, and “senses” questions on this scale, were assessed. Eating and swallowing QOL were examined using the: (1) Eating Assessment Tool³⁵ (EAT-10) - a 10-item self-administered symptom-specific outcome instrument for dysphagia, with a scale from 0–4, with 0 being a normal score and higher scores indicating poorer functioning and (2) MD Anderson Dysphagia Inventory (MDADI)²⁹ - a 30-point self-administered symptom-specific outcome instrument for dysphagia specific to the head and neck cancer population with higher scores indicating better functioning. The Composite, Global, and subdomain (emotional, functional, and physical) scores were used to measure QOL.

Statistical Analysis—Descriptive statistics were used to describe the frequency (percentage) of primary treatment type, tumor site and TNM stage in this population. PSS and QoL measures were summarized using median and range (minimum and maximum). Repeated-measures analysis of variance (ANOVA) were used to examine the bivariate association between saliva weight and the time point of measurement (baseline, post-tx: 1 month, 3 month, 6 month, 12 month, 24 month, 36+ month). It was further analyzed by treatment type and tumor site separately across the time points. Similar analyses were performed to explore the associations between other measures (PSS Normalcy of Diet, complaint of dry mouth, altered taste, and sticky saliva, EAT-10 eating QOL, MDADI Composite, Global, and its three subdomain scores (emotional, functional, physical) and treatment type and tumor site over time. Associations between saliva weight and these measures (performance status, QoL-EAT-10 and MDADI scores) were then examined by repeated measures correlation using the R package (“rmcorr”)³⁶. Correlation coefficients, with 95% confidence intervals and corresponding p-values were calculated. Statistical significance was set at $p < 0.05$. All statistical analysis procedures were performed using

SAS 9.4 software package (SAS Institute Inc., Cary, NC, USA) and R Statistical Software (R-3.4.1, Foundation for Statistical Computing, Vienna, Austria).

Results

582 patients (422 males and 160 females), with a mean age of 60.5 (SD: 11.7), were included in this study. Across the span of this study, only 3 patients did not provide consent to participate. The mean age for male subjects was 60.4 (SD: 10.9) and 60.5 (SD: 13.8) for female subjects. One hundred eleven patients were treated with surgery alone, 136 with surgery + (C)RT; 36 with RT alone, and 299 with CRT. Distribution of treatment modality, tumor site and TNM stage can be found in Table 1. There were missing data regarding TNM stage, particularly for patients evaluated early in this study.

As shown in Figure 1, the boxplot indicated that saliva weight had the largest reduction from baseline to 3 month post-treatment. Repeated measures ANOVA showed saliva weight from post-treatment visits to be significantly lower than baseline (Table 2). Similar trends were found when breaking down into treatment groups (Figure 2, Table 3) and tumor sites (Figure 3, Table 4). Patients in the Surgery Alone group demonstrated the least change in saliva weight over time. The (C)RT group showed the greatest reduction in saliva weight during the first three months post-treatment while the surgery + (C)RT group had the lowest saliva weight at 6 month post-treatment. Overall, saliva weight decreased in the first 6 months and improved thereafter. The pre-treatment baseline was not reached by surgery + (C)RT and (C)RT groups (saliva weight at baseline vs. 36+ months, $p < 0.05$), but was reached in the RT only and surgery only groups, which had an average saliva weight higher than baseline by 36+ months. Across all anatomic sites reviewed, the saliva weight showed the greatest decline at 3 months. In patients with oral, oropharyngeal, and larynx/pharynx sites, there was improvement noted by 6 months, but no return to baseline by 36+ month post-treatment. All patients except those with larynx/pharynx sites had significant reduction in saliva weight at 36+ month compared to baseline ($p < 0.05$). Repeated-measures ANOVA results showed a significant relationship between saliva weight and treatment group ($p < .0001$) as well as saliva weight and tumor site ($p < .0001$) after accounting for potential within-subject correlation over time.

PSS and QoL

The median and range of PSS and QoL measures collected at each follow-up visit (Baseline, 1 month, 3 month, 6 month, 12 month, 24 month, first one after 36 month) are shown in Table 4. Across patients, scores on the PSS Normalcy of Diet domain and all QoL scales declined following treatment, with the greatest decline seen at 1–3 months post-treatment. When adjusting for treatment group, the MDADI Composite scores showed a significant relationship between treatment groups and these responses over time using repeated measures ANOVA. Using the same method, all measures other than EAT-10 score and MDADI Global and subdomain scores showed a significant association with tumor site over time.

Correlations of PSS and QoL with Saliva Weight

When examining the correlation between saliva weight and patient-rated dry mouth, sticky saliva, and senses from the EORTCHN35, the EAT-10 total score, MDADI GLOBAL score and the Normalcy of Diet domain on the PSS scale, all measures were shown to have a significant correlation with saliva weight ($p < .0001$) (Table 5), when accounting for the intra-individual variation in repeated measures. Dry mouth questions from the EORTCHN35 ($r = -0.59$) had the strongest (negative) association with saliva weight among these measures (i.e., lower saliva weight correlated with poorer (higher) QoL scores). Senses ($r = -0.46$) and sticky saliva ($r = -0.43$) from the EORTCHN35, the Normalcy of Diet domain on the PSS scale ($r = 0.38$), EAT-10 scores ($r = -0.34$), MDADI Composite scores ($r = 0.33$), Functional scores ($r = 0.33$), Physical scores ($r = 0.30$), MDADI Global scores ($r = 0.25$), and Emotional scores ($r = 0.24$) indicated a weak to moderate association with saliva weight.

Correlations of PSS and QoL by Treatment Type, Tumor Site

We further examined the correlation between saliva weight and PSS and QoL measures stratified by treatment type and tumor site (Table 6). Overall, the RT and (C)RT groups, contributed the most to the relationship between saliva weight and PSS and QoL measures. When examining by site, oropharynx and nasopharynx also contributed the most to the relationship between saliva weight and PSS and QoL measures.

Discussion

Saliva weight declined over the first 3 months, followed by recovery in all treatment groups, other than the Surgery+(C)RT group, which continued to drop after 3 months and showed a dip in saliva weight between 12 and 24 months. The Surgery Only group had the least change in saliva weight, performing better than the Surgery + (C)RT groups at all time points. Others have found that adjuvant (C)RT results in poorer function and QOL as compared to surgery alone^{17,37–39}. Decrements in dry mouth QOL have been demonstrated by others^{21,40}, however, these authors found continued deterioration in function and QOL seen by 24 months post-treatment which was not observed in our cohort. This discordance might be explained by differing radiotherapy techniques. For example, patients in the Cartmill study were treated with altered fractionation radiotherapy, while patients in our cohort received IMRT. Our results were similar to those seen by Teguh and colleagues²², with correlations of patient-reported dysphagia and xerostomia on the EORTCHN35 dry mouth and PSS scales. Our results were also consistent with those found by Goepfert and colleagues⁴¹, who observed a drop in MDADI scores at 6 months, with recovery by 24 months in the treated “low-intermediate risk” oropharyngeal cancer patient population.

The dip in saliva weight in the Surgery + (C)RT group between 12 and 24 months’ time point was an unexpected finding. This group was comprised primarily of oral cancer patients. The drop in saliva weight may be due to their reduced ability to chew well enough to stimulate saliva. Another reason may be due to the smaller sample size of this group. The lower saliva weight seen in the Surgery + (C)RT was also surprising.

While other studies may not have shown recovery of saliva function in patients undergoing IMRT, our analysis suggests return of saliva weight to baseline.. This may be due to this being the largest cohort with careful measurements of salivary function across an extended period of time. While we cannot explain this mechanistically, this does warrant further study of salivary gland function in long-term survivors of head and neck cancer radiation treatment.

The perception of dry mouth on the EORTCHN35 had the strongest correlation with saliva weight across all measures. Patients in this study reported poorer dry mouth QOL scores even at the 36+ time point, when some patients demonstrated saliva weight similar to baseline. It has been shown that patient perception of dry mouth and its effect on food manipulation does not necessarily correlate with saliva weight or with ability to propel foods and liquids from the oral cavity^{14,42–46}. These studies have examined xerostomia and complaints of dysphagia, as objectively examined with videofluoroscopy, where patient-reported dysphagia and xerostomia did not correlate with swallowing outcomes. Vainshtein and colleagues¹⁴ found that patient-reported dysphagia and xerostomia persisted and correlated highly up to 24 months post-treatment, despite no/mild videofluoroscopic abnormalities. In our cohort of patients, although saliva weight improved over time across treatment groups, it did not return to baseline in any group other than RT alone and surgery alone groups. It appears that further improvements in technology are needed to preserve salivary gland functioning in this population.

Salivary flow testing can be problematic in the treated head and neck cancer population. The method described here, the Saxon Test, provides a simple, inexpensive, and reliable technique for assessment of stimulated saliva weight in this population. Patients rarely find it difficult to maintain and chew gauze for a designated amount of time, even in cases where extensive resection and reconstruction of the oral cavity has been performed. One limitation of this test, however, is the inability to assess each saliva gland separately. However, there was good correlation between stimulated saliva weight and overall QOL in this cohort. Another limitation was the fact that some patients chewed more slowly than others, due to oral pain or structural changes. Future studies will examine saliva weight and associated diet, swallowing ability, and patient-reported QOL in treated head and neck cancer patients in later post-treatment timepoints (e.g., 7–10 years post-treatment). An additional limitation of this study was the inability to examine the impact of unilateral vs. bilateral radiotherapy on saliva weight. This was because data were not available for all patients and in addition, data would not necessarily have been binary, with a spectrum of RT dosage to the contralateral tissues and saliva glands. Prospectively, we will examine laterality of RT treatment and dosage to salivary glands.

An additional limitation was the lack of information regarding TNM staging in a number of early patients enrolled in this study. However, the main outcome was saliva weight according to treatment type. While TNM staging would have been helpful to have for all patients, the missing data points did not affect our conclusions.

Conclusion

This is the first study to correlate saliva weight with diet, eating QOL, and perception of dry mouth, sticky saliva, and dysguesia in a large cohort of oral, oropharyngeal, nasopharyngeal and laryngeal/hypopharyngeal carcinoma treated with primary (C)RT or surgery +/- (C)RT. Saliva weight testing using the Saxon Test is simple and precludes the need for salivary flow rate testing that is not readily available to clinicians. In this cohort of patients, saliva weight worsened post-treatment across treatment groups and across sites, with improvement by 36+ months. Patients with larynx/hypopharynx tumor sites performed better in saliva production than those with oral cavity, oropharynx, and nasopharynx sites. Saliva weight correlated with diet, eating QOL, and perception of dysguesia across timepoints. Despite dose-sparing IMRT radiotherapy, newer technologies are needed to improve salivary sparing for better saliva production and patient-rated quality of life outcomes.

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Figure 1.

Box plot of saliva weight using the Saxon chewing method for all patients at baseline/pre-treatment, 1, 3, 6, 12, 24, and 36+ months post-treatment

Footnote: The boxes denote the interquartile range (IQR), the whiskers represent values observed within 1.5 times the IQR from either end of the box, outliers are any values that lie outside the range of whiskers denoted as dots, the dark lines indicate medians and the diamonds indicate means.

Figure 2.

Saliva weight by treatment type at baseline/pre-treatment, 1, 3, 6, 12, 24, and 36+ months post-treatment.

Figure 3.
Saliva weight by tumor site at baseline/pre-treatment, 1, 3, 6, 12, 24, 36+ months post-treatment.

Table 1

Breakdown of patient characteristics by primary treatment type, tumor site and TNM stage.

	Overall	Radiotherapy	Surgery
N	582	335 (57.6%)	247 (42.4%)
Tx modality (%)			
Surgery only	111 (19.1)	/	111 (19.0)
Surgery + C/RT	136 (23.3)	/	136 (23.3)
RT only	36 (6.2)	36 (6.2)	/
CRT	299 (51.4)	299 (51.4)	/
Tumor Site (%)			
Oral Cavity	202 (34.7)	4 (1.2)	198 (80.2)
Tongue Base	246 (42.3)	207 (61.8)	39 (15.8)
Larynx/Pharynx	92 (15.8)	83 (24.8)	9 (3.6)
Nasopharynx	42 (7.2)	41 (12.2)	1 (0.4)
T (%)			
T (%)	233 Missing		
T1	68 (19.5)	33 (16.0)	35 (24.5)
T2	114 (32.7)	60 (29.1)	54 (37.8)
T3	101 (28.9)	81 (39.3)	20 (14.0)
T4	62 (17.8)	28 (13.6)	34 (24.8)
Tx	4 (1.2)	4 (1.9)	0 (0.0)
N (%)			
N (%)	241 missing		
N-	94 (27.6)	35 (17.2)	59 (42.8)
N1	50 (14.7)	31 (15.3)	19 (13.8)
N2	180 (52.8)	122 (60.1)	58 (42.0)
N3	11 (3.2)	11 (5.4)	0 (0.0)
Nx	6 (1.8)	4 (2.0)	2 (1.5)
M (%)			
M (%)	253 missing		
M0	309 (93.9)	182 (92.4)	127 (96.2)
M1	2 (0.6)	1 (0.5)	1 (0.8)
Mx	18 (5.5)	14 (7.1)	4 (3.0)

Abbreviation: C/RT: Chemoradiotherapy or Radiotherapy; RT: Radiotherapy; CRT: Chemoradiotherapy

Table 2

Average reduction in saliva weight compared to baseline

	Reduction in saliva weight	p-value
Baseline	Ref	
1 Month	1.97 (1.72, 2.23)	<.0001
3 Month	2.69 (2.43, 2.94)	<.0001
6 Month	2.50 (2.23, 2.77)	<.0001
12 Month	1.94 (1.62, 2.26)	<.0001
24 Month	1.54 (1.13, 1.95)	<.0001
36 Month	1.16 (0.79, 1.53)	<.0001

Average reduction estimates and p-values obtained from repeated-measures ANOVA.

P-value < 0.05 in bold.

Table 3

Saliva weight across treatment modalities at each time point

		Difference in saliva weight compared to Sx only group (95% CI)	p-value
Baseline	Sx	Ref	
	Sx + C/RT	-0.38 (-1.04, 0.29)	0.2662
	RT only	0.01 (-0.67, 0.69)	0.9697
	C/RT	-0.09 (-0.61, 0.43)	0.7362
1 Month	Sx	Ref	
	Sx + C/RT	-0.15 (-0.92, 0.61)	0.6976
	RT only	-0.99 (-1.91, -0.06)	0.0371
	C/RT	-2.37 (-3.03, -1.71)	<.0001
3 Month	Sx	Ref	
	Sx + C/RT	-0.85 (-1.7, 0)	0.0493
	RT only	-0.69 (-1.83, 0.45)	0.2324
	C/RT	-1.88 (-2.59, -1.18)	<.0001
6 Month	Sx	Ref	
	Sx + C/RT	-2.43 (-3.28, -1.58)	<.0001
	RT only	-0.13 (-1.32, 1.06)	0.8312
	C/RT	-1.79 (-2.52, -1.06)	<.0001
12 Month	Sx	Ref	
	Sx + C/RT	-1.53 (-2.65, -0.41)	0.0074
	RT only	0.33 (-0.91, 1.57)	0.5982
	C/RT	-1.09 (-1.98, -0.21)	0.0150
24 Month	Sx	Ref	
	Sx + C/RT	-1.03 (-2.67, 0.61)	0.2162
	RT only	0.83 (-1.17, 2.83)	0.4137
	C/RT	-0.92 (-2.3, 0.47)	0.1944
36 Month	Sx	Ref	
	Sx + C/RT	-2.11 (-3.66, -0.56)	0.0077
	RT only	0.15 (-1.42, 1.72)	0.8493
	C/RT	-1.44 (-2.74, -0.15)	0.0290
		Reduction in saliva weight (95% CI)	
Sx	Baseline vs. 36 Mo	0.00 (-1.25, 1.25)	0.9943
Sx + C/RT	Baseline vs. 36 Mo	1.73 (0.70, 2.76)	0.0010
RT only	Baseline vs. 36 Mo	-0.14 (-1.18, 0.89)	0.7853
C/RT	Baseline vs. 36 Mo	1.35 (0.96, 1.74)	<.0001

Difference in mean saliva weight estimates and p-values obtained from repeated-measures ANOVA.

P-value < 0.05 in bold.

Table 4

Saliva weight across tumor sites at each time point

		Difference in saliva weight compared to Oral Cavity group (95% CI)	p-value
Baseline	Oral Cavity	Ref	
	Oropharynx	0.25 (−0.22, 0.72)	0.2884
	Larynx/Pharynx	−0.49 (−1.09, 0.11)	0.1069
	Nasopharynx	−0.93 (−1.67, −0.2)	0.0126
1 Month	Oral Cavity	Ref	
	Oropharynx	−1.51 (−2.08, −0.93)	<.0001
	Larynx/Pharynx	−0.91 (−1.68, −0.14)	0.0209
	Nasopharynx	−2.43 (−3.34, −1.51)	<.0001
3 Month	Oral Cavity	Ref	
	Oropharynx	−1.11 (−1.71, −0.51)	0.0003
	Larynx/Pharynx	−0.76 (−1.56, 0.03)	0.0606
	Nasopharynx	−2.23 (−3.11, −1.34)	<.0001
6 Month	Oral Cavity	Ref	
	Oropharynx	0.01 (−0.61, 0.63)	0.9842
	Larynx/Pharynx	0.21 (−0.6, 1.01)	0.6123
	Nasopharynx	−1.42 (−2.34, −0.5)	0.0025
12 Month	Oral Cavity	Ref	
	Oropharynx	0.44 (−0.33, 1.22)	0.2610
	Larynx/Pharynx	0.41 (−0.63, 1.45)	0.4386
	Nasopharynx	−1.27 (−2.35, −0.19)	0.0211
24 Month	Oral Cavity	Ref	
	Oropharynx	0.06 (−0.98, 1.1)	0.9077
	Larynx/Pharynx	0.22 (−1.1, 1.55)	0.7394
	Nasopharynx	−1.38 (−2.95, 0.18)	0.0834
36 Month	Oral Cavity	Ref	
	Oropharynx	0.29 (−0.67, 1.25)	0.5508
	Larynx/Pharynx	0.07 (−1.15, 1.29)	0.9090
	Nasopharynx	−1.82 (−3.05, −0.59)	0.0038
		Reduction in saliva weight (95% CI)	
Oral Cavity	Baseline vs. 36 Mo	1.24 (0.34, 2.14)	0.0069
Oropharynx	Baseline vs. 36 Mo	1.2 (0.74, 1.66)	<.0001
Larynx/Pharynx	Baseline vs. 36 Mo	0.67 (−0.17, 1.51)	0.1156
Nasopharynx	Baseline vs. 36 Mo	2.12 (1.25, 2.99)	<.0001

Difference in mean saliva weight estimates and p-values obtained from repeated-measures ANOVA.

P-value < 0.05 in bold.

Table 5

Repeated Measures Correlations of Saliva weight with PSS Normalcy of Diet domain, Eat-10, MDADI Composite, Global and subdomain scores (emotional, functional, physical), EORTCHN35 senses, dry mouth, and sticky saliva questions.

	r	95% CI	p-value
PSS Normalcy of Diet	0.38	[0.32, 0.44]	<.0001
Eat-10	−0.34	[−0.41, −0.27]	<.0001
MDADI Composite	0.33	[0.26, 0.41]	<.0001
MDADI Global	0.25	[0.15, 0.33]	<.0001
MDADI Emotional	0.24	[0.15, 0.33]	<.0001
MDADI Functional	0.33	[0.24, 0.42]	<.0001
MDADI Physical	0.30	[0.21, 0.39]	<.0001
EORTCHN35 Senses	−0.46	[−0.53, −0.4]	<.0001
EORTCHN35 Dry mouth	−0.59	[−0.64, −0.53]	<.0001
EORTCHN35 Sticky saliva	−0.43	[−0.49, −0.36]	<.0001

r: correlation coefficient; CI: Confidence Interval;

p<0.05 in bold.

Table 6

Correlations of Saliva Weight with PSS Normalecy of Diet domain, Eat-10, MDADI Composite, Global and subdomain (emotional, functional, physical) scores, EORTCHN35 senses, dry mouth, and sticky saliva questions by Treatment Type and Tumor Site.

	Treatment	r	95% CI	p-value	Tumor site	r	95% CI	p-value
PSS Normalecy of Diet	Sx	0.26	[0.07, 0.44]	0.0087	Oral Cavity	0.27	[0.14, 0.4]	0.0001
	Sx + C/RT	0.26	[0.11, 0.41]	0.0013	Oropharynx	0.44	[0.36, 0.51]	<0.0001
	RT	0.37	[0.09, 0.6]	0.0107	Larynx/Pharynx	0.27	[0.07, 0.45]	0.0083
	C/RT	0.45	[0.37, 0.52]	<0.0001	Nasopharynx	0.62	[0.38, 0.78]	<0.0001
Eat-10	Sx	-0.14	[-0.35, 0.09]	0.2268	Oral Cavity	-0.25	[-0.39, -0.09]	0.0018
	Sx + C/RT	-0.25	[-0.41, -0.07]	0.0055	Oropharynx	-0.39	[-0.48, -0.3]	<0.0001
	RT	-0.51	[-0.71, -0.25]	0.0004	Larynx/Pharynx	-0.22	[-0.41, 0]	0.0444
	C/RT	-0.38	[-0.47, -0.3]	<0.0001	Nasopharynx	-0.63	[-0.81, -0.34]	0.0002
MDADI Composite	Sx	0.22	[-0.03, 0.44]	0.0765	Oral Cavity	0.32	[0.15, 0.46]	<0.0001
	Sx + C/RT	0.30	[0.11, 0.46]	0.0016	Oropharynx	0.36	[0.26, 0.45]	<0.0001
	RT	0.49	[0.2, 0.7]	0.0016	Larynx/Pharynx	0.24	[0.02, 0.44]	<0.0001
	C/RT	0.35	[0.25, 0.44]	<0.0001	Nasopharynx	0.38	[-0.05, 0.69]	0.0696
MDADI Global	Sx	0.03	[-0.27, 0.33]	0.8338	Oral Cavity	0.05	[-0.16, 0.26]	0.6340
	Sx + C/RT	0.08	[-0.13, 0.29]	0.4459	Oropharynx	0.34	[0.22, 0.44]	<0.0001
	RT	0.40	[0.08, 0.65]	0.0138	Larynx/Pharynx	0.15	[-0.12, 0.4]	0.2613
	C/RT	0.32	[0.2, 0.43]	<0.0001	Nasopharynx	0.16	[-0.46, 0.67]	0.5912
MDADI Emotional	Sx	0.28	[-0.02, 0.53]	0.0650	Oral Cavity	0.14	[-0.07, 0.34]	0.1909
	Sx + C/RT	0.04	[-0.17, 0.26]	0.6886	Oropharynx	0.30	[0.18, 0.41]	<0.0001
	RT	0.59	[0.32, 0.77]	0.0001	Larynx/Pharynx	0.21	[-0.05, 0.45]	0.1086
	C/RT	0.27	[0.14, 0.38]	<0.0001	Nasopharynx	-0.23	[-0.71, 0.4]	0.4289
MDADI Functional	Sx	0.16	[-0.15, 0.44]	0.2990	Oral Cavity	0.30	[0.1, 0.48]	0.0042
	Sx + C/RT	0.26	[0.05, 0.45]	0.0148	Oropharynx	0.38	[0.26, 0.48]	<0.0001
	RT	0.56	[0.28, 0.75]	0.0003	Larynx/Pharynx	0.23	[-0.03, 0.47]	0.0762
	C/RT	0.35	[0.24, 0.46]	<0.0001	Nasopharynx	-0.05	[-0.61, 0.54]	0.8553
MDADI Physical	Sx	0.26	[-0.05, 0.52]	0.0887	Oral Cavity	0.22	[0, 0.41]	0.0433

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	Treatment	r	95% CI	p-value	Tumor site	r	95% CI	p-value
	Sx + C/RT	0.12	[-0.1, 0.32]	0.2851	Oropharynx	0.35	[0.23, 0.45]	<0.0001
	RT	0.64	[0.39, 0.8]	<0.0001	Larynx/Pharynx	0.24	[-0.03, 0.48]	0.0701
	C/RT	0.34	[0.22, 0.45]	<0.0001	Nasopharynx	0.23	[-0.4, 0.71]	0.4390
EORTCHN35 Senses	Sx	-0.27	[-0.47, -0.04]	0.0221	Oral Cavity	-0.37	[-0.5, -0.22]	<0.0001
	Sx + C/RT	-0.38	[-0.53, -0.22]	<0.0001	Oropharynx	-0.51	[-0.58, -0.43]	<0.0001
	RT	-0.56	[-0.75, -0.3]	0.0001	Larynx/Pharynx	-0.37	[-0.55, -0.16]	0.0009
EORTCHN35 Dry mouth	C/RT	-0.51	[-0.58, -0.43]	<0.0001	Nasopharynx	-0.56	[-0.78, -0.22]	0.0023
	Sx	-0.31	[-0.51, -0.08]	0.0073	Oral Cavity	-0.48	[-0.6, -0.34]	<0.0001
	Sx + C/RT	-0.56	[-0.67, -0.41]	<0.0001	Oropharynx	-0.64	[-0.69, -0.57]	<0.0001
EORTCHN35 Sticky saliva	RT	-0.65	[-0.8, -0.42]	<0.0001	Larynx/Pharynx	-0.42	[-0.59, -0.21]	0.0001
	C/RT	-0.62	[-0.68, -0.56]	<0.0001	Nasopharynx	-0.75	[-0.88, -0.52]	<0.0001
	Sx	-0.09	[-0.32, 0.15]	0.4573	Oral Cavity	-0.27	[-0.42, -0.11]	0.0010
	Sx + C/RT	-0.38	[-0.53, -0.21]	<0.0001	Oropharynx	-0.48	[-0.55, -0.39]	<0.0001
	RT	-0.60	[-0.77, -0.35]	<0.0001	Larynx/Pharynx	-0.42	[-0.59, -0.21]	0.0001
	C/RT	-0.47	[-0.55, -0.39]	<0.0001	Nasopharynx	-0.68	[-0.85, -0.4]	0.0001

r: correlation coefficient; CI: Confidence Interval;

p<0.05 in bold.