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The impact of head and neck radiotherapy on salivary flow and quality of life: Results of the ORARAD study

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ABSTRACT

Objectives: Salivary hypofunction and xerostomia, are common side effects of radiotherapy, negatively impacting quality of life. The OraRad study presents results on the longitudinal impact of radiotherapy on salivary flow and patient-reported outcomes.

Patients and Methods: Prospective, multicenter cohort study of 572 patients receiving curative-intent head and neck radiotherapy (RT). Stimulated salivary flow (SSF) rate and patient-reported outcomes were measured prior to RT and at 6- and 18-months post-RT. Linear mixed effects models examined the relationship between RT dose and change in salivary flow, and change in patient-reported outcomes.

Results: 544 patients had baseline salivary flow measurement, with median (IQR) stimulated flow rate of 0.975 (0.648, 1.417) g/min. Average RT dose to parotid glands was associated with change in salivary flow post-RT ($p < 0.001$). Diminished flow to 37% of pre-RT level was observed at 6 months (median: 0.358, IQR: 0.188 to 0.640 g/min, $n = 481$) with partial recovery to 59% of pre-RT at 18 months (median: 0.575, IQR: 0.338 to 0.884 g/min, $n = 422$). Significant improvement in patient-reported swallowing, senses (taste and smell), mouth opening, dry mouth, and sticky saliva (p-values < 0.03) were observed between 6 and 18 months post-RT. Changes in swallowing, mouth opening, dry mouth, and sticky saliva were significantly associated with changes in salivary flow from baseline (p-values < 0.04).

Conclusion: Salivary flow and patient-reported outcomes decreased as a result of RT, but demonstrated partial recovery during follow-up. Continued efforts are needed to improve post-RT salivary function to support quality of life.

Introduction:

Head and neck cancer is a common malignancy, with an estimated incidence of 66,630 new cases and 14,620 deaths in the United States in 2021 [1]. Radiotherapy (RT) is a standard-of-care treatment modality commonly used in the treatment of head and neck cancer, but is associated with treatment-related morbidity. Salivary hypofunction (diminished salivary production) and xerostomia (sensation of dry mouth) are common side effects of therapy [2] which negatively impact quality of life [3,4], and can be partially mitigated with advanced forms of RT to better spare radiation dose delivered to critical normal tissues such as the parotid gland [4–6]. Furthermore, with the rising incidence of human papilloma virus (HPV)-associated oropharyngeal squamous cell carcinoma, which is associated with improved survival [7–9],

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strategies to mitigate toxicity are of critical importance.

Previous investigators have shown that the use of intensity-modulated radiotherapy (IMRT), as compared to less conformal methods of radiation, can lessen the severity of treatment-induced salivary gland hypofunction and xerostomia, and can improve quality of life [4–6,10,11]. The OraRad study represents the largest, prospective, multicenter cohort study of salivary flow and quality of life in patients receiving head and neck RT, delivered at high-volume, academic centers of expertise. The objective of this analysis from the OraRad study was to describe salivary flow and associated patient-reported outcomes at 6- and 18-months after RT.

Patients and Methods:

The OraRad study, previously described [12], enrolled head and neck cancer patients at six clinical centers: Brigham and Women's Hospital, University of Pennsylvania, Atrium Health Carolinas Medical Center, University of Connecticut, New York University, and University of North Carolina with the Data and Coordinating Center at the University of Minnesota. Institutional Review Board approval was obtained at all sites and participants were consented and enrolled before initiating curative-intent (definitive or postoperative) head and neck RT. Patients were eligible if: age 18 or older; diagnosed with head and neck squamous cell carcinoma (SCC) or a salivary gland cancer (SGC), or with a non-SCC, non-SGC malignancy of the head and neck region; planned to receive at least 4500 cGy RT to the head and neck region; and had no prior RT to the head and neck region. A total of 572 participants were enrolled between April 2014 and October 2018 and eligible for follow-up post-RT.

To assess the effect of RT on salivary flow, whole stimulated salivary flow rate was measured at baseline (prior to RT), and at 6 months and 18 months post-RT [12]. Individuals who missed their salivary flow measurements at the month 6 or month 18 visit were allowed to make up the measurement at the next subsequent visit: month 12 (n = 30) or month 24 (n = 40), respectively. Participants were provided with unflavored paraffin (gum base) and two 50 ml test tubes. They were instructed to chew the gum base for 2 min, meanwhile expectorating saliva into one of two test tubes. This was done as practice to standardize the technique and stabilize the flow rate. The same chewing/expectorating method was used for 5 min for the final flow rate assessment, timed using a digital timer. The saliva collected in 5 min was weighed and recorded.

To examine whether increased parotid sparing was associated with better preservation of salivary flow, the average doses delivered to the left and right parotid glands were recorded for each patient. At one of the participating institutions, additional information was available for its patients (N = 144) in the form of average doses delivered to the left and right submandibular glands as well as the oral cavity (surrogate for the sublingual and minor salivary glands), as it was the standard treatment protocol for the radiation oncologists at this institution to delineate and record doses to these normal organs.

The association between primary site of RT and salivary flow was evaluated, with primary sites classified into the following 5 anatomic regions: oropharynx (consisting of base of tongue, tonsil, oropharynx, and soft palate); oral cavity (consisting of oral tongue, oral cavity, gingival/alveolar ridge, mandible, buccal/labial mucosa, floor of mouth, maxilla, retromolar trigone, hard palate, and lip); larynx/hypopharynx (consisting of larynx, hypopharynx, and epiglottis); salivary gland (consisting of submandibular gland, parotid, and sublingual gland); and other (consisting of neck, nasopharynx, pharynx, maxillary sinus, nasal cavity and other sites).

To investigate the impact of RT on patient-reported quality of life, patients were administered questions corresponding to RT-specific scales of the EORTC QLQ-H&N35 [13] questionnaire at baseline, and then every 6 months post-RT for 2 years. An Academic User Agreement was obtained for use of specific scales from the EORTC QLQ-H&N35 in the OraRad study prior to administration. The chosen questions evaluate the extent (four-point scale ranging from "not at all" to "very much") to which participants experienced problems with their oral health during the past week. Scale scores are transformed into 0-to-100 scales, with higher scores representing higher level of symptoms. The specific aspects of oral health included the following scales: swallowing (problems swallowing liquids, pureed food, and solid foods and choking when swallowing), senses problems (problems with sense of smell and taste), teeth, mouth opening, dry mouth, and sticky saliva.

Statistical methods

Linear mixed-effects models with patient specific random intercepts were used to evaluate change in salivary flow across study time points (baseline, visit 6 months, and visit 18 months; treated as a categorical variable). An interaction term between study visit and average of mean dose to the left and right parotids (scaled by 100 cGy) was included in the model to test the relationship between RT dose and change in salivary flow over time. For individuals who had partial or complete removal of a parotid gland (n = 49), the average dose to the remaining parotid was used. Similar models were constructed to evaluate the relationship between average RT dose to the contralateral parotid for individuals with unilateral RT treatment, average RT dose to the salivary glands (defined as a composite of the bilateral parotid and submandibular glands, as well as the oral cavity), primary site of RT, and use of chemotherapy with respect to change in salivary flow. Due to the right skew of the salivary flow values, a sensitivity analysis evaluated models with the outcomes square-root transformed. These models gave similar findings as the model with untransformed outcomes so for ease of explanation only the results from models with untransformed outcomes are presented.

EORTC scales were treated as continuous measures and evaluated using linear mixed effects models with subject specific random intercepts. We evaluated the association between change in salivary flow (expressed as percentage of baseline value) and change in patient-reported outcomes by testing the interaction between change in salivary flow from baseline and study visit (visit at 6 months and visit at 18 months) in a linear mixed effects models parameterized with fixed effects for intercept, visits (6 months and 18 months), and interaction terms between change in salivary flow and visits (6 months and 18 months). The results presented exclude one individual with extreme changes in salivary flow (>2000% change). The analyses including this individual are provided in Supplementary Table S1.

Holm's method was used to adjust for multiple comparisons in evaluating pairwise differences between study timepoints. All analyses were done using R version 3.6.0

Results:

A total of 572 patients were enrolled, with a median (range) age of 59 (21 to 97) years, and the majority being male (77%) (Table 1). Squamous cell carcinoma was the most common pathology (82%), and oropharynx the most common primary site for RT (46%). Although most patients (60%) presented with early tumor stage (T1/T2) disease, nodal involvement was common (75%). The median (range) RT dose delivered was 6600 (636, 7802) cGy delivered over 33 (3, 62) fractions; 64% of patients received concurrent chemotherapy. Radiotherapy fields often included the nodal regions of the neck (95%; bilateral neck RT in 76%). More than half of the cohort (55%) underwent initial surgical resection.

Stimulated salivary flow after radiotherapy: Five-hundred forty-four patients (95%) had baseline salivary flow measurement, with a median (interquartile range, IQR) stimulated salivary flow (SSF) rate of 0.975 (0.648 to 1.417) g/min. A nadir in SSF rate, among evaluated timepoints, was observed at the 6 month post-RT evaluation, to 37% of pre-RT level (N = 481, median = 0.358 g/min, IQR = 0.188 to 0.640 g/min). Subsequent measurement at 18 months demonstrated an increased

Table 1
Baseline Characteristics of the OraRad Cohort. Abbreviations: no. = number; RT = radiation therapy; AJCC = American Joint Committee on Cancer.

	(N = 572)
Age at baseline visit— median (range)	59 (21, 97)
Gender— no. (%)	
Female	132 (23.1%)
Male	440 (76.9%)
Tobacco use — no. (%):	
Ever Used	322 (56.3%)
Never used	248 (43.4%)
Histology— no. (%):	
Squamous cell	469 (82.0%)
Salivary gland	66 (11.5%)
Other	37 (6.5%)
Primary site of RT— no. (%):	
Oropharynx	262 (45.8%)
Oral Cavity	82 (14.3%)
Larynx/Hypopharynx	40 (7.0%)
Salivary Gland	54 (9.4%)
Other	134 (23.4%)
AJCC (7th edition) Classification— no. (%):	
Tumor stage:	
1 or 2	344 (60.1%)
3 or 4	178 (31.1%)
Nodal involvement:	
Negative	136 (23.8%)
Positive	429 (75.0%)
Total number of radiation fractions delivered — median (range)	33 (3, 62)
Dose per fraction (cGy) — median (range)	200 (120, 250)
Total RT dose to primary site (cGy) — median (range)	6600 (636, 7802)
RT treatment to neck— no. (%)	542 (94.8%)
Bilateral	433 (75.7%)
Unilateral	109 (19.1%)
Chemotherapy — no. (%)	364 (63.6%)
Surgery — no. (%)	314 (54.9%)

salivary flow rate (N = 422, median = 0.575 g/min, IQR = 0.338 to 0.884 g/min, Figure 1) compared to the 6 month post-RT timepoint, to 59% of pre-RT level. The mean salivary flow at each time-point differed significantly from the other time-points with all p-values ≤ 0.001.

Participants who received concurrent chemotherapy experienced a significant decrease in salivary flow compared to those who did not (p-value ≤ 0.001). Use of chemotherapy was associated with an additional decrease in salivary flow of 0.318 (95% CI: 0.410 to 0.226) g/min from baseline to 6 months and an additional decrease of 0.217 (95% CI: 0.313 to 0.121) g/min from baseline to 18 months (p-values ≤ 0.001). Specifically, for individuals who received chemotherapy the estimated SSF rate at baseline was 1.15 (95% CI: 1.09 to 1.21) g/min which decreased to 0.38 (95% CI: 0.32 to 0.44) g/min at 6 months (33% of baseline value), with only partial recovery to 0.61 (95% CI: 0.55 to 0.67) g/min (53% of baseline value) at 18 months. For individuals with RT alone the estimated salivary flow was 1.02 (95% CI: 0.94 to 1.09) g/min at baseline, 0.56 (95% CI: 0.49 to 0.65) g/min at 6 months (55% of baseline value), and 0.69 (95% CI: 0.61 to 0.77) g/min at 18 months (68% of baseline value).

The primary site of RT was also strongly associated with change in salivary flow (Figure 2; Supplementary Table S2; p-value ≤ 0.001). We specifically found that individuals who had a primary site of salivary gland had less of a decrease from baseline to 6 months compared to individuals who had a primary RT site of oral cavity (p-value = 0.037), oropharynx (p-value ≤ 0.001), and other regions (p-value = 0.011), whereas individuals who had a primary site of oropharynx experienced a sharper decrease compared to those who had a primary RT site of larynx/hypopharynx (p-value = 0.014) and other regions (p-value = 0.037). Forty-nine patients had a primary parotid gland malignancy, treated first by surgical resection followed by limited-field RT (omitting RT to the contralateral neck). In these patients, the contralateral parotid gland received a median of 654 Gy, with no significant relationship between dose to the contralateral parotid and change in salivary flow (p = 0.28). For all patients, by the 18-month visit, change in salivary flow from baseline was only significantly different between individuals who had a primary site of oropharynx compared to individuals who had a primary site of salivary gland (estimated difference in change from baseline between groups −0.24 g/min, SE: 0.08; p-value = 0.036).

Average dose to the parotid glands was associated with reduced salivary flow (Figure 3). Each additional 100 cGy in RT was associated with an additional decrease in salivary flow of 0.018 (95% CI: 0.021 to 0.014) g/min from baseline to 6 months and an additional decrease of 0.014 (95% CI: 0.018 to 0.010) g/min from baseline to 18 months (p-values ≤ 0.001). For individuals with unilateral RT treatment (n = 342), dose to the contralateral parotid followed similar trends with each additional 100 cGy in RT associated with an additional decrease in salivary flow of 0.020 (95% CI: 0.015 to 0.025) g/min from baseline to 6 months and an additional decrease of 0.015 (95% CI: 0.010 to 0.020) g/min from baseline to 18 months (p-values ≤ 0.001). Similarly, for a subset of 144 study participants with information on average dose to the salivary gland each additional 100 cGy in RT to the salivary gland was associated with an additional decrease in salivary flow of 0.024 (95% CI: 0.031 to 0.017) g/min from baseline to 6 months and an additional decrease of 0.019 (95% CI: −0.027 to 0.0119) g/min from baseline to

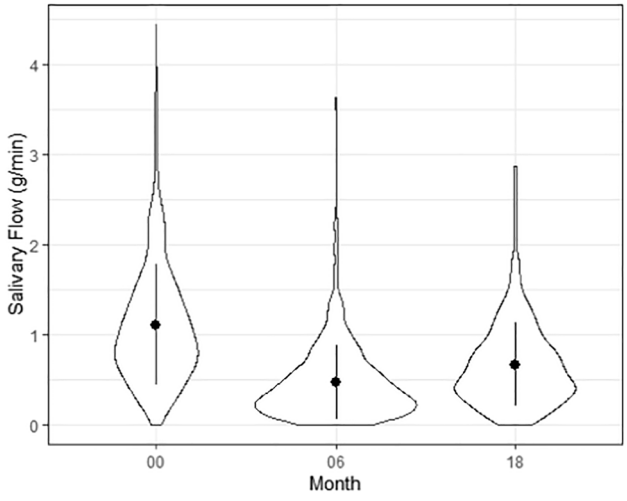

Figure 1. Distribution of salivary flow at baseline (n = 544), 6 months post-RT (n = 481), and 18 months post-RT (n = 422). The dot and line represent mean ± SD at each visit.

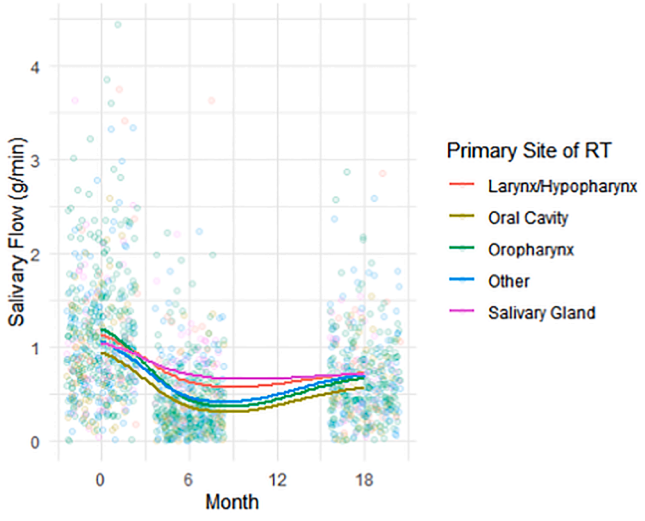

Figure 2. Loess curve for salivary flow rate (g/min) by primary site of RT (N = 564).

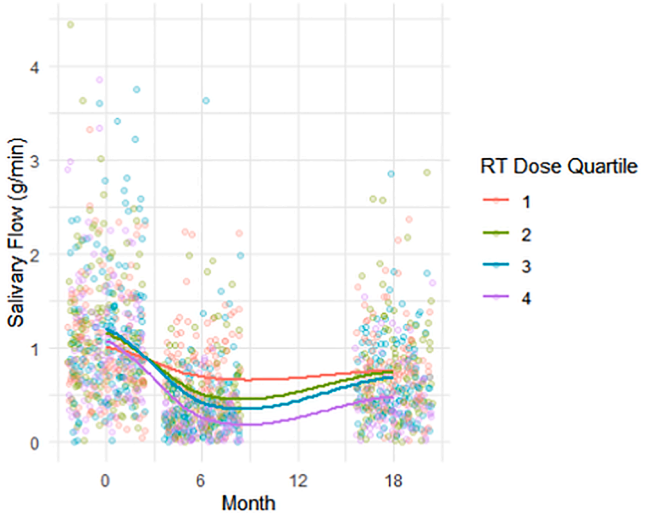

Figure 3. Loess curve for salivary flow rate (g/min) by quartiles of average RT dose to the parotid glands (N = 563). Dose to the parotids is categorized based on quartiles: quartile 1 ≤ 2018 (cGy), quartile 2 > 2018 and ≤ 2586 (cGy), quartile 3 > 2586 and ≤ 3358 (cGy), and quartile 4 > 3358(cGy). Visit month has been jittered for visualization purposes. Statistical comparisons between quartiles are provided in Supplementary Table S4.

18 months (p-values ≤ 0.001).

For 144 patients for which additional dosimetric information was available for the left and right submandibular glands and the sublingual gland, the doses delivered to these glands were combined with the doses delivered to the parotid glands to create a composite salivary gland dose. Similar to what was observed for dose to the parotid glands, each additional 100 cGy in RT delivered to the composite salivary glands was associated with an additional decrease in salivary flow of 0.024 (95% CI: 0.031 to 0.017) g/min from baseline to 6 months and an additional decrease of 0.019 (95% CI: −0.027 to 0.0119) g/min from baseline to 18 months (p-values ≤ 0.001).

Patient-reported outcomes: Several quality of life measures related to saliva production were negatively impacted after RT (Supplementary Table S3). Patient-reported problems with swallowing, senses, mouth opening, dry mouth, and sticky saliva worsened at 6-months after RT ($p < 0.002$, Figure 4). With the exception of swallowing ($p = 0.42$) and mouth opening ($p = 0.65$), all other domains demonstrated significant improvement at 18 months (versus 6 months post-RT) ($p < 0.03$, Figure 4), but were still significantly worse compared to baseline ($p < 0.001$). Change in swallowing, mouth opening, dry mouth, and sticky saliva were significantly associated with change in salivary flow after RT (p-values < 0.04; Table 2).

Discussion:

Our multicenter study demonstrates that head and neck cancer patients experience significant decreased stimulated salivary production, with associated impact on patient-reported quality of life, after standard of care approaches with RT (organ preservation chemo-RT or initial surgical resection followed by adjuvant RT). Improvements in salivary flow and patient-reported outcomes, observed with time, suggest that recovery may be possible for patients during post-treatment follow-up. Collectively, these findings suggest that although RT-associated side effects can improve with time, they still continue to be a significant

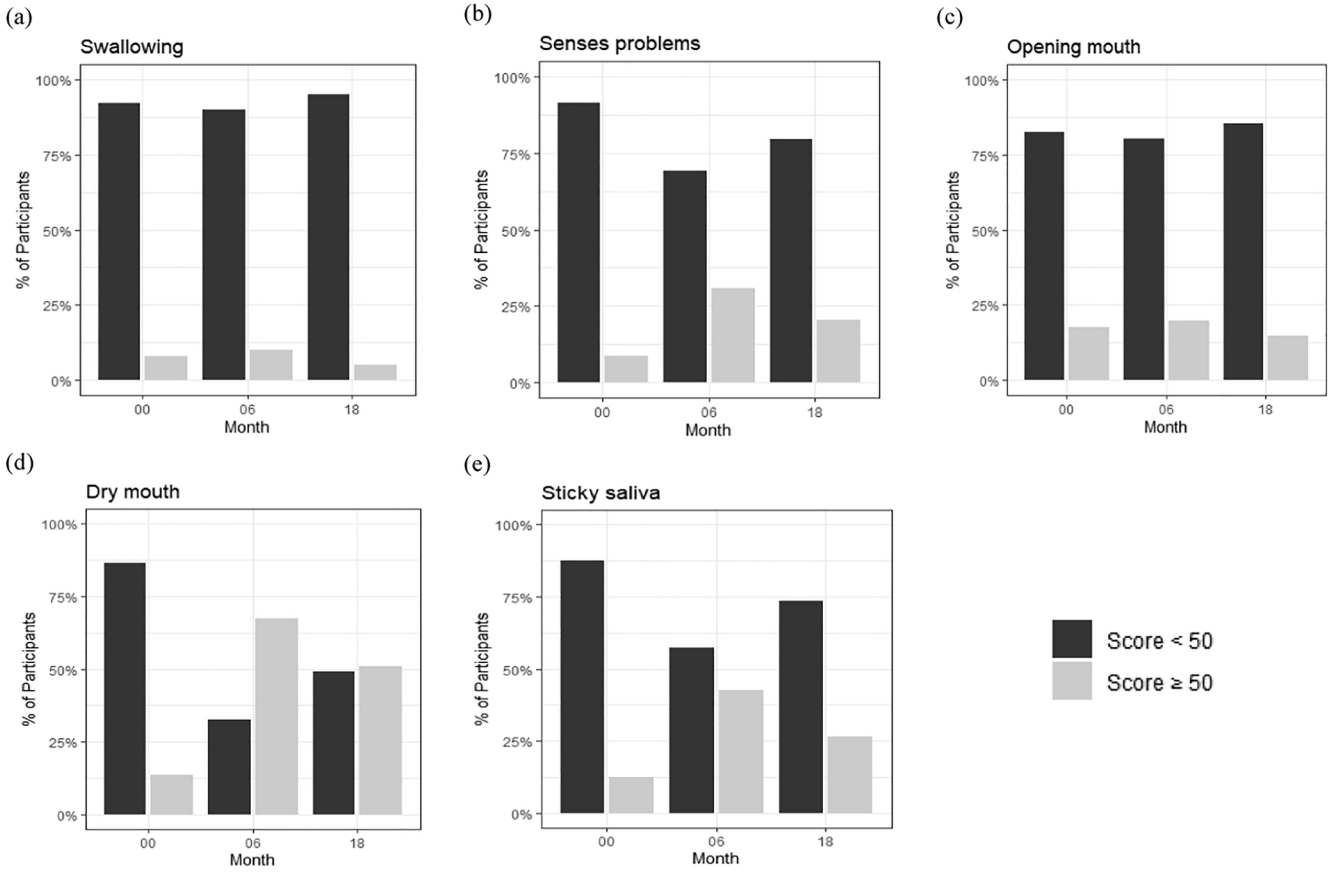

Figure 4. (a-e): Selected EORTC QLQ-H&N35 scales at baseline, 6 months post-RT, and 18 months post-RT for a) swallowing b) senses problems c) opening mouth and d) dry mouth, and e) sticky saliva. A score ≥ 50 corresponds to responses of "quite a bit" or "very much" for the opening mouth, dry mouth, and sticky saliva scale.

Table 2
Relationship between change in salivary flow and change in patient reported EORTC scales. Individual with extreme change in salivary flow excluded from analysis. Estimate represents the change in scale score from baseline to specified visit associated with additional increase of 10% of baseline salivary flow at specified visit. Higher values correspond to worse symptoms.

	Swallowing	Senses Problems	Teeth	Opening Mouth	Dry Mouth	Sticky Saliva
Overall p-value	≤0.0001	0.0653	0.4530	0.0301	≤0.0001	≤0.0001
	Estimate (95% CI); p-value					
6 Mo. Visit	−0.64 (-0.94, −0.35); ≤0.0001	−0.34 (-0.68, 0.01); 0.0561	−0.23 (-0.63, 0.16); 0.2479	−0.48 (-0.93, −0.02); 0.0410	−1.73 (-2.21, −1.25); ≤0.0001	−1.18 (-1.68, −0.69); ≤0.0001
18 Mo. Visit	−0.35 (-0.66, −0.04); 0.0270	−0.3 (-0.67, 0.06); 0.1044	−0.14 (-0.56, 0.28); 0.5114	−0.5 (-0.98, −0.01); 0.0455	−1.12 (-1.64, −0.61); ≤0.0001	−0.77 (-1.3, −0.23); 0.0049

challenge for patients, and future efforts and strategies to mitigate toxicity are needed.

Such future efforts focus on novel approaches of preserving salivary function that complement current efforts of limiting the dose of RT delivered to salivary gland regions via conformal radiation techniques. These include approaches such as surgery, in the form of transfer of the submandibular glands to a non-radiated location [14], the administration of chemical radioprotectants [15], or focused RT sparing of salivary gland stem cells [15,16].

Similar to prior studies [4,6], we found that RT decreases salivary flow and negatively impacts patient quality of life, with partial recovery with time. However, the OraRad study is the largest multicenter, prospective study focusing on post-treatment salivary hypofunction and its effects on patient-reported outcomes. Unlike previous studies, OraRad included patients treated with both organ-preservation RT or adjuvant therapy after surgical resection, both of which are consistent with current standards of care. Although prior publications have suggested a goal of limiting the average dose delivered to the parotid to 2600 cGy to minimize xerostomia [17], we found that patients in the first quartile of average dose to the parotid glands (≤2018 cGy) had significantly less decrease in salivary flow compared to participants whose average dose was between 2018 and 2586 cGy (in the secondary quartile; Supplementary Table S4). Whether this improvement in salivary flow with lower dose means that a new consensus constraint for average radiation dose to the parotid glands should be considered, it is sensible and recommended for radiation oncologists to practice the principle of ALARA (as low as reasonably achievable) when it comes to normal tissue sparing, provided that this does not result in compromises in disease control. We also observed that in patients who received limited-field RT (sparing of the contralateral neck), the median dose delivered to the contralateral salivary glands was very low (approximately 10% of the prescribed dose), with no observed relationship between dose delivered to the contralateral parotid and change in stimulated salivary flow. This suggests that there is a dose threshold or situation (such as when the contralateral neck is not radiated) under which stimulated salivary flow may not be significantly altered by limited field RT. This has implications on current and future efforts to mitigate RT-induced toxicity by further decreasing required RT dose [18], as well as limiting the extent of the radiation required field [18,19].

There are several limitations in our study that warrant mention. Patient follow-up was limited to up to 2 years, with only two measured post-RT timepoints (at 6 and 18 months for salivary flow). As a result, the nadir that we observed at 6 months may not be the true nadir, and may have occurred either before or after the 6 month timepoint. Also, it is unclear whether the improvement observed from 6 to 18 months will plateau, or will continue with additional followup. To better understand the long-term effects of therapy, current efforts are underway to obtain long-term follow-up (at 7 years) for patients in the OraRad study. Patients in our study were treated with either organ-preservation or post-operative RT, reflecting different doses delivered (typically around 7000 cGy versus 6000 cGy); however, inclusion of both types of patients is a reflection of a current, real-world, multidisciplinary approach to the treatment of head and neck cancer, where equipoise exists between both approaches [20]. While we report results on patients who received concurrent chemotherapy and RT, we do not have information on specific chemotherapy agents, doses, or cycles. While this information is important, we do not believe that the lack of this information changes the main findings of this manuscript, that RT delivered to the head and neck decreases salivary flow and negatively impacts quality of life.

Our study has relevance and implications for future prospective investigations. It helps us to better understand the overall impact of RT on post-treatment patient quality of life, so that future advances and approaches can be measured against current standards of care for factors beyond recurrence and survival rates. Such approaches are already being investigated, with initial studies reporting on the safety of decreasing the standard volume [21,22] or dose [23–26] of RT, and current trials examining whether radiation modality (proton therapy) can improve the toxicity profile [27]. However, patient selection for alternative approaches and incorporation into standard practices will require further investigations centered on efficacy and quality of life. Until then, for patients who receive standard of care head and neck cancer treatment, our study provides additional information as to the potential impact of RT on their quality of life, as well as reassurance that many of their early, post-treatment side effects can and will improve with time.

We found that head and neck RT leaves patients with reduced salivary flow and xerostomia 6 months after treatment and is negatively associated with their quality of life. Further sparing of radiation dose to the parotid glands and other critical regions in the head and neck may improve salivary outcomes. Although recovery is observed with additional follow-up at 18 months, it does not return to pre-treatment baselines. An understanding of these effects and their duration over longer timepoints is necessary to inform our future approaches, so as to improve post-treatment quality of life without negatively impacting disease-specific outcomes.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2022.105783.

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