Impact of Oral Cavity Dosimetry on Patient Reported Xerostomia and Dysgeusia in the Setting of Deintensified Chemoradiotherapy

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Abstract

Purpose: To determine the relationship between mean oral cavity (OC) dose (treated as a singular organ at risk) to patient reported xerostomia and dysgeusia. In addition, we will examine the relationship between oral cavity substructure doses to patient reported xerostomia and dysgeusia. All patients were treated in the setting of deintensification (60 Gy).

Methods and Materials: In the study, 184 and 177 prospectively enrolled patients for de-escalated chemoradiotherapy (CRT) for human papillomavirus (HPV)-positive oropharyngeal cancer submitted PROs at 6 and 12 months, respectively using Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events questionnaire. Patient’s OC consisting of the following substructures were segmented: oral tongue, base of tongue, floor of mouth, hard and soft palate, cheek mucosa, and upper and lower lip mucosa. Ordinal logistic regression (no/mild vs moderate vs severe/very severe symptoms) was used to compare organs at risk dosimetry to patient reported xerostomia and dysgeusia at 6 and 12 months. Multivariate ordinal logistic regression models were generated.

Results: Mean dose to the contralateral parotid ($P = .04$), OC ($P = .04$), and baseline patient reported xerostomia ($P = .009$) were significantly associated with xerostomia severity at 6 months. Only baseline xerostomia ($P = .02$) and mean dose to the contralateral submandibular gland ($P = .0001$) were significantly associated with xerostomia severity at 12 months. The only significant factor related to dysgeusia at either time point was mean dose to the OC at 12 months ($P = .009$). On examining substructures, the mean dose to the floor of mouth was implicated for the dose relationship to 6-month xerostomia ($P = .04$), and the oral tongue was found to be implicated for the relationship for 12-month dysgeusia ($P = .04$).

Conclusions: The mean dose to the OC was found to relate to xerostomia symptoms at 6 months post-CRT and dysgeusia symptoms at 12 months post-CRT. The mean dose to the floor of mouth and oral tongue appeared to drive this relationship for xerostomia and dysgeusia symptoms, respectively. This work suggests the floor of mouth and oral tongue should be prioritized during planning over the rest of the OC. The effect of OC dose relative to other salivary structures for xerostomia appeared to depend on time post-CRT.

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Introduction

Standard chemo-radiation therapy for human papillomavirus-associated oropharyngeal squamous cell carcinoma yields high rates of survival and local control but is associated with considerable toxicity.1,2 Recent efforts have focused on deintensifying radiation or

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chemotherapy in the hopes of reducing post-treatment toxicity.\textsuperscript{3–5} Two of the most common and impactful toxicities experienced by patients according to our studies are dry mouth (xerostomia) and changes in taste (dysgeusia).\textsuperscript{6} Limited publications exist that examine dosimetric correlates between patient reported xerostomia and dysgeusia in the setting of deintensification. This is particularly true for evaluation of substructures of the oral cavity compared with treating the entire oral cavity as a singular structure, which could potentially aid planners to prioritize specific areas that lead to toxicity.

In the setting of standard dosing, radiation induced xerostomia has been consistently shown to relate to the dose received by the major salivary glands, such as the parotid and submandibular glands. The literature is limited and conflicting in terms of the relationship between oral cavity dose and its relationship to patient reported xerostomia.\textsuperscript{7–13} In addition, studies have often assessed the entirety of the oral cavity as a single organ at risk (OAR) rather than an anatomic assessment of each substructure. Similar issues are prevalent in the literature for evaluating radiation induced dysgeusia.

We herein present a pooled analysis of 244 patients treated with deintensiﬁed chemoradiotherapy (CRT). We aimed to assess the effect of oral cavity (single OAR) mean dose to patient dry mouth and dysgeusia in the context of other OARs (eg, salivary glands). In addition, we examined oral cavity substructures doses and their relationship to patient reported xerostomia and dysgeusia treated with our deintensiﬁed CRT regimen.

**Methods and Materials**

**Patient cohort and treatment**

Data was obtained from patients enrolled from 3 multi-institutional phase 2 studies (NCT01330997, NCT02281955, NCT03077243) and pooled for analysis. Patients were excluded if they had less than 6 months of follow-up or if their plans could not be restored for analysis, yielding 244 patients. All 3 studies were designed to evaluate the efﬁcacy of deintensiﬁed treatment for favorable-risk oropharyngeal squamous cell carcinoma. Patients were comprised of those who had human papillomavirus or p16 positive squamous cell carcinoma of the oropharynx or unknown primary, T0-T3, N0-N2c, and M0 (according to American Joint Committee on Cancer seventh edition staging), age \(\geq 18\) years, and an Eastern Cooperative Oncology Group performance status of 0 to 1. Patients were simulated in a neck ﬂexed position. Positron emission tomography/computed tomographs (CT) were obtained on a patient-by-patient basis to aid in target delineation.

All patients received intensity-modulated radiotherapy to a dose of 60 Gy in 30 fractions to their high-risk planning target volume (gross disease plus a 3 mm volume expansion). The standard risk planning target volume (subclinical disease plus a 3 mm volume expansion) was treated to 54 Gy or 50 Gy in \(\approx 30\) fractions depending on the trial the patient was enrolled on. Concurrent chemotherapy was administered in the form of weekly cisplatin (30 mg/m\(^2\)) or cetuximab (250 mg/m\(^2\)) if patients were cisplatin ineligible (unless patient had T0-T2 and N0-N1 disease in which they received radiation therapy alone).

**Oral cavity segmentation of substructures**

Contouring of organs at risk was done in Raystation treatment planning system (Raysearch Laboratories). The OARs were generally segmented as described in a publication by Brouwer et al.\textsuperscript{14} The anterior two-thirds of the tongue were deﬁned as the oral tongue, and the posterior third as the base of tongue. The region inferior and anterior to the tongue was delineated as the ﬂoor of mouth. Nineteen total structures were contoured including the left and right parotid glands, left and right submandibular glands, left and right sublingual glands, oral tongue, base of tongue, ﬂoor of mouth, soft and hard palates, buccal mucosa, upper and lower lips. Structures that were contoured for clinical treatment planning (eg, parotid glands, submandibular glands, larynx, and pharyngeal constrictors) were used when possible and the other structures were then contoured retrospectively.

**Patient reported quality of life measurement**

Patients submitted Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE), The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire- Head and Neck Module, and EAT-10 (Eating Assessment Tool) questionnaires pretreatment, during treatment at 3 weeks, immediately after treatment and post-treatment at 3 months, 6 months, 12 months, and every subsequent 6-month follow-up. The PRO-CTCAE contained 85 questions with responses on a scale of 1 to 5, which represented none, mild, moderate, severe, and very severe symptoms. The questions from the PRO-CTCAE pertaining to the patient’s severity of dry mouth and change of taste were used as the outcomes for this analysis. The validity of the PRO-CTCAE questionnaire has been conﬁrmed in previous studies.

**Statistical analysis**

Statistical analysis for this thesis was done using R version 3.6.3. Logistic regression was used to relate dosimetric and clinical data to the patient reported outcome questions. Ordinal logistic regression (no/mild vs moderate vs severe/
very severe symptoms) was used to compare OAR dosimetry to patient reported xerostomia and dysgeusia at 6 and 12 months. A P value less than .05 determined significance and a rejection of the null hypothesis.

**Impact of oral cavity mean dose**

We generated a multivariable analysis using ordinal logistic regression to fit a logistic regression model to ordered factor responses (none/mild, moderate, severe/very severe) using the oral cavity mean dose, contralateral parotid mean dose, ipsilateral parotid mean dose, contralateral submandibular gland mean dose and presence of toxicity before treatment for both toxicities. The use of an ordered logistic regression model was chosen because it fit the outcome data well and allowed using a third category, moderate, instead of a somewhat arbitrary cut-off to determine whether xerostomia or dysgeusia were present. A stepwise forward-backward Akaike Information Criterion (AIC) minimization ordinal regression was then used to balance the complexity of the model with the fit. This methodology adds or removes covariates to determine, which of the different possible models best fits the data. By minimizing the AIC, the resulting model explains the greatest amount of variation using the fewest possible independent variables.

**Effect of oral cavity substructure mean dose**

The dose-volume histogram of each structure (oral cavity substructures and major salivary glands) was broken into different metrics to be analyzed independently. These metrics were as follows: mean dose, median dose, max dose, V5 Gy to V60 Gy (in increments of 5 Gy), and the baseline presence (none or any) of patient reported toxicity were assessed independently. The patients age (in years) was also assessed. A multivariate analysis was then conducted to fit an ordered logistic regression model to the ordered outcome responses (none/mild, moderate, severe/very severe) using a single covariate (the aforementioned metrics) for all metrics for all structures for both toxicities. In effort to reduce the number of eligible covariates, only significant covariates from this large, univariable analysis were then entered into the final multivariate analysis, which used the aforementioned stepwise forward-backward AIC minimization ordinal regression to yield a final multivariate model. This analysis was conducted for both xerostomia and dysgeusia at 6 and 12 months.

**Results**

Patient characteristics are shown below in Table 1. The summary of doses received by the OARs are shown in Table 2.

### Table 1  Patient characteristics

| Factor                        | No. | Percent |
|-------------------------------|-----|---------|
| Median age (y)                | 62  | NA      |
| Median HR PTV volume (cc)     | 181.1| NA      |
| Prescribed SR PTV dose        |     |         |
| 54 GY                         | 143 | 58.6    |
| 50 GY                         | 101 | 41.4    |
| T stage                       |     |         |
| T0                            | 15  | 6.2     |
| T1/T2                         | 196 | 80.3    |
| T3                            | 27  | 11.1    |
| N stage                       |     |         |
| N0/N1                         | 57  | 23.4    |
| N2/N2c                        | 181 | 74.2    |
| Smoking status                |     |         |
| Never                         | 138 | 56.6    |
| ≤10 pack-years                | 60  | 24.6    |
| >10 pack-years                | 43  | 17.6    |
| Xerostomia at 6 mo            |     |         |
| None/mild                     | 67  | 34      |
| Moderate                      | 80  | 41      |
| Severe/very severe            | 49  | 25      |
| Xerostomia at 12 mo           |     |         |
| None/mild                     | 99  | 51      |
| Moderate                      | 69  | 36      |
| Severe/very severe            | 25  | 13      |
| Dysgeusia at 6 mo             |     |         |
| None/mild                     | 123 | 62      |
| Moderate                      | 52  | 26      |
| Severe/very severe            | 22  | 12      |
| Dysgeusia at 12 mo            |     |         |
| None/mild                     | 143 | 73      |
| Moderate                      | 38  | 20      |
| Severe/very severe            | 15  | 7       |

*Abbreviations: HR PTV = high-risk planning target volume; SR PTV = standard-risk planning target volume.*

### Impact of oral cavity mean dose

The results of the stepwise AIC minimized multivariable ordered logistic regression relating oral cavity mean dose, contralateral parotid mean dose, ipsilateral parotid mean dose, contralateral submandibular gland mean dose and presence of toxicity before treatment to 6- and 12-month xerostomia is shown in Table 3.
Table 2  Doses planned to the organs at risk

| OAR                              | Mean (cGy) | Range (cGy) |
|----------------------------------|------------|-------------|
| Oral cavity                      | 3855       | 2410-5336   |
| Base of tongue                   | 5818       | 4279-6508   |
| Oral tongue                      | 3909       | 2168-5766   |
| Buccal mucosa                    | 2649       | 1214-4214   |
| Floor of mouth                   | 3967       | 1630-6100   |
| Hard palate                      | 2394       | 267-4692    |
| Soft palate                      | 5487       | 3351-6552   |
| Lips                             | 1504       | 459-3235    |
| Contralateral parotid            | 2137       | 284-4717    |
| Ipsilateral parotid              | 3983       | 1880-6116   |
| Contralateral submandibular gland| 4274       | 692-6632    |
| Larynx                           | 3302       | 1439-6268   |
| Inferior pharyngeal constrictor  | 3833       | 1489-6260   |
| Middle pharyngeal constrictor    | 5546       | 3229-6380   |
| Superior pharyngeal constrictor  | 5577       | 3699-6635   |

Abbreviation: OAR = organs at risk.

Table 3  Multivariable effect of mean dose to organs-at-risk on patient reported xerostomia at 6- and 12-months post-treatment

| Covariate                        | Odds ratio per Gy (95% CI) | P value |
|----------------------------------|-----------------------------|---------|
| Patient reported xerostomia at 6 mo post-treatment |                            |         |
| Oral cavity mean dose            | 1.064 (1.004-1.129)         | .038 *  |
| Contralateral parotid mean dose  | 1.039 (1.002-1.078)         | .039 *  |
| Baseline xerostomia              | 2.32 (1.240-4.407)          | <.01 *  |
| Intercept                        | Value (95% CI)              | P value |
| None/mild vs moderate            | 2.70 (0.46-4.94)            | .018    |
| Moderate vs severe/very severe   | 4.67 (2.35-6.99)            | <.01    |

| Covariate                        | Odds ratio per Gy (95% CI) | P value |
|----------------------------------|-----------------------------|---------|
| Patient reported xerostomia at 12 mo post-treatment |                           |         |
| Contralateral parotid mean dose  | 0.96 (0.915-1.010)          | .120    |
| Contralateral submandibular mean dose | 1.06 (1.028-1.088)         | <.01 *  |
| Baseline xerostomia              | 2.31 (1.13-4.74)            | .022 *  |
| Intercept                        | Value (95% CI)              | P value |
| None/mild versus moderate        | 1.77 (0.66-2.87)            | <.01    |
| Moderate versus severe/very severe| 3.89 (2.66-5.12)            | <.01    |

Abbreviation: CI = confidence interval.
* Statistically significant.
Effect of oral cavity substructure mean dose

The results of the AIC minimized stepwise multivariable ordered logistic regression relating the aforementioned covariates to dysgeusia only yielded a model for 12-month patient reported dysgeusia (Table 4). Final models, using oral cavity substructures rather than the total oral cavity mean dose, relating to 6- and 12-month xerostomia and dysgeusia are shown in Tables 5 and 6.

Discussion

The results from our multivariable analysis of xerostomia (Tables 2 and 4) shows mixed results dependent on the timeframe post-treatment. At 6 months post-treatment, the oral cavity mean dose and contralateral parotid gland mean dose were significantly associated with patient reported xerostomia (P = .038 and P = .039, respectively) and the odds of experiencing xerostomia increase by approximately 6% and 4% per Gy, respectively (ie, for this timepoint, sparing the oral cavity is just as important as sparing the contralateral parotid gland). However, at 12 months post-treatment the oral cavity was not included in the model post stepwise regression and the contralateral parotid gland mean dose was no longer significant. Instead, at 12 months post-treatment the contralateral submandibular gland mean dose remained as a significant predictor (P < .01) with the odds of experiencing xerostomia increasing by 6% per Gy. At both 6- and 12-months post-treatment, baseline patient reported xerostomia was significantly associated with xerostomia (P < .01 and .022, respectively). Furthermore, the presence of baseline patient reported xerostomia increased the odds of patient reported xerostomia at 6 and 12 months by 2.3 times compared with those without baseline patient reported xerostomia.

The results regarding the multivariable analysis of dysgeusia are similar. Mean oral cavity dose was not included in the AIC minimized model relating to patient reported dysgeusia at 6 months post-treatment; however, it was significantly associated at 12 months post-treatment (P = .009). Examining substructures of the oral cavity, the floor of mouth appeared to be related most to patient reported dysgeusia (significantly at 6 months post-treatment), and the oral tongue appeared to be related most to

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**Table 4** Multivariable effect of mean dose to organs-at-risk on patient reported dysgeusia at 12 months post-treatment

| Organ-at-risk                      | Odds ratio per Gy (95% CI)       | P value  |
|------------------------------------|----------------------------------|----------|
| Oral cavity mean dose              | 1.109 (1.027-1.201)              | <.01*    |
| Intercept                          | Value (95% CI)                   | P value  |
| None/mild vs moderate              | 5.17 (2.07-8.27)                 | <.01     |
| Moderate vs severe/very severe     | 6.65 (3.47-9.84)                 | 4.1 × 10^{-5} |

* Abbreviation: CI = confidence interval.

**Table 5** Multivariable effect of mean dose to organs-at-risk (including oral cavity substructures) on patient reported xerostomia at 6- and 12-months post-treatment

**Patient reported xerostomia at 6 mo post-treatment**

| Covariate               | Odds ratio per Gy (95% CI)       | P value |
|-------------------------|----------------------------------|---------|
| Contralateral parotid   | 1.039 (1.002-1.078)              | .039    |
| Floor of mouth          | 1.042 (1.002-1.084)              | .039    |
| Baseline xerostomia     | 2.365 (1.263-4.487)              | <0.01   |

**Patient reported xerostomia at 12 mo post-treatment**

| Covariate               | Odds ratio per Gy (95% CI)       | P value |
|-------------------------|----------------------------------|---------|
| Contralateral Parotid   | 0.958 (0.911-1.006)              | .089    |
| Contralateral submandibular gland | 1.056 (1.028-1.087) | <.01   |
| Buccal mucosa V35Gy     | 1.015 (0.995-1.035)              | .141    |
| Baseline xerostomia     | 2.203 (1.073-4.541)              | .031    |

* Abbreviation: CI = confidence interval.
patient reported dysgeusia (significantly at 12-month post-treatment). These results make sense because the floor of mouth includes the sublingual salivary glands and is immediately adjacent to the submandibular glands. Because these glands are difficult to visualize on CT, the floor of mouth could be acting as a surrogate. The oral tongue also contains the vast majority of taste buds and could explain the relationship between oral tongue dose and dysgeusia.

Our findings validate the importance of dose to patient’s oral cavity on both patient-reported xerostomia and dysgeusia. OARs related to patient reported xerostomia did not appear to relate to patient reported dysgeusia. There was not a consistent relationship between OAR dose and patient reported symptoms that spanned both 6 and 12 months. If one places the most importance on long-term symptom burden, our data suggest that minimizing dose to the contralateral submandibular gland and oral tongue are paramount particularly in elderly patients with baseline patient reported xerostomia. This suggests that long term xerostomia may be more related to the absence of mucinous saliva as generated by the submandibular glands.

Although this analysis was performed on patients receiving 60 Gy compared with the conventional 70 Gy, the doses achieved in this study are achievable in patients treated with standard of care. The geometric relationship between target(s) and OARs dictates the received dose more so than a 10 Gy reduction in prescription and therefore the results from this work are translatable regardless of differences in prescribed dose.

The study has several limitations. First the pooled nature patients across 3 different, albeit similar, studies, may introduce biases that effect the analyses (eg, different elective doses to low-risk volumes across studies). However, these interstudy differences are small. Furthermore, the patients were treated by the same group of physicians throughout on a sequential series of studies (with each building on its predecessor), thus minimizing unforeseen biases often seen in pooled analyses. Second, patient-reported quality of life metrics were not always completed by each patient at both time points, which led to missing data. However, we had sufficient numbers to exclude those with missing data at each timepoint as our follow-up rates were around 85%. Our studies’ strengths include a large number of patients with oropharyngeal cancer treated with deintensified CRT assess prospectively and longitudinally. In addition, all patients were treated with modern intensity-modulated radiotherapy delivery.

Conclusions

In summary, our study confirms previous work suggesting the importance of sparing the oral cavity and extends this into the deintensified setting. Our results suggest reducing dose to the floor of mouth and oral tongue are the most important oral cavity substructures that relate to patient reported xerostomia and dysgeusia, respectively.

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