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Scientific Article

Radiation-Induced Volume Changes in the Parotid and Submandibular Glands, Intragland Dose Distribution, and Quality of Life Scores Over a Long Follow-Up Period

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Purpose: Xerostomia remains a common toxicity after head and neck radiation therapy that significantly impacts patients' quality of life. Although intensity modulated radiation therapy reduces the dose to the salivary glands, many patients still experience salivary gland toxicity.

Methods and Materials: This study examined the association between radiation-induced volume changes in the parotid and submandibular glands, mean dose to the salivary glands, and intragland dose distribution, as well as its relationship to quality of life scores, over a median follow-up period of 47 months.

Results: Analysis of 329 patients using a linear mixed-effects model revealed distinct volume change patterns. The parotid glands initially underwent significant volume reduction but subsequently showed dose-dependent recovery, increasing in volume by an average rate of 2.4% per doubling of time. This recovery was negatively impacted by higher age and poor performance status (PS). Conversely, the submandibular glands gradually reduced in volume over time by 5.3% per doubling of time without evidence of recovery, even at low doses. Voxel-wise analysis of the parotid glands indicated that dose constraints targeting the cranial-ventral-lateral portion were critical for accurately predicting volume recovery. No regional dose effects were found for the submandibular gland. Persistent associations were found between salivary gland volumes and chronic xerostomia symptoms, including dry mouth and sticky saliva.

Conclusions: Objective measurement of salivary gland volume can be used as an indicator of damage and recovery. The observed differential longitudinal patterns suggest that distinct dosing strategies and regenerative approaches may be necessary for the parotid and submandibular glands.

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Introduction

Xerostomia is one of the most common acute and late toxicities associated with head and neck radiation therapy (RT). It has been shown to significantly impact patients' quality of life (QOL).[1,2] Compared with conventional RT, intensity modulated RT (IMRT) reduces doses to salivary glands while maintaining target dose coverage. Reduced doses to the salivary glands as a result of IMRT have been shown to significantly alleviate patients' symptoms.[3,4] A randomized phase 3 trial comparing parotid-sparing IMRT with conventional RT demonstrated significantly improved salivary flow recovery at 12 and 24 months after RT.[5] Xerostomia tends to subside over time after treatment completion. Studies have shown that in cases where the mean parotid dose is below a certain level, salivary flow exhibits partial recovery 6 months after treatment, with further improvement over 12 to 24 months.[6,7] However, even with IMRT, most patients with head and neck cancer who undergo RT experience salivary gland toxicities to some degree. Many studies have attempted to improve xerostomia recovery after RT using biological, pharmacologic, and regenerative medicine approaches. Although these studies have demonstrated encouraging results in preclinical settings, more research is needed to preserve salivary gland function and improve recovery. A significant body of research suggests that using only the whole-gland mean dose is insufficient for organ recovery. Although salivary glands are considered parallel organs, the radiosensitivity of the parotid gland is not homogeneous. Thus, constraints targeting specific intraparotid subvolumes may be more predictive and beneficial.[8-14]

Studying radiation-induced xerostomia requires objectively measuring salivary gland damage and recovery. Several methods have been used for this purpose. One simple, widely used method is measuring whole-mouth salivary output. The benefit of this method is that it accounts for the function of the major and minor salivary glands as a whole. Whole-mouth salivary output has been shown to significantly correlate with subjective symptoms of xerostomia.[4,5] However, this benefit becomes a drawback when analyzing the impact of radiation dose distribution on salivary flow in specific glands. Thus, researchers have used specialized equipment to collect salivary flow from each orifice of the major salivary glands.[5,11] Ultrasound, magnetic resonance imaging (MRI) sialography, and technetium 99m pertechnetate salivary gland scintigraphy (Tc-99) scans have also been used to assess changes in salivary glands after RT.[15] The usefulness of computed tomography in evaluating post-RT changes in salivary glands has not been well defined.[16] Studies have shown that parotid gland volumes decrease during fractionated head and neck RT.[17-20] One study observed parotid gland volumes up to 2 years after RT in 33 patients with oropharyngeal cancer.[21] Parotid gland volume decreased alongside increased xerostomia symptoms that did not recover for 2 years. In another study, parotid gland volumes and xerostomia symptoms were prospectively observed for up to 15 months in 58 patients with head and neck cancer who underwent definitive or postoperative RT.[22] Similarly, the authors found reduced parotid gland volumes and increased xerostomia after RT. However, little is known about long-term changes in salivary gland volume, especially during the recovery phase. In this study, we examined the association between radiation-induced volume changes in the parotid and submandibular glands, intragland dose distribution, and QOL scores over a period of up to a median of 47 months after RT. Our results reveal distinct longitudinal volume patterns in the parotid versus submandibular glands, suggesting that different strategies may be necessary to enhance tissue regeneration and preserve function in these 2 major salivary glands.

Methods and Materials

Salivary gland volume data acquisition

This study included patients who received RT for malignant diseases in the head and neck regions from June 2010 to April 2019. This included various primary head and neck sites, unknown primary cervical lymph node metastasis, and patients who received whole-brain RT (WBRT). Patients with a prior history of RT to the head and neck regions were excluded. Patients were excluded if they did not undergo head and neck computed tomography and/or MRI at least twice during routine surveillance after completing RT. The volume data were retrospectively measured and analyzed. All images were imported into a treatment planning system (Varian Eclipse), and the volumes of the bilateral parotid and submandibular glands were measured using manual contouring. All contouring of salivary glands was conducted by a single radiation oncologist (the first author). When contours were conducted by treating physicians or dosimetrists/physicists at the time of treatment planning, all contouring was redone for consistency. Metal artifact reduction and/or images with angled axial planes were used whenever available. However, dental artifacts influenced accurate contouring, and interpolations were used to generate the best estimated gland volumes.

Dose analysis of the salivary glands

RT was administered using 3-dimensional conformal therapy or IMRT with the simultaneous integrated boost technique. The dose constraints for parotid and

Table 1 Relations between radiation field and salivary gland dose

Radiation field	Prescribed dose (N)	Salivary gland mean dose (SD)		
Bilateral neck	70 Gy in 35 fx (148) 66 Gy in 33 fx (64) 60 Gy in 30 fx (10) 56 Gy in 28 fx (3) 50 Gy in 25 fx (3) 36 Gy in 18 fx (1)	Parotid	Ipsilateral*	35.1 Gy (11.8)
			Contralateral	28.3 Gy (8.6)
		Submandibular	Ipsilateral	60.5 Gy (10.5)
			Contralateral	54.0 Gy (9.9)
Unilateral neck	70 Gy in 35 fx (13) 66 Gy in 33 fx (14) 60 Gy in 30 fx (7) 50 Gy in 25 fx (1) 39.6 Gy in 22 fx (1) 36 Gy in 20 fx (1)	Parotid	Ipsilateral	39.0 Gy (17.1)
			Contralateral	8.5 Gy (5.7)
		Submandibular	Ipsilateral	53.4 Gy (11.2)
			Contralateral	16.1 Gy (9.0)
No elective nodal irradiation	70 Gy in 35 fx (9) 66 Gy in 33 fx (21) 63 Gy in 28 fx (1) 60 Gy in 25 fx (1) 60 Gy in 30 fx (9) 51 Gy in 17 fx (1) 50.4 Gy in 28 fx (1) 50 Gy in 25fx (3) 45 Gy in 25 fx (1) 40 Gy in 20 fx (1)	Parotid	Ipsilateral	7.8 Gy (13.8)
			Contralateral	4.9 Gy (10.8)
		Submandibular	Ipsilateral	6.1 Gy (8.2)
			Contralateral	5 Gy (8.1)
Whole-brain radiation therapy	40 Gy in 20 fx (1) 37.5 Gy in 15 fx (4) 35 Gy in 14 fx (3) 30 Gy in 10 fx (3) 25 Gy in 10 fx (3) 12 Gy in 8 fx (1)	Parotid	Ipsilateral	24.7 Gy (8.4)
			Contralateral	23.3 Gy (8.3)
		Submandibular	Ipsilateral	2.2 Gy (2.6)
			Contralateral	1.4 Gy (1.4)

*Ipsilateral was defined as the side with a higher dose when there was no laterality in the disease locations and/or radiation fields.

submandibular glands were a mean dose (Dm) of less than 26 Gy and 39 Gy, respectively. The number of patients who received elective nodal irradiation is summarized in Table 1. WBRT was delivered using slightly angled opposed lateral fields. The radiation dose to each salivary gland was assessed using Dm for either the whole organ (Dm-w) or a partial voxel volume (Dm-v). A treatment plan for each patient was exported from the treatment planning system as a Digital Imaging and Communications in Medicine - Radiotherapy (DICOM-RT) file. Then, the dose grids and contours were imported into R 4.3.1 for Windows (www.r-project.org) using the *RadOnc* package.[23] Each gland was divided into 343 voxels using a 7 × 7 × 7 grid in the axial, coronal, and sagittal directions to calculate Dm-v. The right glands were flipped horizontally to analyze both sides simultaneously.

Longitudinal analysis of salivary gland volume

We modeled longitudinal patterns in relative volume as a function of time from RT using a linear mixed-effects model with the following fixed-effect covariates: Dm, age, Eastern Cooperative Oncology Group PS, and use of chemotherapy. Chemotherapy consisted of triweekly cisplatin 100 mg/m^2 or weekly cisplatin 20 mg/m^2 and docetaxel 10 mg/m^2 in the setting of a phase 2 study. Superselective intraarterial infusion of cisplatin 100 mg/m^2 weekly was used for maxillary sinus cancer. Time from RT was log-transformed to account for decelerated volume changes over time. We then standardized the continuous covariates to make the coefficients comparable. To allow the covariates to impact the rate of volume

change, we included interaction terms between time and each covariate. We specified a 2-level random-effects structure to account for repeated measurements at the patient and nested bilateral gland levels for both intercepts and slopes over time. The model can be expressed as follows (Equation 1):

$$rVol_{ijt} = Intercept + Slope \times \log(Time_{ijt}) + \varepsilon_{ijt}$$

$$Intercept = \beta_0 + \beta_1 \cdot Dm_i + \beta_2 \cdot Age_i + \beta_3 \cdot PS_i + \beta_4 \cdot Chemo_i + u_{0i} + v_{0ij}$$

$$Slope = \beta_5 + \beta_6 \cdot Dm_i + \beta_7 \cdot Age_i + \beta_8 \cdot PS_i + \beta_9 \cdot Chemo_i + u_{1i} + v_{1ij}$$

rVol, relative salivary gland volume; β, fixed-effect coefficient; u, patient-specific random intercepts and slopes; v, gland-level random intercepts and slopes within patients; ε, residual error. i indexes the patients, j indexes the gland side within the patients, and t indexes the time points.

As Dm increases, the rate of parotid volume change shifts from an increase to a decrease. A preliminary analysis using segmental regression indicated that the transition point occurred at 5.7 Gy (data not shown). Therefore, the subsequent analysis was limited to Dm greater than 5 Gy.

Voxel-wise analysis

This analysis compared the original whole-gland model, where Dm-w was used for both the intercept and slope, with 2 alternate voxel-based models. Voxel-based model 1 replaced Dm-w with Dm-v in the slope while retaining it for the intercept. Alternatively, voxel-based model 2 replaced Dm-w with Dm-v for the intercept while retaining it for the slope. Model performance was evaluated using 20 repetitions of 10-fold cross-validation, assessing the mean squared error between the whole-gland model and voxel-based models 1 and 2. We assessed statistical significance using 2-sided paired t-tests and applied false discovery rate correction to all 343 voxel-wise comparisons to adjust for multiple testing.

QOL analysis

Patient-reported outcomes were assessed using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Head and Neck Cancer Module (QLQ-H&N35)[24] and analyzed according to the EORTC QLQ Scoring Manual.[25] Of the 13 symptom domains, 7 consisted of multiple questionnaires: Pain, Swallowing, Senses problems, Speech problems, trouble with social eating, trouble with social contact, and less sexuality. The symptom scores within each domain were averaged and rounded up. The remaining 6 domains consisted of single questionnaires (Dry mouth, Sticky saliva, Teeth, Opening mouth, Coughing, and Felt ill), and the scores were directly used for analysis. Because the number of scores of 4 was limited in most domains, the scores were analyzed as an ordinal outcome with 3 ordered levels (scores of 1, 2, and 3 or greater; higher scores indicate worse outcomes). The study cohort included 15 patients with brain metastasis and 15 patients with salivary gland cancer who underwent resection of at least 1 major salivary gland. These patients were excluded from QOL analysis because they may exhibit different symptom characteristics with volume changes. The QLQ-H&N35 was administered during routine follow-up visits. However, acquisition timing did not always align with imaging acquisition. Therefore, predicted rVol was calculated using the whole-gland model. Associations between predicted rVol and QOL scores were examined using a cumulative link mixed model. The fixed effects included gland type (parotid or submandibular) and questionnaire domain. A random intercept for patient ID accounted for repeated measures at multiple time points across bilateral glands and domains. Odds ratios were estimated to quantify the influence of rVol on the probability of reporting more severe symptoms. Statistical significance levels were adjusted using the Bonferroni method to account for multiple testing.

Results

Salivary gland dose and xerostomia symptoms

A total of 329 patients were analyzed in this study. Patient characteristics are summarized in Table 2. Of the patients, 186 were treated with IMRT, and 143 received 3-dimensional conformal RT. The cohort included 229 patients with bilateral neck irradiation, 37 with unilateral irradiation, 48 with no elective node irradiation, and 15 with WBRT (Table 1). For patients who received bilateral neck irradiation, the average parotid Dm was 35.1 Gy (SD 11.8 Gy) for the ipsilateral gland and 28.3 Gy (SD 8.6 Gy) for the contralateral gland. The average submandibular Dm was 60.5 Gy (SD 10.5 Gy) for the ipsilateral gland and 54.0 Gy (SD 9.9 Gy) for the contralateral gland. Salivary gland doses were substantially lower in patients with no elective nodal irradiation and in the contralateral gland in patients who received unilateral neck irradiation. WBRT delivered clinically meaningful doses to the parotid glands (Table 1). We examined the association

Table 2 Patient characteristics

Age (y)	
Median (range)	66 (15-89)
Sex	
M; F	262; 67
PS	
0; 1; 2; 3; 4	243; 74; 10; 2
Primary sites	
Larynx	76
Oropharynx	77
Hypopharynx	73
Nasopharynx	13
Oral cavity	17
Nasal cavity/paranasal sinus	25
Others*	33
Brain metastasis	15
Chemotherapy	
Yes; No	183; 146
Surgery	
Yes; No	49; 280
IMRT	
Yes; No	186; 143
Total prescribed dose (Gy)	
Median (range)	66 (25-78)
Number of imaging studies after radiation therapy	
Median (range)	3 (2-5)
Time to first imaging study (mo)	
Median (range)	4.2 (0.7-62)
Time to last imaging study (mo)	
Median (range)	47 (9.5-108)
	Total (N = 329)

Abbreviations: IMRT = intensity modulated radiation therapy; PS = performance status.
*Others included thyroid gland, eye and adnexa, salivary gland, unknown primary, lymphoma/plasmacytoma, and sarcoma.

between salivary gland dose and QOL after RT. As expected, patients who received greater than 26 Gy of parotid Dm, greater than 39 Gy of submandibular Dm, or both had worse QOL scores for dry mouth and sticky saliva (Fig. E1A). These scores showed partial improvement over time for both dry mouth and sticky saliva (Fig. E1B). These results confirmed the radiation dose-response relationship of xerostomia symptoms and their long-term changes in our patient cohort.

Salivary gland volume evolution after RT

RT impacted salivary gland volumes. Over the years after RT, both parotid and submandibular glands showed volume changes (Fig. 1A). Initially, there were significant reductions in parotid gland volume. Subsequently, the parotid glands showed dose-dependent volume recovery. In contrast, the submandibular gland exhibited gradual volume reductions over time without any obvious initial drops.

To further characterize these volume changes, we applied a linear mixed-effects model (Equation 1). Multivariate analysis was conducted to identify factors impacting the rate of volume recovery or reduction. Figure 1B shows the observed versus fitted curves for 30 randomly selected representative patients, capturing both patient- and side-specific patterns. Only 30 patients are shown for illustrative purposes.

Table 3 summarizes the regression model results for the parotid and submandibular glands, respectively. For interpretability, 2 forms of regression results are shown: (1) standardized coefficients (β), which represent the effect of a 1-SD increase in each continuous predictor, and (2) original-scale interpretations (eg, per a 10-Gy increase in Dm). Since time was log-transformed, results were interpreted as a doubling of time (eg, from 6 months to 12 months). Categorical covariates were not standardized and are shown on the original scale. On average, parotid gland volumes increased by 2.4% for each doubling of time, whereas submandibular gland volumes decreased by 5.3%. Radiation dose negatively impacted post-RT baseline volumes (intercept) and rates of volume change (slope) for both glands. Interestingly, the magnitude of the impact was similar for both glands (approximately 5% baseline volume loss per 10 Gy and a 1.5% decrease per doubling of time per 10 Gy). Age, PS, and chemotherapy were not associated with baseline volumes in either gland. However, age and PS significantly modified the rate of volume recovery in the parotid gland. Higher age was associated with less volume recovery, corresponding to a 0.68% decrease per doubling of time per 10-year increase. Poor PS was also a significant predictor, reducing the recovery rate by 3.6% per doubling of time. Chemotherapy showed only borderline significance. In contrast to the parotid glands, age, PS, and chemotherapy were not associated with submandibular gland volume change rates.

The model illustrates the significance of salivary gland doses and patient age in predicting salivary gland volume changes after RT (Fig. 1C). The slope of the time-volume response curves decreased as Dm increased. Age also affected the slope of the time-volume responses (Fig. 1D). Depending on age, the slopes in the parotid glands transitioned from positive to negative values in the 30 to 50 Gy range. This suggests a complete loss of regenerative

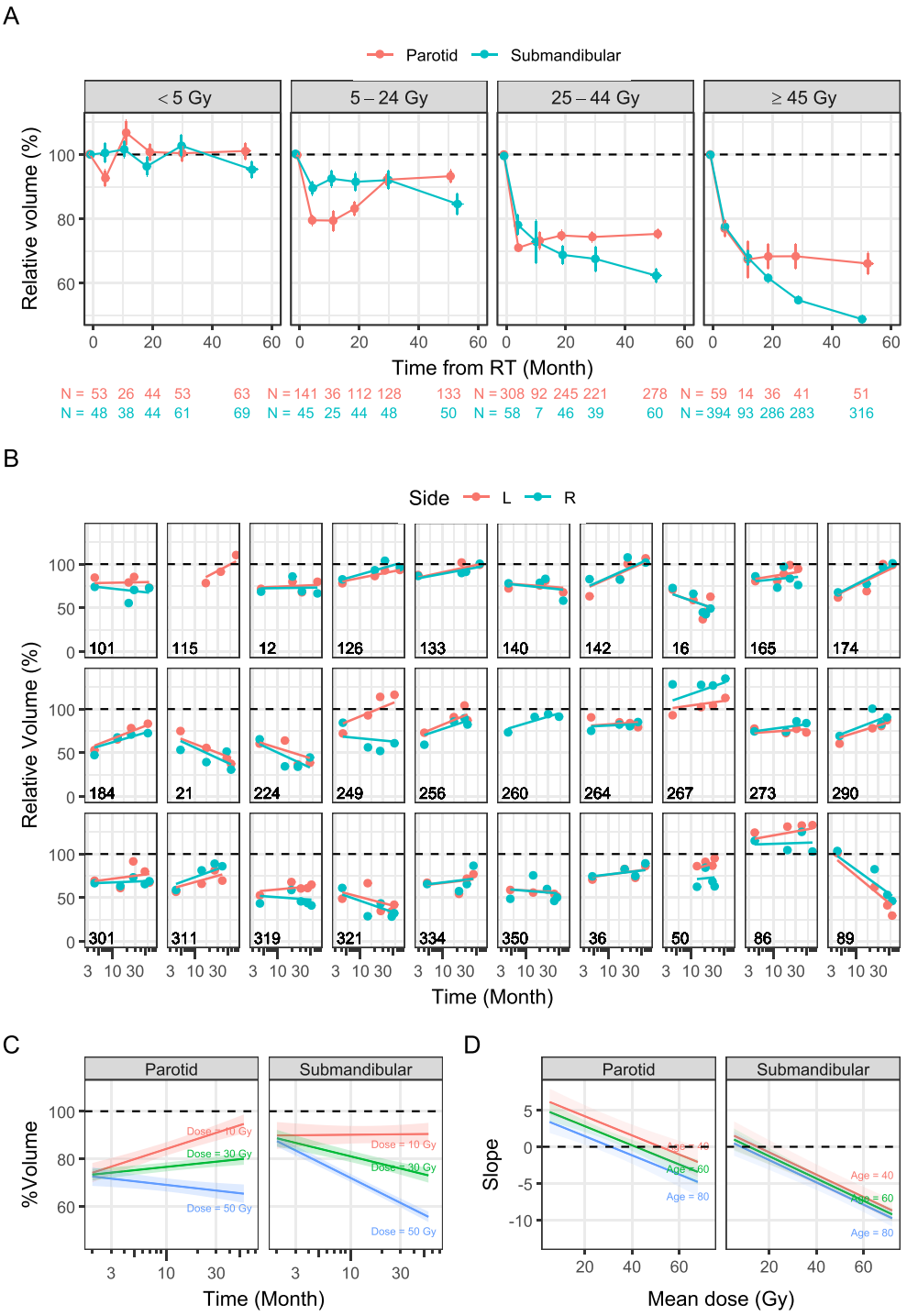

Figure 1 Salivary gland volume changes after radiation therapy (RT). (A) Volume changes in salivary glands stratified by whole-gland mean dose. The parotid gland showed significant initial reductions followed by dose-dependent volume recovery, whereas the submandibular gland showed gradual volume reductions over time without obvious initial drops. (B) Observed versus fitted volume changes by the linear mixed-effects model for 30 randomly selected patients. Numbers in each panel are patients' IDs. L: left gland; R: right gland. (C) Predicted salivary gland volume based on the linear mixed-effects model at different whole-gland mean doses. (D) Model-predicted slopes (rate of volume change) across the dose range, stratified by age.

Table 3 Linear mixed-effects model to predict relative volume of parotid and submandibular glands after radiation therapy

Predictors	Coefficients (95% CI)	Interpretation with original units (95% CI)
Parotid gland (N = 288)		
(Intercept)	$\beta_0 = 78.2^{\ddagger}$ (75.0, 81.3)	78.2% (75.0, 81.3) at 17 mo
Dm	$\beta_1 = -7.11^{\ddagger}$ (−8.67, -5.55)	−4.9% (−5.9, −3.8) per 10 Gy at 17 mo
Age	$\beta_2 = -0.55$ (−2.47, 1.36)	N.S.
PS	$\beta_3 = 7.98$ (−1.75, 17.7)	N.S.
Chemo	$\beta_4 = 0.762$ (−3.25, 4.77)	N.S.
log(time)	$\beta_5 = 3.68^{\ddagger}$ (2.09, 5.27)	2.4% (1.9, 3.5) per doubling of time
Dm × log(time)	$\beta_6 = -2.90^{\ddagger}$ (−3.84, -1.96)	−1.3% (−1.7, −0.9) per doubling of time per 10 Gy
Age × log(time)	$\beta_7 = -1.26^{\dagger}$ (−2.24, -0.273)	−0.68% (−1.2, −0.15) per doubling of time per 10 y
PS × log(time)	$\beta_8 = -5.50^{\dagger}$ (−10.8, -0.179)	−3.6% (−7.1, −0.1) per doubling of time with poor PS
Chemo × log(time)	$\beta_9 = -1.74^{*}$ (−3.75, 0.277)	N.S.
Submandibular gland (N = 286)		
(Intercept)	$\beta_0 = 70.0^{\ddagger}$ (67.3, 72.8)	70.0% (67.3, 72.8) at 17 mo
Dm	$\beta_1 = -13.4^{\ddagger}$ (−15.2, -11.6)	−5.8% (−6.6, −5.0) per 10 Gy at 17 mo
Age	$\beta_2 = 1.02$ (−0.784, 2.82)	N.S.
PS	$\beta_3 = 4.02$ (−6.26, 14.3)	N.S.
Chemo	$\beta_4 = -1.16$ (−4.78, 2.46)	N.S.
log(time)	$\beta_5 = -8.12^{\ddagger}$ (−9.55, -6.69)	−5.3% (−6.3, −4.4) per doubling of time
Dm × log(time)	$\beta_6 = -5.36^{\ddagger}$ (−6.40, -4.33)	−1.5% (−2.0, −1.0) per doubling of time per 10 Gy
Age × log(time)	$\beta_7 = -0.487$ (−1.41, 0.439)	N.S.
PS × log(time)	$\beta_8 = -2.76$ (−8.03, 2.51)	N.S.
Chemo × log(time)	$\beta_9 = 0.136$ (−1.73, 2.00)	N.S.

Abbreviations: PS = performance status; Dm = mean dose; N.S. = not significant.
*$P < .1$.
†$P < .05$.
‡$P < .01$.

capability within this dose range. In contrast, the slopes of the submandibular glands were close to 0 even at very low doses, independent of age.

Next, we examined the effects of regional doses on salivary gland volume changes by comparing the whole-gland model with voxel-based models 1 and 2. Voxel-based model 1 uses a voxel dose (Dm-v) in the interaction term (time × Dm-v), that is, the slope. For the parotid glands, a total of 343 models were compared with the whole-gland model. After correcting for multiple comparisons using the false discovery rate, 75 (21.8%) voxels demonstrated significantly lower prediction error (adjusted $P <$ .05). These voxels were spatially clustered in the cranial-ventral-lateral portion of the parotid gland, which may correspond anatomically to the main ductal region (Fig. 2A). We compared the probability of achieving positive slopes between the whole-gland model and voxel-based model 1 using a partial volume dose based on the 75 voxels to determine an appropriate region-specific dose constraint (Fig. 2E, F). The analysis suggested that the regional dose should be less than 17 Gy to achieve a comparable probability of parotid gland recovery to a whole-gland mean dose of 26 Gy. In contrast, the model fit was poorer using voxel-based model 2 in which Dm-v replaced Dm-w only in the main term, that is, the intercept (Fig. 2B), indicating that voxel-level dose alone does not adequately capture the overall dose response. These findings support the idea of 2 complementary roles: a global dose for predicting post-RT baseline volume and a region-specific dose for volume recovery.

We also compared the voxel-based model and whole-gland model in a subset of patients with primary head and neck cancers, excluding patients who received WBRT. The results of this subset analysis were qualitatively similar (Fig. E2).

Interestingly, substituting Dm-v into neither the slope nor the intercept improved the model fit for the submandibular gland (Fig. 2C, D). The original whole-gland

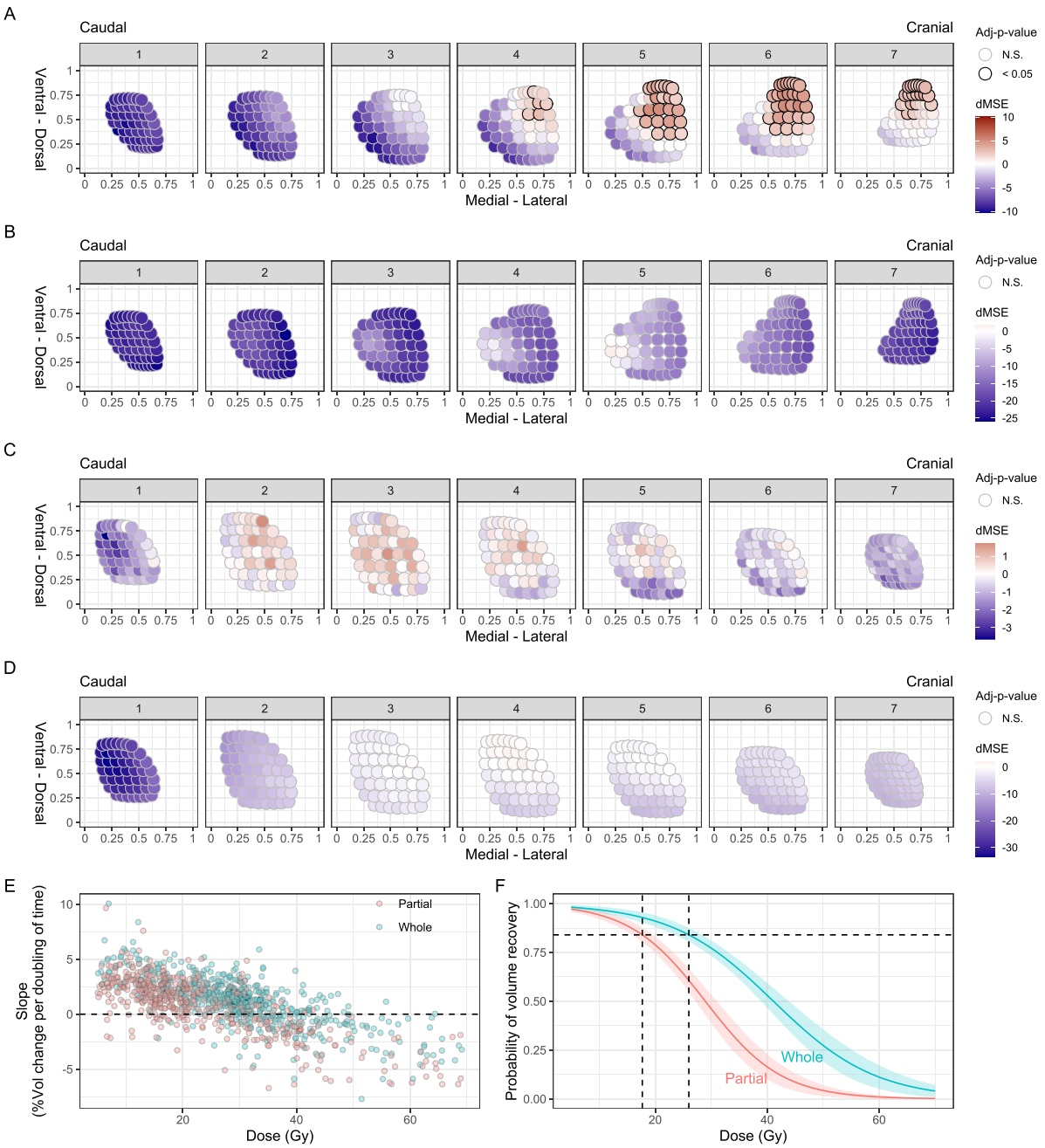

Figure 2 Voxel-based analysis. (A) Cross-validated model comparison of the whole-gland model and voxel-based model 1 (voxel dose in the slope component) for parotid glands (N = 288). The heatmap colors represent the difference in prediction error (or differential mean squared error [dMSE]). Greater dMSE indicates an improved model fit. Voxels showing a significantly improved model fit (false discovery rate [FDR]-adjusted $P < .05$) are outlined in black. These voxels were clustered in the cranial-ventral-lateral region of the gland. (B) A cross-validated model comparison between the whole-gland model and voxel-based model 2 (voxel dose in the intercept component) for parotid glands (N = 288). No significant improvement in model fit was observed. Panels C and D show a similar analysis to the panels A and B for submandibular glands (N = 286). No significant improvement in the model fit was observed. (E) The slopes of the longitudinal dose-volume responses are shown as a function of parotid gland doses. This compares the whole-gland mean dose with the partial-gland mean dose of the clustered voxels that showed significant improvements in the model fit in panel A. (F) A logistic regression model was used to analyze the probability of volume recovery by defining it as a positive slope. Using the partial-gland dose, the equivalent dose to achieve a similar probability to the whole-gland mean dose of 26 Gy was 17 Gy.

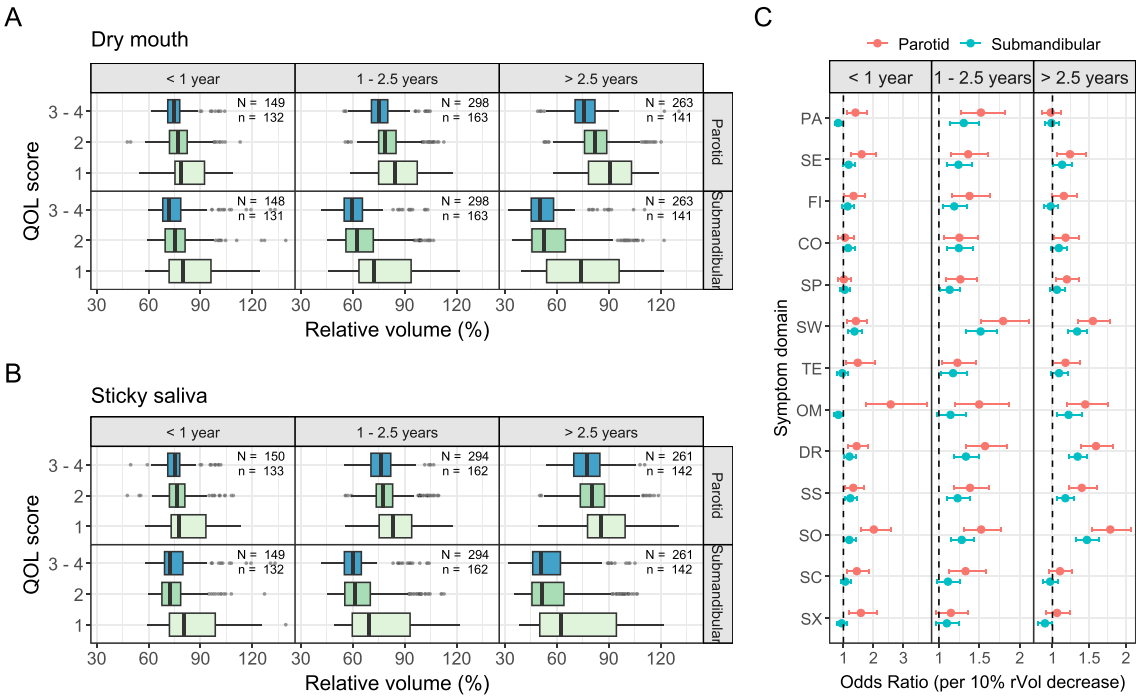

Figure 3 Quality of life (QOL) outcomes by salivary gland volumes. Dry mouth (A) and sticky saliva (B) scores from the EORTC QLQ questionnaire are shown as a function of the predicted relative volumes in the parotid and submandibular glands. QOL assessments were grouped into 3 timeframes. (C) The scores were summarized into 13 symptom domains: pain (PA), senses problems (SE), felt ill (FI), coughing (CO), speech problems (SP), swallowing (SW), teeth (TE), opening mouth (OM), dry mouth (DR), sticky saliva (SS), trouble with social eating (SO), trouble with social contact (SC), less sexuality (SX). The symptom scores were analyzed as an ordinal outcome with 3 ordered levels (higher scores indicate worse outcomes). Associations between QOL scores and predicted relative volumes were examined using a cumulative link mixed model. Odds ratios were estimated to quantify the influence of a 10% reduction in salivary gland volume. Statistical significance levels were adjusted using the Bonferroni method for a 95% confidence interval to account for multiple comparisons.

Abbreviations: N = total number of QOL score measurements, including repeated measurements at different time points from the same patients; n = number of patients in each category; rVol = relative salivary gland volume.

model best predicted both baseline volumes and rates of volume changes, suggesting that the parotid and submandibular glands have differential tissue-regeneration properties.

Salivary gland volume changes and QOL

We examined the association between salivary gland volume changes and patient-reported symptom outcomes using QLQ-H&N35 scores. Larger volumes of parotid and submandibular glands were associated with better symptom scores for dry mouth and sticky saliva (Fig. 3A, B). Associations between salivary gland volumes and all 13 symptom domains are shown in Fig. E3. On average, larger volumes were associated with a lower likelihood of symptom worsening. However, this effect varied considerably across the 13 symptom domains and the timing of symptom score acquisition. Many domains demonstrated a significant association with volumes in the acute (less than 1 year) or early chronic (1 to 2 and a half years) phases. This may be due to confounding factors such as radiation doses to the mucosa, muscles, or bones. In the late chronic phase (>2.5 years), many domains were no longer associated with volumes, including pain, feeling ill, coughing, teeth, trouble with social contact, and less sexuality. However, dry mouth, sticky saliva, trouble with social eating, and swallowing persistently showed statistically significant associations with volumes throughout the entire timeframe (Fig. 3C). These results support the hypothesis that volume changes directly reflect functions and related symptoms.

Discussion

Studies have shown that parotid volume decreases significantly during a course of fractionated RT. This reduction is apparent even with lower doses using IMRT. Many patients experience substantial xerostomia as an acute

adverse effect of RT. However, symptoms may gradually improve over months to years with parotid-sparing IMRT. In this study, we found that the parotid glands recovered from acute volume reductions and appeared to regenerate during the follow-up period. The critical dose depends on the patient's age and PS.

The mechanisms of salivary gland regeneration are still under investigation. Studies have shown that salivary gland stem cells are primarily found in the intercalated ducts. Sparing the stem cell-rich (SCR) region, where stem cells are more densely distributed, has been shown to preserve saliva production. Our observations in the voxel-based model analysis were consistent with the theory that the parotid gland contains a stem cell population surrounding the area where Stensen's duct first branches. This area is located near the dorsal edge of the mandible.[26] The cranial-ventral-lateral subvolume shown in the voxel-based analysis appeared to roughly match the SCR region. However, we could only speculate about the spatial intragland distribution of Stensen's duct. This should be validated in a correlation study using more precise imaging, such as MRI sialography.

Although previous studies have explored potential target regions inside the parotid gland, these studies have led to various conclusions.[8-10,13,14] These studies used subjective or objective xerostomia scales or whole salivary flow rate as an outcome measure. Because these endpoints are affected by overall consequences in all major and minor salivary glands,[3,27] interpreting the analyses is complicated by many strong confounding factors. The strength of our study lies in the ability to assess the direct association between dose distribution and volume changes in salivary glands at the individual gland level. A prior randomized trial focusing on SCR region-sparing RT failed to show improvement in parotid functional preservation.[11] However, the trial's primary endpoint was a reduction of more than 75% in parotid gland saliva production compared with pretreatment levels 12 months after RT. This endpoint does not necessarily represent the amount of gland recovery itself but rather the total amount of initial injury and recovery. We speculate that this may have diluted the study outcome.

Contrary to the SCR theory, studies have shown that salivary acinar cells can self-replicate and drive proliferation during postnatal development and gland maintenance, similar to the parenchyma of the liver and pancreas.[28] Acinar cell loss triggered by transient ductal ligation can be recovered without direct support from the stem cell pool. Acinar cells have also been found capable of repopulating cells through $SOX2^{+}$ progenitor cell expansion via a parasympathetic nerve-dependent mechanism after radiation damage.[29] These studies suggest that there are multiple backup systems for recovering from salivary gland damage and that several cell types within the salivary gland epithelium can serve as stem/progenitor-like cells.[30,31]

In this study, we observed distinct longitudinal volume patterns in the parotid and submandibular glands. Interestingly, the submandibular glands did not show any volume recovery after RT, even at low doses. In addition, we failed to identify regional doses that could improve the model fit for submandibular volume changes. Alternatively, because no initial volume drops were observed, the submandibular glands may exhibit distinct cell loss kinetics rather than distinct regeneration mechanisms. Most preclinical studies to date have used submandibular glands in rodents due to their accessibility and availability. Therefore, the existence of differential molecular or cellular mechanisms between parotid and submandibular glands is currently unknown.

This study consisted of a highly heterogeneous patient cohort with various primary sites that were treated with different techniques, with or without concurrent chemotherapy. A previous study showed that the dose received by the parotid glands from WBRT significantly impacts QOL.[32] Thus, we included patients who underwent WBRT for brain metastasis. The heterogeneous data set provided a wide range of spatial dose distribution patterns inside the parotid and submandibular glands. This allowed us to efficiently examine the regional dose effect within the glands. We identified the subvolume and dose constraints that impacted the volume kinetics of the parotid glands in our study cohort. However, given the relationship between target coverage and other organs at risk, it is uncertain how our findings can be applied to specific cases. Caution should be exercised when applying our results to specific types of disease using modern IMRT until more data are accumulated prospectively.

Furthermore, patient symptoms are expected to be significantly influenced by primary disease sites and irradiation techniques. Therefore, caution is required when interpreting the association between salivary gland volume and QOL outcomes in this study. Indeed, we found temporary associations between salivary gland volumes and QOL symptom domains where direct effects from salivary gland damage were unlikely. This observation clearly indicates confounding effects from collateral dosage to organs other than the salivary glands. Our study lacks external data sets to validate the results. In addition, we only assessed salivary gland function using patient-reported outcomes with EORTC QLQ scores. Additional methods, such as objective toxicity grades or functional imaging, are necessary to draw a solid conclusion in the functional relationships between salivary gland volumes and xerostomia. Further prospective studies are necessary to confirm causal relationships among regional parotid dosing, longitudinal salivary gland volume changes, and xerostomia.

Conclusion

The parotid and submandibular glands exhibited distinct volume change patterns after RT. Sparing the

cranial-ventral-lateral portion of the parotid gland (the potential ductal/stem cell region) during RT may be critical for predicting and achieving volume recovery. No regional dose effects were found in the submandibular glands. These findings suggest that distinct dosing strategies and regenerative approaches may be necessary for the 2 major salivary glands.

Disclosures

None.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2026.102074.

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