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Scientific Article

Spatial Radiation Dose Influence on Xerostomia Recovery and Its Comparison to Acute Incidence in Patients With Head and Neck Cancer

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Abstract

Purpose: Radiation-induced xerostomia is one of the most prevalent symptoms during and after head and neck cancer radiation therapy (RT). We aimed to discover the spatial radiation dose-based (voxel dose) importance pattern in the major salivary glands in relation to the recovery of xerostomia 18 months after RT, and to compare the recovery voxel dose importance pattern to the acute incidence (injury) pattern.

Methods and Materials: This study included all patients within our database with xerostomia outcomes after completion of curative intensity modulated RT. Common Terminology Criteria for Adverse Events xerostomia grade was used to define recovered versus nonrecovered group at baseline, between end of treatment and 18 months post-RT, and beyond 18 months, respectively. Ridge logistic regression was performed to predict the probability of xerostomia recovery. Voxel doses within geometrically defined parotid glands (PG) and submandibular glands (SMG), demographic characteristics, and clinical factors were included in the algorithm. We plotted the normalized learned weights on the 3-dimensional PG and SMG structures to visualize the voxel dose importance for predicting xerostomia recovery.

Results: A total of 146 head and neck cancer patients from 2008 to 2016 were identified. The superior region of the ipsilateral and contralateral PG was the most influencial for xerostomia recovery. The area under the receiver operating characteristic curve evaluated using 10-fold cross-validation for ridge logistic regression was 0.68 ± 0.07. Compared with injury, the recovery voxel dose importance pattern was more symmetrical and was influenced by lower dose voxels.

Conclusions: The superior portion of the 2 PGs (low dose region) are the most influential on xerostomia recovery and seem to be equal in their contribution. The dissimilarity of the influence pattern between injury and recovery suggests different underlying

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mechanisms. The importance pattern identified by spatial radiation dose and machine learning methods can improve our understanding of normal tissue toxicities in RT. Further external validation is warranted.

Introduction

Radiation-induced xerostomia is one of the most experienced symptoms after head and neck cancer radiation therapy (RT) resulting from salivary glands damage.[1,2] However, the use of mean parotid (PG) dose and the risk of late xerostomia recovery are conflicting though less numerous in reports.[3-9]

The mean dose does not adequately reflect the potential injury to the anatomic complexity of salivary production and ductal transport. Salivary glands contain acinar cells responsible for salivary production, a ductal network for transporting saliva, and stem cells for recovery of function.[10] They present both parallel and serial components to the function of the glands with a complex spatial pattern. The acinar cells are thought to be parallel in function and distributed evenly across the gland,[11] where the ductal network has serial components such as the major duct transporting most of the produced saliva into the oral cavity.[12] The stem cell distribution within the gland is reported to be along the ductal structure and not evenly distributed.[13] For a given mean PG dose, even when the mean PG dose is kept <26 Gy during RT planning,[6,14] the spatial RT distribution can vary significantly between patients limiting its efficacy if the spatial RT distribution affects the risk of late xerostomia.

This follow-on study is built on our prior efforts to understand the dosimetric factors that are involved in the xerostomia injury.[15] Our study differs from the prior related studies in that the model was applied to xerostomia recovery, as opposed to injury, with the hypothesis that the voxel importance patterns for injury and recovery are different. In addition, the models for both injury and recovery were updated to include smoking status.

Methods and Materials

Study population

The study population included patients who were treated with an ipsilateral or bilateral neck parotid-sparing intensity-modulated radiation therapy from January 2008 to December 2016 and had contours of all 4 major salivary glands (contralateral and ipsilateral PG and submandibular glands [SMG]). All patients received 33 to 36 fractions and 200 to 220 cGy per fraction with curative intent. Patients with xerostomia outcomes captured at baseline and 3-month post-RT (POT) were included in injury cohort. The recovery cohort was formed of patients in the injury cohort with acute xerostomia injury as shown in Figure 1. No active symptom management to promote xerostomia recover (eg, Pilocarpine) was used in this study.

Data collection

Although this is a retrospective study, the data for each patient were collected prospectively at the point of care by the same attending physician. All patients' demographics, clinical pathology, radiation dose, and clinical outcomes were queried from the database.[16] Patients were seen weekly during the treatment and followed up every 3 to 4 months for the first 3 years and every 6 months after.

Features and outcome

Patient's demographic and clinical features were included in the model, including age at start of treatment, sex, race (black, Asian, Pacific Islander, white, Hispanic, and other), smoking status (never smoked, quit smoking, and currently smokers), attending physician, baseline xerostomia grade, tumor stage (TNM stage), chemotherapy (yes, no), human papillomavirus status (positive, negative), feeding tube ever used (yes, no), and tumor site (nasopharynx, oral cavity, oropharynx, hypopharynx, larynx, and other). No missing data was found in the continuous variables. Missing values in categorical variables were labeled as missing and analyzed as a separate category among variables in the model. Tumor site was determined based on *International Classification of Diseases,* Ninth or Tenth Revision code.

The voxel dose features were captured from a radiomorphologic feature generation pipeline. A prior study has described the details about the pipeline and actual steps to generate voxel features.[17] Briefly, each patient's anatomic structures were deformably registered to a common standard frame using the Coherent Point Drift algorithm.[18] Then, the normalized structures were uniformly sampled, and the dose to each voxel in the PGs and SMGs (called voxel dose in the present analysis) were

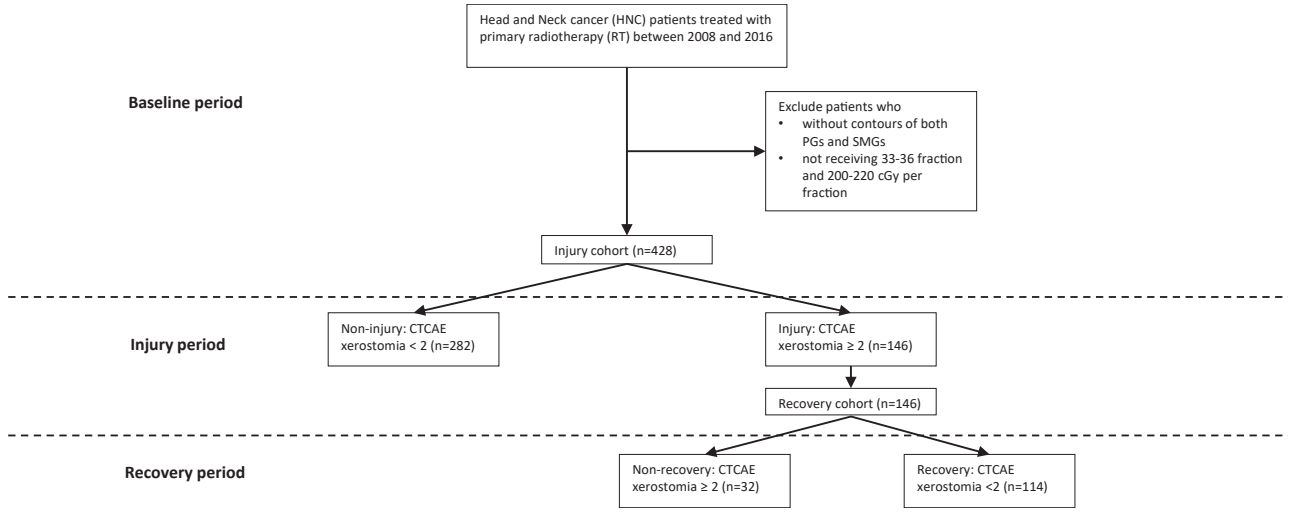

Figure 1 Flowchart of patient selection.

used as dosimetric predictors. The dose was sampled to 942 voxels distributed throughout the PGs and SMGs with each voxel representing a 4.68-mm × 4.68-mm × 3.00-mm volume in the standard patient.

It is difficult to accurately identify the intraparotid ductal region on computed tomography images owing to the limitations in soft tissue delineation without the use of magnetic resonance images. As such, we sought to estimate the location of potential voxels that may represent the intraparotid ductal regions by identifying parotid voxels (within 5 mm of the parotid gland tissue) that were adjacent to the main parotid duct that was readily contoured on computed tomography. Only the voxels of intraparotid ductal region were included in the analysis.

The xerostomia outcome definition was derived from the physician-assessed Common Terminology Criteria for Adverse Events (CTCAE) 4.0 xerostomia grade with the following scoring criteria[19]: 0 indicates no xerostomia symptom; 1 indicates symptomatic without significant dietary alteration; 2 indicates moderate symptoms and oral intake alterations; and 3 indicates inability to adequately aliment orally, tube feeding, or total parenteral nutrition indicated. A binary xerostomia outcome was created: xerostomia with grade ≥ 2 and no-xerostomia with grade <2. According to the prevalence time plot of xerostomia grade in our Oncospace database, the xerostomia grade remained stable beyond 18-month POT[20]; hence we took 3 time points to define xerostomia recovery: (1) baseline period: before or within the first week of the start of treatment; (2) injury period: the end of RT (EOT) to 18 months POT; and (3) recovery period: beyond 18 months POT. Then the maximal CTCAE xerostomia grade was taken from each period. Non-recovered patients were defined by a xerostomia pattern over the 3 periods of $0 \diagdown 1 \diagdown 1$, where 0 represented no-xerostomia and 1 represented xerostomia. The xerostomia pattern for recovered patients was $0 \diagdown 1 \diagdown 0$.

Statistical analysis

Permutation test

The dose difference between the 2 recovery groups was compared using the permutation test, which is a nonparametric approach and accounts for multiple comparisons. No assumption of normal distribution, which is often not true in the case of radiation dose distribution, is made in this method.[21] We randomly permutated the samples 1000 times. A one-sided hypothesis test was performed with a significant level of 0.05.

Prediction model

Logistic regression with ridge regularization was performed to evaluate the voxel importance pattern based on the prior results.[15] The area under the curve (AUC) score with 10-fold cross-validation was used to evaluate the predictive performance of the model. All ridge logistic regression models mentioned in this manuscript refer to the updated model with the inclusion of smoking status. No time trend or rate of recovery was discussed in this analysis; hence models that accounted for variations over time were not considered.

Voxel importance pattern

Learned weight from the recovery ridge logistic regression indicates how much a unit change in a voxel dose affected the probability of a given patient recovering from xerostomia beyond 18 months POT (Table E1,

Table 1 Patient characteristics at baseline for xerostomia recovery cohort

Feature	Xerostomia status		*P* value*
	Recovered (N = 114)	Nonrecovered (N = 32)	
Age†	58.07 (52, 65)	59.38 (55, 64.25)	.55
Sex			.90
Male	96 (84.21%)	26 (81.25%)	
Female	18 (15.79%)	6 (18.75%)	
Race			.90
White	87 (76.32%)	25 (78.13%)	
Black	21 (18.42%)	5 (15.63%)	
Asian/Pacific Islander	4 (3.50%)	2 (6.30%)	
Other	2 (1.74%)	0 (0%)	
Smoking status			.82
Never smoked	43 (37.72%)	10 (31.25%)	
Quit smoking	46 (40.35%)	14 (43.75%)	
Currently smokers	13 (11.40%)	3 (9.38%)	
Unknown	12 (10.53%)	5 (15.63%)	
Attending physician			.25
1	63 (55.26%)	13 (40.63%)	
2	27 (23.68%)	8 (25.00%)	
3	14 (12.28%)	7 (21.88%)	
4	1 (0.88%)	0 (0%)	
Missing	9 (7.89%)	4 (12.50%)	
Chemotherapy			.83
Yes	92 (80.70%)	27 (84.38%)	
No	22 (19.30%)	5 (15.63%)	
HPV			.85
Positive	72 (63.16%)	19 (59.38%)	
Negative	42 (36.84%)	13 (40.63%)	
Feeding tube used			.20
Yes	34 (29.82%)	14 (43.75%)	
No	80 (70.18%)	18 (56.25%)	
Baseline xerostomia grade			.39
0	89 (78.07%)	22 (68.75%)	
1	25 (21.93%)	10 (31.25%)	
Primary tumor stage (T stage)			.76
0	5 (4.39%)	2 (6.25%)	
1	28 (24.56%)	9 (20.00%)	
2	38 (33.33%)	12 (37.50%)	
3	22 (19.30%)	3 (9.38%)	
4	18 (15.79%)	5 (15.63%)	
Missing	3 (2.63%)	1 (3.13%)	
Regional lymph nodes stage (N stage)			.06
0	26 (22.81%)	1 (3.13%)	
1	15 (13.16%)	6 (18.75%)	
2	68 (59.65%)	24 (75.00%)	
3	2 (1.75%)	0 (0%)	
Missing	3 (2.63%)	1 (3.13%)	
Distant metastasis stage (M stage)			.63
Yes	3 (2.63%)	1 (3.13%)	
No	108 (94.74%)	31 (96.88%)	
Missing	3 (2.63%)	0 (0%)	
Tumor site			.29
Oral cavity	39 (34.21%)	9 (28.13%)	
Oropharynx	31 (27.19%)	11(34.38%)	

(*continued*)

Table 1 (*continued*)

Feature	Xerostomia status		*P* value*
	Recovered (N = 114)	Nonrecovered (N = 32)	
Nasopharynx	8 (7.02%)	4 (12.50%)	
Larynx	14 (12.28%)	0 (0%)	
Other	22 (19.30%)	8 (25.00%)	

Abbreviation: HPV = human papillomavirus.
* *P* value is obtained using the 2-sample test.
† Mean and interquartile range for continuous variables.

available online at https://doi.org/10.1016/j.adro.2019.08.009). Negative learned weights in recovery model indicate an improved probability of recovering from xerostomia with a decrease in dose to that voxel.

The learned weights were normalized to visualize the voxel importance pattern. The formulas used to compute the relative importance in recovery and injury are $X' = -X/(Xmin)$ and $X' = (X - Xmin) / (Xmax - Xmin)$, respectively. Then, the relative importance weights were visualized on the 3-dimensional PGs and SMGs structure. Darker red indicates more important.

Software

All data analyses were performed using STATA (StataCorp. 2017. Stata Statistical So ware: Release 15. College Station, TX: StataCorp LLC) and R Project for Statistical Computing (Version 3.5.1, Vienna, Austria). All statistical tests in Table 1 were 2-sided, and *P* values <.05 were considered statistically significant. The 3-dimensional plots were visualized using the Python programming language (Version 2.7.15, Python Software Foundation).

Results

Patient characteristics

The total number of patients in this recovery study cohort is 146 (nonrecovered/recovered: 32/114). As summarized in Table 1, no significant difference are noted in patient's demographic and clinical pathology features between the recovered and nonrecovered groups. According to Figure 2, the majority of patients (103/146) classified as acute injury had xerostomia grade = 1 at the recovery period, and no patients has xerostomia grade = 3 in the nonrecovered group. Therefore, we dichotomized the xerostomia outcome at the cut point of grade 2 to simply the analysis.

Dose comparison

Figure 3a–c shows that the nonrecovered patients were treated with higher doses in the superior portion of the ipsilateral PG, although the dose level to other regions in the PGs and SMGs were comparable. Compared with the recovered group, the dose variability of the nonrecovered group is higher in the superior portion of ipsilateral PG. From the pattern of median dose distribution and its variation, the recovered patients received a consistently lower dose in the superior portion of ipsilateral PG.

To statistically compare the dose difference between the 2 groups, the distribution of *P* value in permutation test is shown in Figure 4b, demonstrating that the lower voxel doses across the green region in superior portion of ipsilateral PG in the recovered group are statistically significant.

Voxel importance pattern

The AUC scores for the ridge logistic regression model evaluated by 10-fold cross-validation for recovery and injury prediction are 0.68 ± 0.07 and 0.74 ± 0.03, respectively. Learned weights and relative importance of

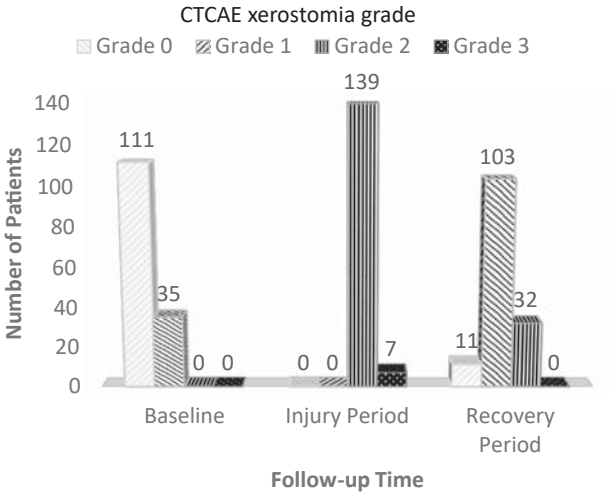

Figure 2 The distribution of Common Terminology Criteria for Adverse Events xerostomia grade at baseline (before or within the first week of the start of treatment), injury period (between the end of radiation therapy and at 18 months post-radiation therapy), and recovery period (beyond 18 months postradiation therapy).

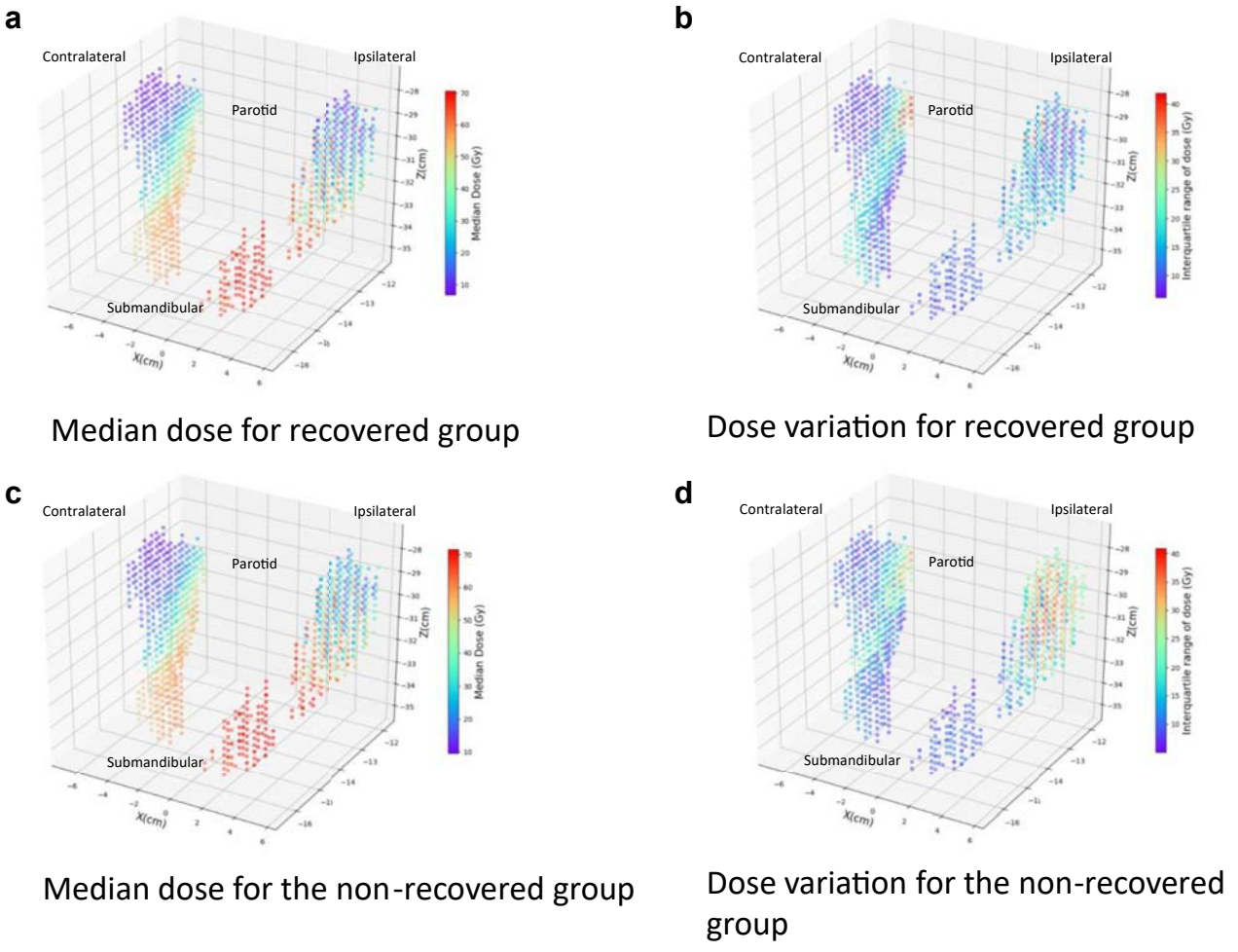

Figure 3 The distribution (median dose) and variation (interquartile range) of radiation dose in parotid and submandibular glands for xerostomia for the recovered (a, b) patients group versus nonrecovered (c, d) group.

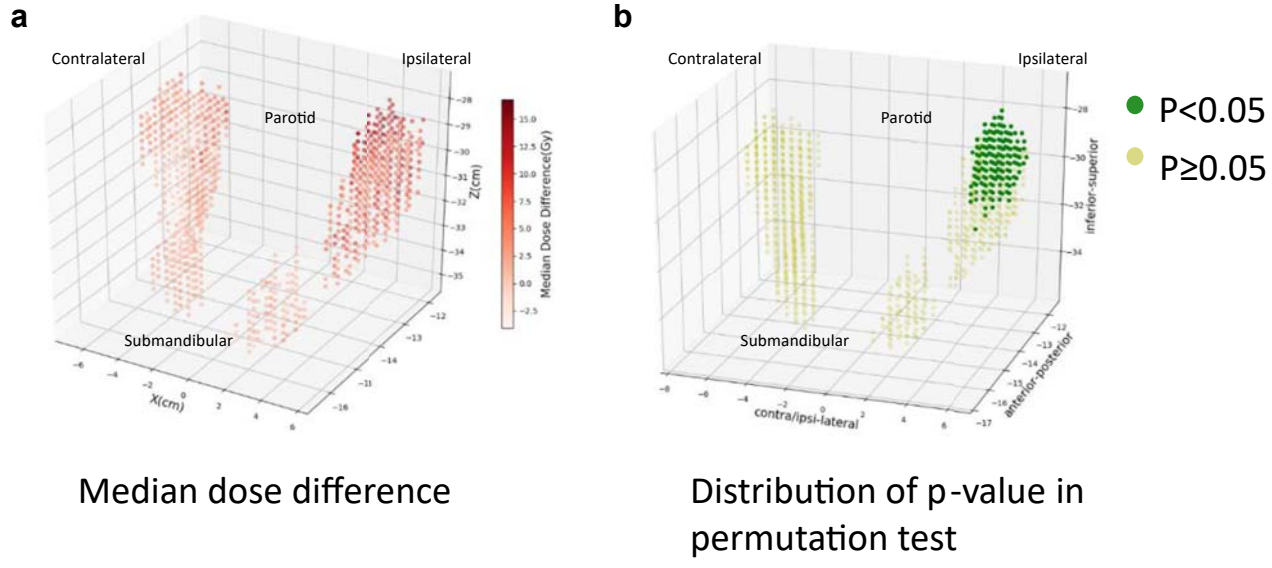

Figure 4 (a) The difference between the median doses compared nonrecovered group to recovered group. (b) Distribution of *P* value for comparing dose difference between nonrecovered group and recovered group by permutation test.

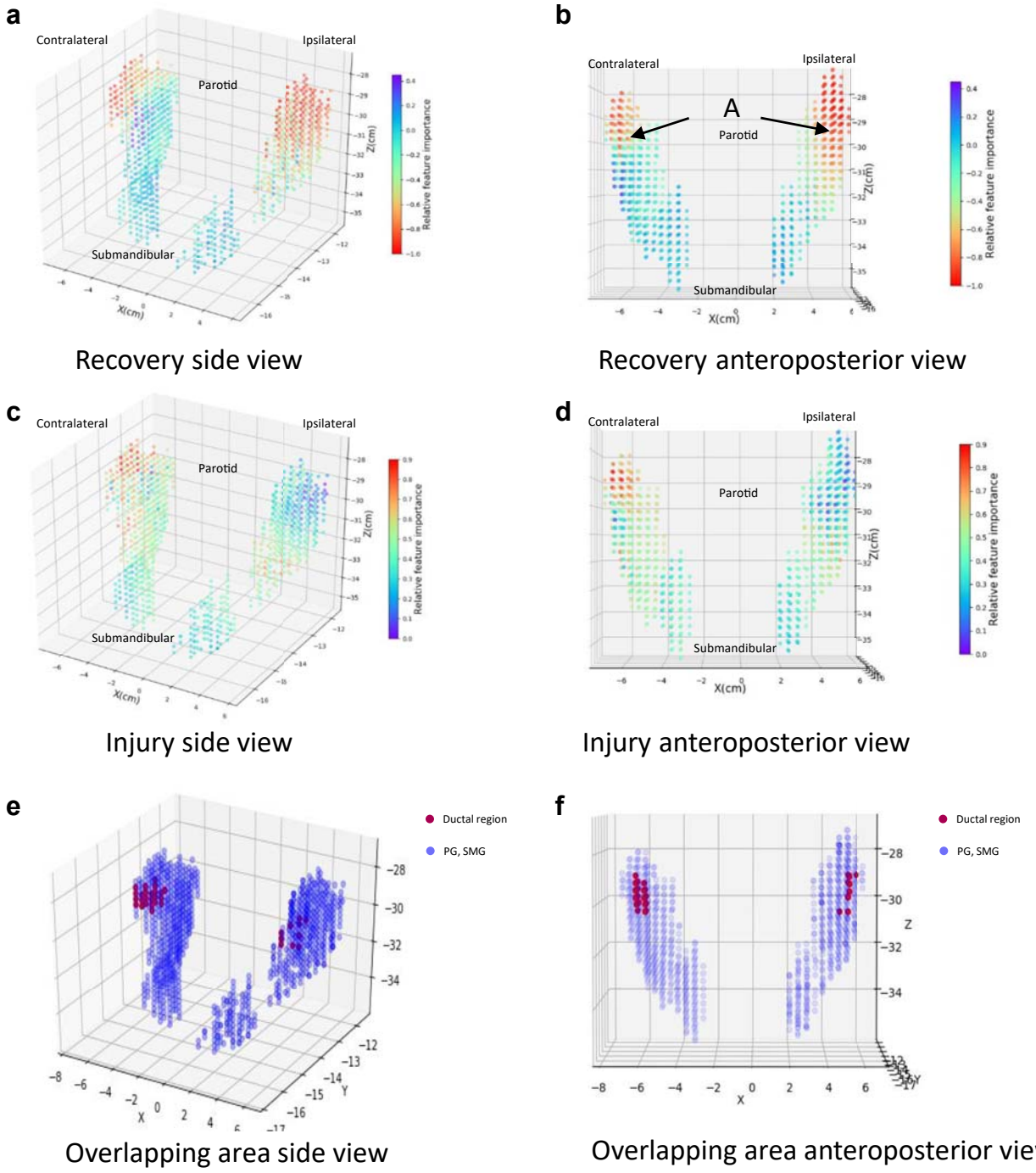

Figure 5 Voxel importance pattern learned from ridge logistic regression for xerostomia recovery and acute xerostomia (injury). (a, b) Recovery voxel importance pattern. (c, d) Injury voxel importance pattern. (e, f) The overlapping area of ductal regions and parotid glands. The more symmetrical nature of the recovery importance perhaps indicates more parallel organ dependence on recovery. *Abbreviations:* PG = parotid glands; SMG = submandibular glands.

voxel dose for injury and recovery model are shown in Tables E1 and E2 It can be seen that in the recovery pattern (Fig 5a-b) that the superior portions of both sides of PGs, colored red and orange, show a strong negative correlation between dose and probability of recovery. That is to say, a lower dose to these regions will result in a greater chance of recovery for the patient. Evaluating the region of high relative importance (from −0.8 to −1.0) for recovery, the median voxel dose for recovered and nonrecovered group in this region range from 6.67 to

16.16 Gy, and 6.81 to 22.08 Gy, respectively. Figure 5e shows the overlapping area of intraductal regions and PGs (red dots). The average of median dose to the ipsilateral intraductal region in recovered and nonrecovered group were 26.83 Gy and 36.55 Gy, respectively. The injury voxel importance pattern from the updated model (Fig 5c-d) shows that dose to the superior and middle contralateral PG and dose to inferior ipsilateral PG are important in raising the probability of occurrence of xerostomia injury.

We also performed the same analysis in the subcohort of recovery with patients without surgery (140 patients). The voxel importance pattern is the same as shown in Figure 5. The learned weights from the subcohort analysis are highly correlated with that from the recovery cohort by Pearson correlation test.

Nondose feature importance

The learned weights of demographic and clinical factors in recovery model are shown in Table E3 (available online at https://doi.org/10.1016/j.adro.2019.08.009). Positive values indicate features that are related to an improved likelihood of recovery such as human papillomavirus positive, never smoked, or being male. The learned weights of nondose features are not directly comparable to the voxel dose learned weights because there are significantly more correlated in the scale of learned weights than voxel dose. It was important to include the nondose features in the ridge logistic regression to account for nondosimetric influences, although the focus of the study was on the evaluation of the influence of the patterns of dose.

Discussion

In this article, we examined the voxel importance pattern on xerostomia recovery and compared it to the injury voxel importance pattern, which was published in our prior study. Moreover, we updated the ridge logistic regression algorithm, which was used in studying xerostomia injury, with the inclusion of smoking status, and improved the 10-fold cross validation AUC from 0.69 ± 0.08 to 0.74 ± 0.03. This suggests that ridge logistic regression model with smoking status had a better prediction in xerostomia injury than the model that was previously published. Applying the updated ridge logistic regression algorithm to predict xerostomia recovery beyond 18-month POT, the 10-fold cross validation AUC was 0.68 ± 0.07. This further demonstrates that the updated ridge logistic regression algorithm is effective in predicting both xerostomia injury and recovery with voxel doses and clinical factors.

In the study, 32 (21.92%) patients were classified as nonrecovered by the definition in 3 periods. Our observation is consistent with studies showing that significant saliva flow rate improvement at 12 and 18 months POT.[4-7] Although the results in our analysis are consistent with most studies, some other studies[22,23] showed that xerostomia patients do not recover. We think the reason why we have a reasonable number of patients who recovered is that we have physicians who follow practices conducive to recovery.

The important voxel doses identified to be associated with xerostomia recovery spatially localized to both the ipsilateral and contralateral superior regions of the PGs. As demonstrated in Figure 5a, the normalized learned weights between −0.8 to −1 tended to occupy the superior portions of both the ipsilateral and contralateral PGs, the overall lower dose regions, especially the lateral aspect of the superior PGs highlighting that there was a spatial dependency to the ability to predict for xerostomia recovery. The region we have found to be the most important overlaps with critical regions reported in previous studies. Clark et al segmented PGs into equal subvolumes and found that the doses to caudal-anterior aspects of PG are the most reliable predictor for 1-year POT xerostomia.[8] Han et al in 2019 explored the dose volume histogram pattern in prediction of xerostomia within 18 month POT and demonstrated that dose to superior and middle contralateral PG and superior-anterior ipsilateral PG are more influential.[20] The exact anatomic information of the substructure is difficult to reveal by the voxel features. To mitigate this limitation, we demonstrated both important regions for xerostomia injury and recovery in align with the schematic of segmentation proposed by Han et al in Figure E1 (available online at https://doi.org/10.1016/j.adro.2019.08.009). It should be noted that the definition of substructures in Han et al is quantitative and is not exactly the same as what we used in this article. Moreover, the rat and human experiment conducted by Van Luijk et al demonstrated a similar symmetrical important pattern, and they indicated that was a result of the distribution of stem or progenitor cell around the excretory ducts in PGs.[24] However, the limitation of heterogeneous study population and use of mean dose to subsections by Van Luijk et al might underscore the finding. The voxels we estimated to be associated with the intraparotid ductal region were identified as important in our analysis for both xerostomia injury (contralateral side only) and for xerostomia recovery (both sides) when all the parotid voxels were evaluated (Fig 5). These observations support the conclusion that there are clear subvolume differences in the irradiated human parotid gland as it relates to xerostomia injury and its recovery. Whether the importance of these dose voxels are due to the presence of stem cells or the transport of the saliva and its obstruction is difficult to clearly determine from our analysis.

We improved upon existing studies primarily by comparing the different spatial dosimetric importance patterns for xerostomia injury and recovery. For injury prediction (Fig 5c), this asymmetrical pattern, where tissue

function should be symmetrical, suggests that the asymmetry of the dose distribution is playing a role. The medial portion of the ipsilateral PG identified as influential was overlapped with the intraductal region, which indicates that, in xerostomia injury, high dose to this region might affect the ductal network for transporting saliva and result in dry mouth. For recovery prediction, given that only the voxel dose difference to superior ipsilateral side is statistically significant, the symmetrical importance pattern in superior portion of PGs might indicate that to preserve the ability to recovery from xerostomia, dose to superior contralateral PG should be as low as possible while keeping the curative coverage dosage to targets. This result suggests that there may be a lower dose threshold for cells responsible for recovering function of the superior PGs somewhere in the 6.81 to 9.61 Gy range based on the minimum median voxel doses in that region. However, the algorithm we used did not account for any known radiosensitivity of different portions of an organ and the effect of stem cell. In contrast, the voxel doses in the SMGs did not emerge to be predictive of both xerostomia injury and recovery. We speculate that the high doses delivered to the SMGs (Fig 3) and the dose variability across SMGs in our data set may not have been sufficiently varied to identify the importance in SMGs.

The observation of the voxel importance pattern suggests that RT treatment planning that limits just the mean dose to the PGs may have limited reproducible efficacy in reducing the risk of severe long-term xerostomia. Alternatively, given the way we currently treat patients, limiting the RT dose to the superior half of each PG, or maintaining some portion of the PGs below the recovery dose threshold, may offer a more effective strategy.

Additional nondose or clinical factors can further modify the risk of xerostomia and its recovery.[25] In the present analysis, patient factors such as patient age and race, smoking status, and additional treatment factors such as concurrent chemotherapy influence the risk of xerostomia recovery. Not surprisingly, as the xerostomia injury and recovery centered on CTCAE grading, the effect of the different physicians grading could also be seen. This further underscores the limitations of a provider-based xerostomia measure and its use in the development of prediction models if it is not considered.

Several additional limitations need further discussion. First, we acknowledge the subjectivity of CTCAE scale. The dichotomized xerostomia outcome might lack the variation of magnitude of recovery and reduce the statistical power to detect the relationship between the dose and patient outcome. However, this limitation was mitigated by (1) all data were prospectively collected at the time point of care of each patient; and (2) the same attending examined the single patient each time followed the same criteria. Future studies would benefit from using objectively assessed xerostomia (salivary volumes). Second, 225 out of 942 learned weight of voxel dose features were positive (though relatively small in magnitude), which means an increase in dose in these regions will increase the probability of recovery. It is possible that this indicates that additional sparing of important regions is possible with an increase in dose to these positive voxels. However, it might also be noise from the relatively small sample size (N = 146) compared with the large number of voxels (N = 942) put in the prediction model. Third, it is important to understand that current protocol dose limits are present in the dose patterns delivered to patients in the data set, and thus are controlled for and suppressed in the resulting influence patterns. The findings are specific to the present recovery cohort and affected by the high dose in SMG and limited dose variation in the cohort. It further underscores the importance of an information infrastructure whereby a diverse data set is collected, curated, and accounted for to limit any bias with the prediction model. Within our information infrastructure, the ability to further validate this prediction model with ongoing accrued treated patients will be an important future strategy.

Conclusions

This study demonstrates how spatial dose varied across salivary glands and the spatial voxel dose pattern influenced the xerostomia recovery. Given the variation of radiosensitivity of different portions of an organ and the complexity of function of salivary glands, a simple mean dose constraint is unreliable to predict the probability of recovery from xerostomia. As we capture the different dose distribution and voxel importance pattern in injury and recovery cohort, the treatment planning guideline should set a lower constraint to salivary glands to prevent injury and preserve recovery ability. Methodologies such as the one described will help us uncover the influence of dose patterns on outcomes offering insight into new RT planning strategies to optimize the therapeutic ratio.

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Supplementary data

Supplementary material for this article can be found at https://doi.org/10.1016/j.adro.2019.08.009.

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