# Machine Learning Methods Uncover Radio-Morphologic Dose Patterns in Salivary Glands that Predict Xerostomia in Head and Neck Cancer Patients

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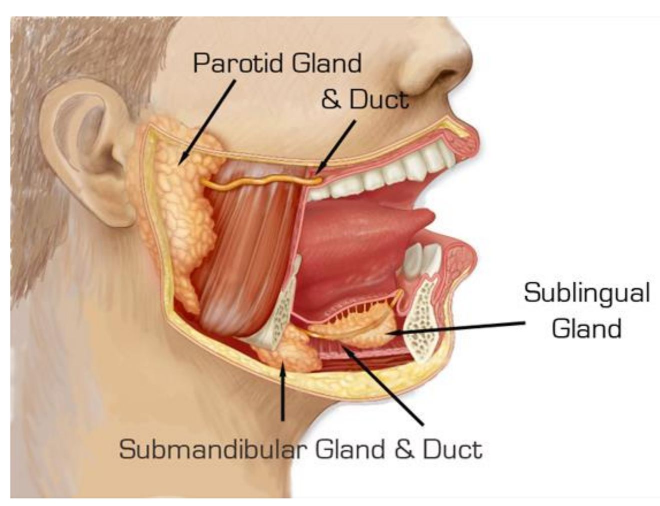
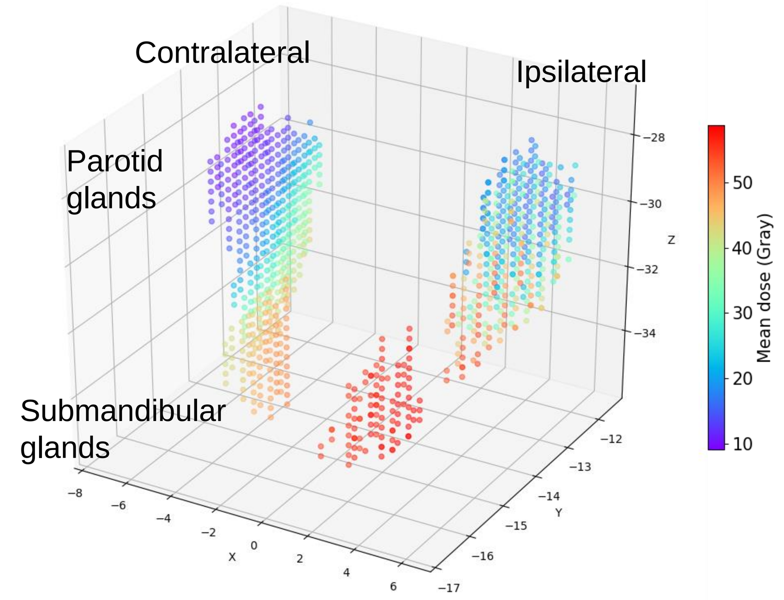
## Purpose/Objectives

- To understand the spatial dependence of radiation dose in the salivary glands on the influence of acute xerostomia injury and later recovery of salivary function
- To investigate appropriate machine learning methods to uncover spatial importance patterns given the high correlation of radiation dose metrics




**Mean Voxel Dose – All Patients (deformed to atlas)**




## Materials/Methods

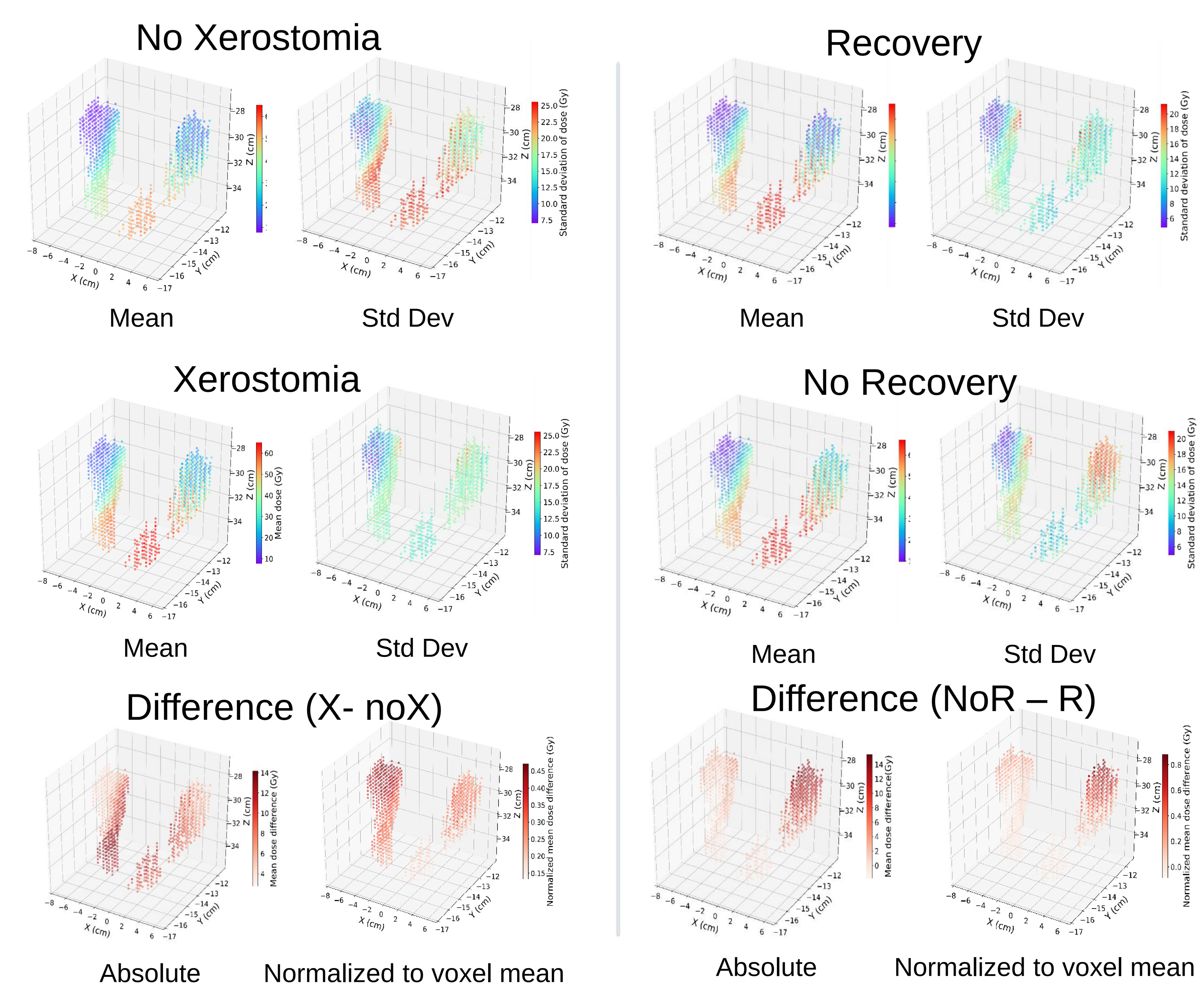
- **Acute xerostomia** is defined as patients reaching CTCAE Grade 2 within 3 months post-treatment
- **Recovery** is defined as those patients with acute xerostomia that reduced to CTCAE Grade 1 or less at 18 months
- Radiomorphology was used to map 961 dose voxels in the parotid and submandibular glands from 427 head and neck patients to a standard patient atlas with mirroring to preserve ipsi- and contra-lateral relationships to the primary tumor
- Doses to each voxel were included as features in machine learning methods to investigate the influence of each voxel on both initial injury and later recovery of salivary function
- Voxel importance for logistic regressions are the feature weights. For random forest, voxel (or feature) importance was determined by the decrease in squared error during training.
- Clinical factors in table below were included in the models

| | | P-Values | |
|---|---|---|---|
| Predictor | Categories | Acute Xerostomia | Recovery |
| Age | Continuous | 0.77 | 0.55 |
| Gender | Male, Female | 0.61 | 0.9 |
| Race | Caucasian, African American, Asian/Pac Isl, Other | 0.24 | 0.9 |
| Physician | 1, 2, 3, 4, missing | 0.22 | 0.25 |
| Chemotherapy | Yes, No | <0.01 | 0.83 |
| HPV | Positive, Negative | <0.01 | 0.85 |
| Feeding Tube Use | Yes, No | 0.06 | 0.2 |
| Baseline Xerostomia | Grade 0, Grade 1, Grade >=2 excluded | <0.01 | 0.39 |
| T Stage | 0, 1, 2, 3, 4, missing | 0.89 | 0.76 |
| N Stage | 0, 1, 2, 3, missing | 0.11 | 0.06 |
| M Stage | Yes, No, missing | 0.51 | 0.63 |
| Tumor Site | Oral Cavity, Oropharynx, Nasopharynx, Other | <0.01 | 0.29 |

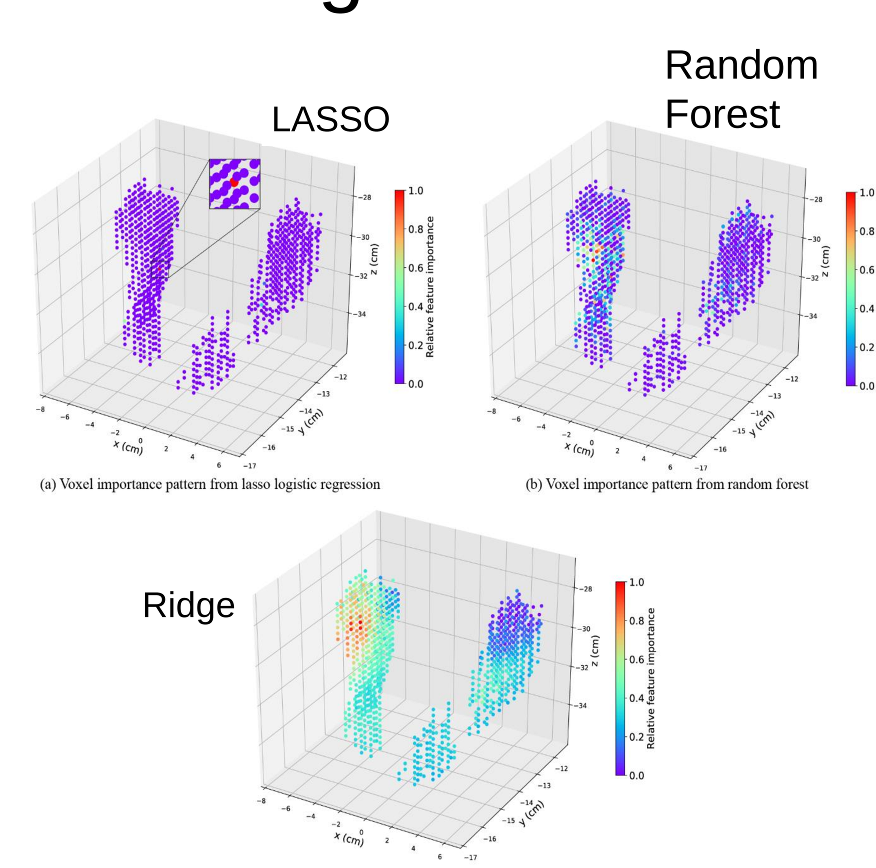
## Results

### Characteristics of the dose patterns

**Acute xerosotomia** | **Recovery**




### Selecting best method for **acute xerostomia**

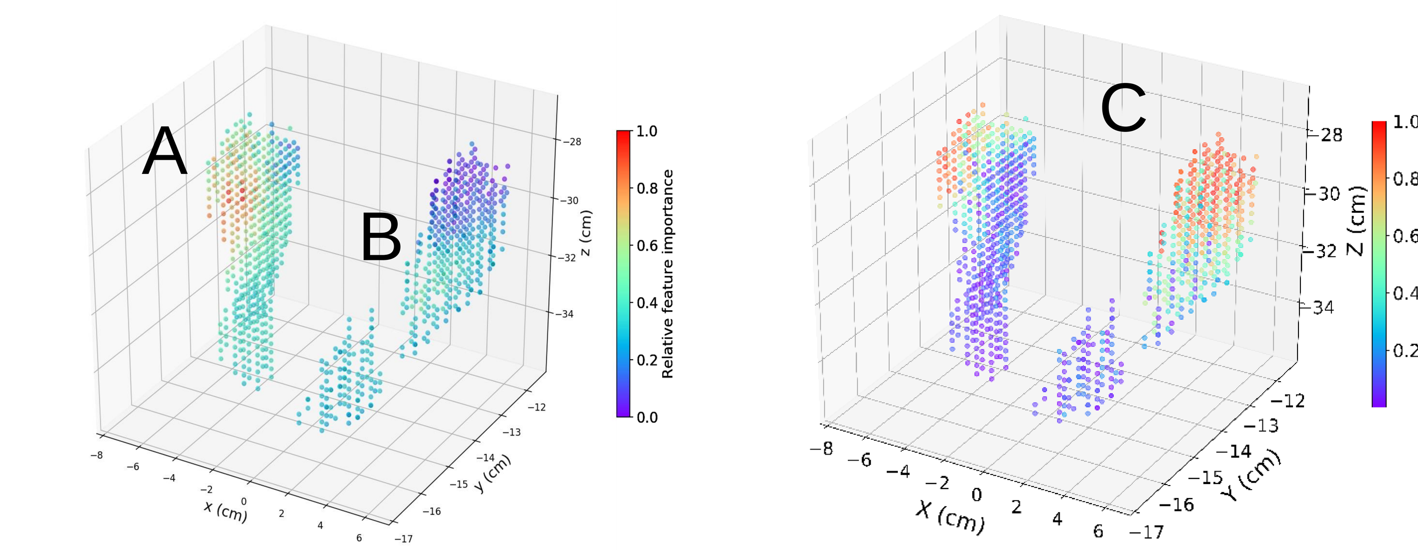



| Models | Data set (dimension: 427*961) |
|---|---|
| | AUC (10-fold cross-validation) Out-of-sample score |
| Ridge logistic regression | 0.70 ±0.04 |
| Lasso logistic regression | 0.67±0.04 |
| Random forest | 0.69±0.06 |

- LASSO tends to select a few features in the presence of high correlation and amplifies importance
- Random Forest highlights a few features, but noisy due to lower number of samples relative to the feature number
- **Ridge Logistic Regression** treats correlated variables as "equals" and presents an importance pattern worthy of interpretation

### Voxel Importance Pattern (Ridge)

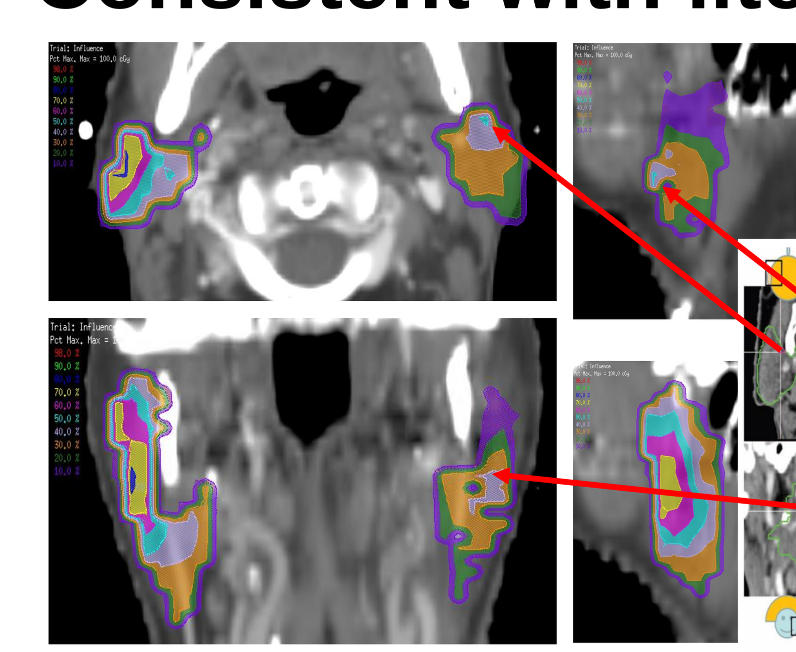
Acute xerostomia | Recovery



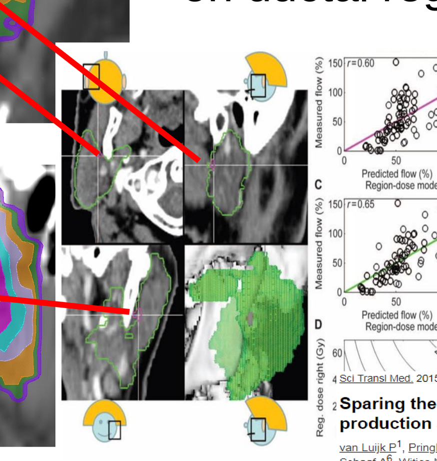

**Potential hypotheses**

A. The superior portion of the contralateral parotid is the last region to be able to spare (lowest mean dose). If a high dose, there is likely high dose everywhere else, increasing xerostomia.
B. Ductal region of ipsilateral parotid has high influence, where the superior portion has very low importance suggesting possible occlusion of duct or serial component of organ function related to injury. (See image below)
C. The superior (lower dose) portions of both parotids influence recovery whereas the higher dose regions have little influence. This suggests a lower dose threshold for preserving the ability to recover salivary function if injured.

### Consistent with literature



Influence pattern for acute xerostomia on the CT of the atlas showing influence on ductal region of ipsilateral parotid



Similar to region found in published study

Sparing the region of the salivary gland containing stem cells preserves saliva production after radiotherapy for head and neck cancer.

## Conclusions

- Influence patterns are different between acute xerostomia and recovery. The recovery pattern is symmetric where acute injury is asymmetric
- Machine learning methods have the potential to uncover new hypotheses that reflect spatial dependencies on radiation dose distributions
- Understanding spatial dependencies has the potential to aid in designing treatment plans best suited for individual patients.

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