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Mechanistic Modeling of Radiation Response of Parotid in Head and Neck Cancer Radiotherapy

Xingyi Zhao, MS[1]; Youfang Lai, PhD[1]; Todd R. McNutt, PhD[1]; Xun Jia, PhD[1]; Peter van Luijk, PhD[2]; Rachel B. Ger, PhD[1]
[1]Johns Hopkins University, [2]Medical Center of Affiliation

ABSTRACT

Radiation-induced xerostomia is a common and debilitating complication of head and neck radiotherapy caused by damage to the parotid glands. Conventional normal tissue complication probability models rely mainly on summary dose metrics and do not explicitly represent the gland's spatial organization or cellular recovery. We developed a three-dimensional voxel-based mechanistic model that simulates radiation damage and post-treatment regeneration of stem, progenitor, and acinar cell populations.

The model was evaluated using individualized dose distributions and longitudinal xerostomia assessments from 585 patients with baseline Grade 0 xerostomia. Radiation-induced cell depletion was modeled using the linear-quadratic formulation, while inter-fraction and post-treatment dynamics included cell proliferation, differentiation, and migration. Model parameters were optimized in two stages to separately characterize acute acinar-cell injury and long-term stem- and progenitor-driven recovery.

The mechanistic model achieved higher predictive performance than the conventional Lyman–Kutcher–Burman model across follow-up timepoints. Acute xerostomia was primarily governed by acinar-cell radiosensitivity, whereas long-term recovery was driven by stem-cell proliferation kinetics and preservation of the ductal region. These findings demonstrate that spatially resolved cellular modeling can improve xerostomia prediction while providing biologically interpretable insight into parotid injury and recovery.

INTRODUCTION

Radiation-induced xerostomia is one of the most common and debilitating complications of radiotherapy for head and neck cancer. Damage to the **parotid glands** can cause persistent dry mouth, dental caries, dysphagia, impaired speech, and a substantial reduction in quality of life. Current treatment planning commonly follows **QUANTEC** recommendations that constrain the mean parotid dose to **approximately 20–25 Gy**. However, mean dose treats the gland as a uniform organ and does not capture its complex spatial organization or the different biological roles of its cellular populations.

The parotid gland contains mature **acinar cells** that produce saliva and a **ductal network** containing **stem and progenitor** cells that support tissue regeneration. Acinar cells are highly radiosensitive and their depletion contributes to **early loss of salivary function**. In contrast, **long-term recovery** depends on the survival, proliferation, differentiation, and migration of regenerative cells. Previous studies have shown that irradiation of specific ductal subregions may lead to persistent dysfunction even when the overall mean dose remains within conventional limits.

To better represent these mechanisms, we developed a **three-dimensional voxel-based mechanistic NTCP model** that explicitly simulates stem, progenitor, and acinar cell populations throughout treatment and recovery. By linking local radiation dose to cellular damage and regeneration, the model provides a time-resolved and biologically interpretable framework for predicting xerostomia. Its performance was evaluated against the conventional **Lyman–Kutcher–Burman** model using longitudinal data from **585 patients** with head and neck cancer.

METHODS AND MATERIALS

This retrospective study included **585 head and neck cancer patients** with **Grade 0 xerostomia** at treatment initiation. Individualized 3D dose distributions and longitudinal toxicity assessments through Day 1,000 were analyzed.

The parotid gland was divided into **ductal and acinar-dominant regions** and discretized into voxels containing **stem**, **progenitor**, and **acinar** cells. Between radiation fractions, cell populations evolved through proliferation, migration, and lineage differentiation:

$$\frac{\partial N_i(x,t)}{\partial t} = \frac{ln2}{T_i} N_i + D_i \nabla^2 N_i + \sum_{j \neq i} k_{ji} N_j - \sum_{j \neq i} k_{ij} N_i$$

At each dose delivery, voxel-specific cell depletion was modeled using the linear-quadratic survival model:

$$N_i(x,t^+) = N_i(x,t^-)\exp[-\alpha_i d(x) - \beta_i d(x)^2]$$

Model parameters were optimized in two stages to characterize **acute acinar-cell injury** and **long-term stem- and progenitor-driven recovery**. Predictive performance was compared with the **Lyman–Kutcher–Burman** model using AUC.

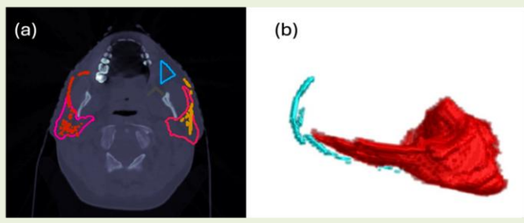

Figure 1. CT parotid contours and 3D parotid/duct visualization.

RESULTS

The voxel-based mechanistic model achieved **higher AUC** values than the Lyman–Kutcher–Burman model across follow-up timepoints. **Early xerostomia** was primarily driven by **acinar-cell radiosensitivity**, whereas **long-term recovery** depended mainly on **stem-cell proliferation** kinetics and **progenitor-cell response**. The **ductal region** emerged as **a critical regenerative niche** supporting sustained parotid recovery.

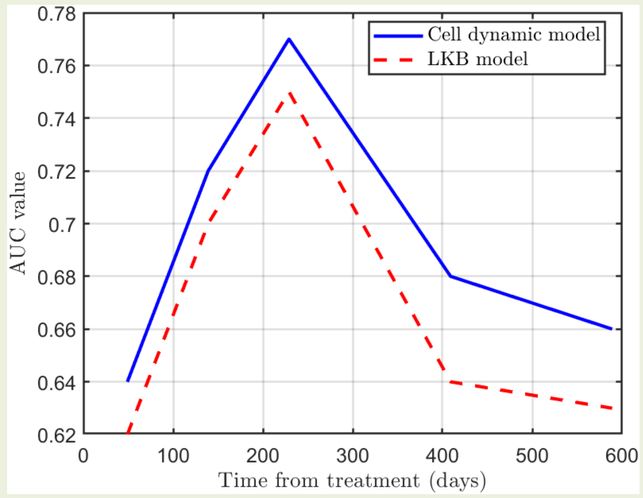

Figure 2. AUC comparison: mechanistic cell dynamic model vs. LKB.

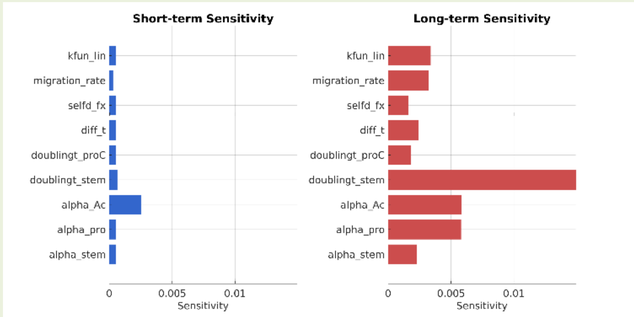

Chart 1. Sensitivity analysis highlights temporal drivers of response.

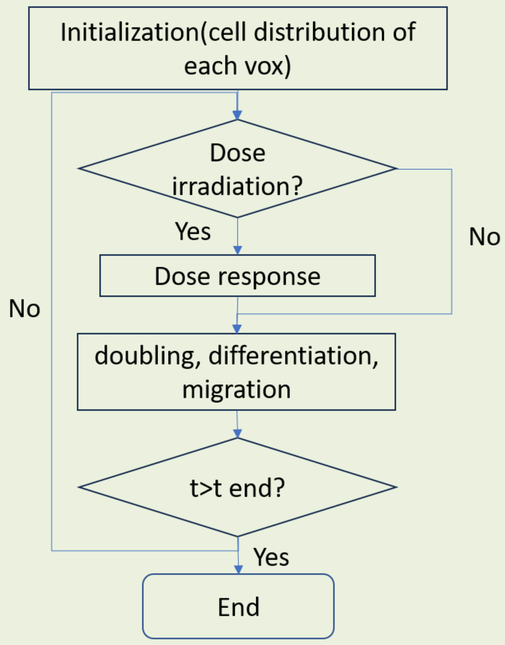

Figure3. Workflow of the voxel-based mechanistic model..

DISCUSSION

The voxel-based mechanistic model provides a **biologically interpretable description of parotid injury and recovery** following radiotherapy. Its improved performance over the LKB model suggests that spatial dose distribution and time-dependent cellular dynamics contain predictive information not captured by conventional mean-dose metrics.

The sensitivity analysis also revealed distinct temporal mechanisms. **Acute xerostomia** was mainly associated with **radiosensitive acinar-cell depletion**, whereas **long-term recovery** depended on **stem-cell proliferation** and **progenitor-cell response**. These findings support the importance of preserving the ductal stem-cell niche during treatment planning.

Predictive performance decreased at later follow-up times, likely because fewer patients had long-term toxicity assessments. Future work will incorporate **patient-specific parameters** and evaluate the framework for **adaptive and nonconventional** radiotherapy strategies.

CONCLUSIONS

The proposed voxel-based mechanistic model improved xerostomia prediction compared with the conventional LKB model by incorporating spatial dose distributions and time-dependent cellular dynamics. The results indicate that acute toxicity is primarily driven by acinar-cell radiosensitivity, while long-term recovery depends on stem and progenitor cell kinetics within the ductal region. This framework provides a biologically interpretable platform for personalized toxicity prediction and treatment planning.

Table 1. Fitted parameters

Parameter	Value
Stem C alpha	0.1
Progenitor C alpha	0.3
Acinar C alpha	0.3
Stem C beta	0.05
Progenitor C beta	0.15
Acinar C beta	0.15
Stem C doubling t	40day
Pro C doubling t	100day

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CONTACT

Xingyi Zhao, MS
Department of Radiation Oncology and Molecular Radiation Sciences
Johns Hopkins University School of Medicine
xzhao109@jh.edu

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