Development of a Multimodal Imaging Framework to Assess Mandibular Osteoradionecrosis in a Rat Model

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ABSTRACT

Purpose: Mandibular osteoradionecrosis (ORN) is a severe late complication of head-and-neck radiotherapy. Vascular compromise is thought to play a key role in ORN pathogenesis, yet early progression preceding bone failure remains poorly characterized. While computed tomography (CT) identifies advanced bone changes, recent clinical dynamic contrast-enhanced MRI (DCE-MRI) studies report increased vascular permeability in ORN, suggesting earlier sensitivity. This study aimed to develop and validate a multimodal imaging framework combining DCE-MRI, µCT, and cryo-fluorescence tomography (CFT) to link early perfusion and metabolic changes to structural damage in a rat model of mandibular ORN.

Methods: A multimodal imaging framework was designed incorporating µCT, DCE-MRI and CFT with cross-modality co-registration. µCT quantified bone volume and alveolar bone height. DCE-MRI data were denoised using higher-order total variation (HOTV) spatiotemporal filtering prior to pharmacokinetic modeling (Tofts) to extract transfer constant (K^{trans}), extravascular extracellular space volume fraction (v_e), and plasma volume fraction (v_p), along with semi-quantitative metrics including area under curve, peak enhancement, and wash-in/out slopes. Denoising performance was evaluated using signal-to-noise ratio (SNR), edge preservation metrics, and noise power spectrum (NPS). Model performance was assessed using coefficient of determination (R^2) and root mean square error (RMSE). Registration accuracy was quantified using target registration error (TRE).

Results: HOTV denoising reduced noise by 29% in the mandible, improving SNR from 14.7 dB to 17.8 dB while preserving 70% of edge information based on gradient magnitude ratios. In an adjacent 2D muscle region, NPS analysis demonstrated 9.7 dB noise suppression. Pharmacokinetic modeling produced stable fits within mandibular tissue (median R^2 = 0.88, RMSE = 0.006 mM). Representative TREs were 168 µm (µCT-to-CFT) and 217 µm (MRI-to-CFT).

Conclusion: This multimodal framework enables quantitative ORN assessment through integrated perfusion, metabolic, and structural imaging. HOTV denoising improves DCE-MRI data quality, enabling robust perfusion modeling to detect vascular compromise preceding morphological changes.

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Problem and Motivation

Head & Neck Radiotherapy — Normal tissue complications

Vascular Compromise — Detectable by DCE-MRI

ORN — Bone necrosis Rates between 2-20%[1]

- Head and Neck Squamous Cell Carcinoma (HNSCC) has an **annual incidence ~65,000 in the US[2];** with many being treated with external beam radiotherapy (EBRT)
- HNSCC patients are living longer (especially HPV+ tumors) leading to a higher cumulative risk for late normal tissue toxicities[2]
- **Osteoradionecrosis (ORN) is a severe late normal tissue toxicity of head and neck radiation therapy**
- **Goal:** detect vascular compromise *before* ORN structural damage is irreversible and correlate CT and MRI findings to Cryofluorescence Tomography for future surgical guidance methods
  - *Poster goal*: develop an imaging pipeline

Imaging Methodology

1. **T1 Mapping** — NLLS fit | 6 flip angles (5°, 10°, 15°, 30°, 40°, 50°)
2. **AIF Estimation** — Population modeled (n=8) bi-exponential decay
3. **HOTV Denoising** — Higher-order total variation denoising
4. **Tofts Modeling** — NTM (Extended Tofts) + LRRM (AIF-free)
5. **Tracking longitudinal CT metrics**

T1 Mapping

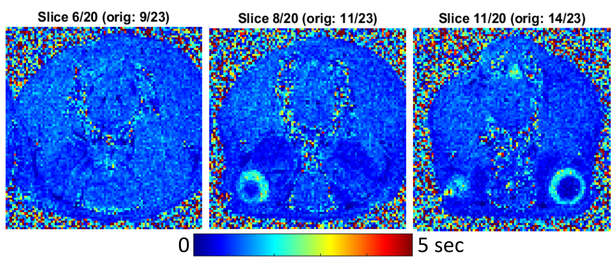

Fig 1. Representative T1 maps for three axial slices within the rat head.

- Pre-contrast T1 mapping performed using a Variable Flip Angle (VFA) method
- Nonlinear least squares (NLLS) fitting applied across all six flip angles, using the full SPGR signal equation
- Voxel-wise T1 maps generated at 0.313 mm isotropic resolution show valid T1 values in soft tissue (mean ROI in muscle = 2.01 +/- 0.27 seconds)

Population-based AIF

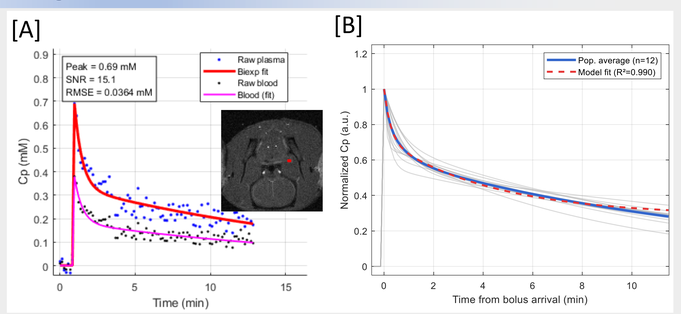

Fig 2. Arterial input function estimation. [A] Representative single animal AIF estimate with inset of drawn ROIs and [B] population modeled (n=8) AIF estimate using bi-exponential decay.

- Across 12 acquisitions between 8 animals, individual AIFs were time-aligned to bolus arrival, normalized, and averaged to derive a population-average AIF (Fig. 2)
- Bi-exponential model fit the curve with R^2 = 0.990 with a leave-one-out analysis R^2 of 0.919 +/- 0.065

HOTV denoising

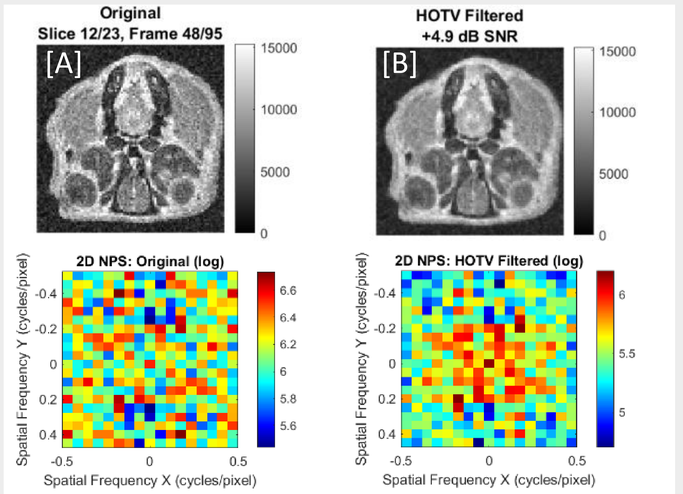

Fig 3. Higher order total variation denoising (HOTV). [A] First column: MR slice without HOTV (top) and its corresponding 2D noise power spectrum (NPS) (bottom). [B] Analogous with [A], but after HOTV.

- Denoises in space and time before pharmacokinetic modeling, using higher-order (second-order) total variation
- NPS plot post HOTV denoising displays fewer contributions from higher frequencies (edges of NPS plot) indicating removal of noise (Fig. 3)
- Preserves curve shape while suppressing high-frequency noise (Fig. 4): noise reduction confirmed by 2D NPS before and after filtering (+4.9 dB SNR)

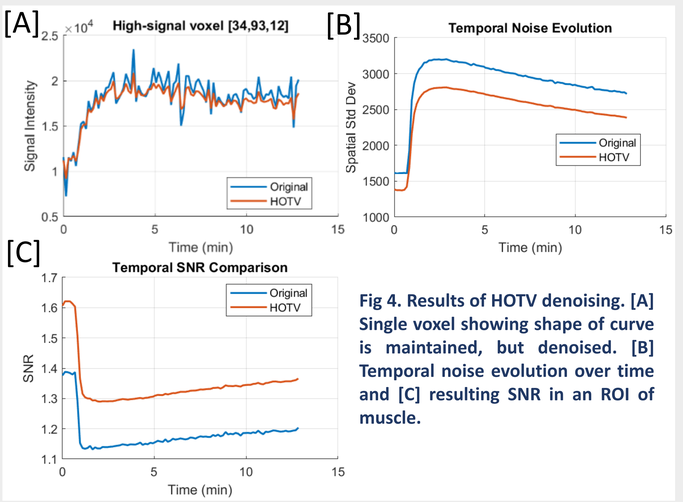

Fig 4. Results of HOTV denoising. [A] Single voxel showing shape of curve is maintained, but denoised. [B] Temporal noise evolution over time and [C] resulting SNR in an ROI of muscle.

Extended Tofts model output

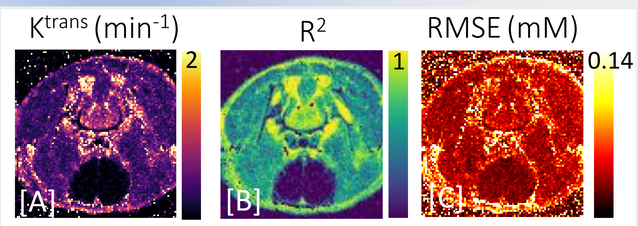

Fig 5. Voxel-wise pharmacokinetic modeling results. [A] K^{trans} map (min^{-1}) derived from the Extended Tofts Model, showing elevated transfer constants in peripheral soft tissue and vasculature with near-zero values in the brain, consistent with an intact blood-brain barrier. [B] R^2 goodness-of-fit map; high values in soft tissue and mandibular regions confirm reliable model convergence, while low values in brain and air are expected and excluded from analysis by R^2 thresholding. [C] RMSE map (mM); lower residuals in soft tissue confirm that concentration-time curves are well described by the model.

Baseline vascular permeability signature prior to radiation injury (Fig. 5):

A. K^{trans} distributions are visualized across brain, muscle, incisor pulp, and soft mandibular tissue

B. Goodness-of-fit maps confirm reliable model performance in regions of interest: $R^2 > 0.6$

C. Low RMSE in mandibular soft tissue regions of interest

Preliminary CT Results

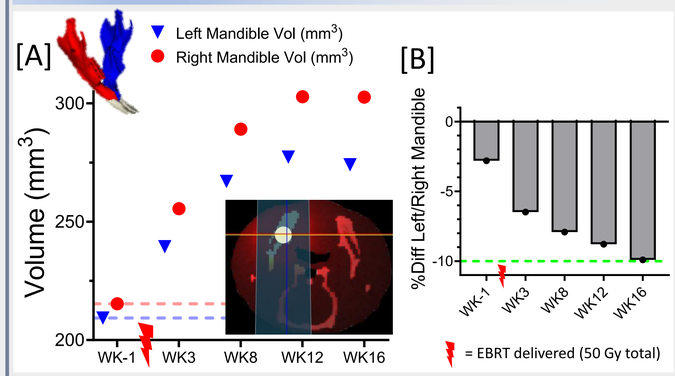

Fig 6. CT bone volume analysis for a single representative animal. [A] Bone volume differences between left and right mandible longitudinally tracked. Inset of single 10Gy fraction of a 50Gy plan performed during WK0 indicated by the red lightning bolt. [B] Percent bone volume difference between left and right mandible. Green dotted-line represent a 10% volume difference which may indicate ORN[3].

- Preliminary CT results for a single animal show early signs of ORN
- WK16 showing a 9.9% difference in bone volume from left to right mandible

Conclusions

- DCE-MRI quantifies vascular permeability within the incisor pulp and mandibular marrow
- HOTV denoising significantly improves SNR (+4.9 dB SNR) while preserving anatomical edges, enabling reliable pharmacokinetic modeling
- Strong goodness-of-fit (R^2, RMSE) confirms the Extended Tofts Model accurately characterizes gadolinium kinetics in mandibular soft tissue

References

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