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Clinical Validation of IVIM Parameter Estimation for Treatment Response Assessment in Head-and-Neck Cancer Radiotherapy

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ABSTRACT

Purpose
To clinically validate an implicit neural representation (INR)-based fitting approach for IVIM diffusion MRI parameter estimation against conventional non-linear least squares (NLLS), and to evaluate a robustness metric (R-index, ≈2fp + Dt) designed to mitigate collinearity and reduce estimation uncertainty, in head-and-neck cancer patients imaged before and during radiotherapy.

This leverages IVIM-derived biomarkers to characterize individual treatment response and support biology-driven adaptive radiotherapy decision-making.

INTRODUCTION

- IVIM diffusion MRI separates tissue diffusion (Dt) from microvascular perfusion (fp), offering biomarkers for treatment response beyond conventional ADC.
- Conventional NLLS fitting is unstable: it systematically overestimates fp and underestimates Dt due to parameter collinearity and noise sensitivity.
- INR offers a continuous, noise-robust alternative. This work provides its first clinical validation and evaluates the R-index as a robust composite biomarker.

METHODS AND MATERIALS

- **Patients & Imaging**
  Six head-and-neck cancer patients underwent IVIM diffusion MRI before and during radiotherapy (~1-month interval).
- **Parameter Estimation**
  ADC and IVIM parameters — perfusion fraction (fp), tissue diffusion coefficient (Dt), and R-index (≈2.5fp + Dt) — were estimated with both INR and NLLS.
- **Analysis**
  Parameters were compared between time points; relative changes (%) computed; individual responses interpreted from synergistic patterns of parameter change.

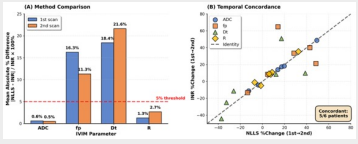

Figure 1. Method comparison and temporal concordance. (A) Mean absolute % differences between NLLS and INR: systematic bias in fp (11.3–16.3%) and Dt (18.4–21.6%), while ADC (<1%) and R-index (<3%) stay below the 5% threshold (red dashed). (B) %change from pre- to mid-treatment; points near identity indicate concordant trends (5/6 patients).

RESULTS

- **Systematic inter-method bias**
  Vs. NLLS, INR consistently yielded lower fp (−13% to −65%) and higher Dt (+14% to +49%), consistent with prior digital phantom results.
- **R-index and ADC are robust**
  R-index showed mean inter-method differences of 1.3% and 2.7% at the 1st and 2nd scans (well below 5%); ADC differed by <2%.
- **Concordant temporal trends**
  Both methods captured consistent directional change in 5/6 patients across all parameters.
- **Composite biomarkers need caution**
  An ADC increase (+17%) co-occurred with rising Dt and fp in one patient, while an ADC decrease (−11%) occurred despite increased Dt due to marked fp reduction in another — identical ADC trends, different biology.

Table 1. Treatment response patterns and IVIM biomarker interpretation in six H&N cancer patients. % change at mid-treatment vs. pre-treatment. Cases with ambiguous patterns (patients 4, 5) require correlation with anatomical imaging and

Pt	ΔADC	ΔDt	Δfp	Response	IVIM biomarker interpretation
1	+17%	+8%	+8%	Favorable	ADC↑ with definite Dt↑ indicates reduced cellularity and true diffusion-driven response.
2	−11%	+10%	−13%	Indeterminate	Dt↑ suggests partial effect, but conflicting ADC↓/fp↓ — intermediate pattern, neither clear responder nor non-responder.
3	+18%	−11%	+40%	Good response	Meaningful ADC↑ with large fp↑ favors partial-to-good response; discrepant Dt adds microstructural complexity.
4	+14%	−41%	+39%	Partial	Moderate ADC↑ and large fp↑ (vascular remodeling), but paradoxical Dt↓ — response not unequivocally complete.
5	−4%	−44%	+65%	Atypical	Marked Dt↓ (restriction) with large fp↑ — incomplete response vs. post-radiation inflammation/fibrosis.
6	+49%	+51%	+21%	Strong responder	Large diffusion↑ reflects substantial cell death; fp↑ indicates favorable vascular remodeling.

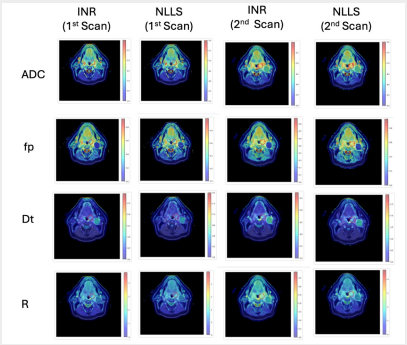

Figure 2. Representative IVIM parameter maps from one H&N cancer patient, pre- (1st) and mid-treatment (2nd). Columns: INR vs. NLLS at each timepoint; rows: ADC, fp, Dt, R-index. ADC and R-index show high inter-method agreement; fp is systematically lower and Dt higher with INR; both methods show similar spatial patterns and temporal evolution.

DISCUSSION

- **INR corrects NLLS bias**
  INR corrects the systematic NLLS biases (fp overestimation, Dt underestimation), enabling more accurate quantification of IVIM-derived imaging biomarkers for radiotherapy response evaluation.
- **Disentangle diffusion vs. perfusion**
  Similar changes in composite metrics (ADC, R-index) can arise from distinct combinations of diffusion and perfusion alterations — underscoring the need to interrogate individual IVIM parameters, not ADC alone.
- **R-index outperforms ADC**
  The R-index (R≈2.5f+Dt), validated through mathematical modeling and simulation [1], showed <3% mean inter-method difference, outperforming ADC in robustness while remaining clinically interpretable.
- **Impact**
  Together these establish INR and R-index as reliable, clinically applicable tools for quantitative IVIM cancer imaging biomarker development.

CONCLUSIONS

- This first clinical validation confirms the superior accuracy of INR-based IVIM parameter estimation.
- Interpreting composite biomarkers (ADC, R-index) requires disentangling diffusion and perfusion contributions.
- Future studies correlating IVIM parameter dynamics with clinical outcomes are warranted to establish prognostic value.

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