Biologically Adaptive Dose Compensation Based on Tumor Radiosensitivity Derived from In-Treatment Volume Dynamics

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ABSTRACT

Purpose:
Adaptive radiotherapy is mainly guided by geometric changes, although patient-specific tumor response may alter biological dose adequacy. We developed a biologically adaptive radiotherapy (BART) framework that incorporates tumor response derived radiosensitivity scaling into BED based dose compensation.

Methods:
Weekly CBCT derived tumor volumes in head and neck cancer were analyzed using latent class mixed modeling and a mechanistic ODE-LQ model. A radiosensitivity scaling factor $\boldsymbol{S}$ was estimated with α/β fixed at 10 Gy, and BED deficits were compensated using TPS-based replanning.

Results:
The poor response subgroup showed reduced radiosensitivity scaling ($\boldsymbol{S}$ =0.872), resulting in an approximately 13% PTV BED deficit under standard physical dose. BART compensation reduced target BED-DVH deviations to within $\pm$1% of the reference plan, while OAR physical dose increases remained within clinical constraints.

Conclusion:
Tumor response derived radiosensitivity scaling can quantify response related BED deficits and guide deliverable TPS-based BED compensation.

INTRODUCTION

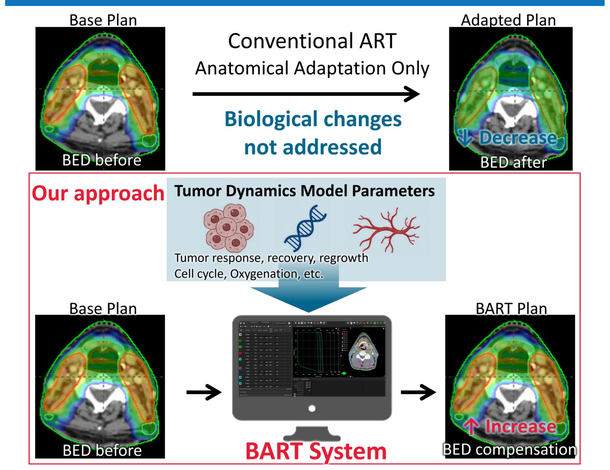

Figure 1. BART concept for biology-informed BED compensation.

Adaptive radiotherapy (ART) is widely used to compensate for anatomical changes during radiotherapy. In head-and-neck cancer, weight loss and contour changes often require frequent CBCT-based IGRT and adaptive replanning.

However, ART is mainly geometry-driven. Tumor volume changes during treatment may reflect biological processes such as regrowth and clearance of damaged cells [1]. These factors are not directly incorporated into conventional physical dose evaluation.

Patient-specific estimation of multiple radiobiological parameters from CBCT-derived volume data alone is unstable. To improve robustness, we used LCMM-based trajectory classification and a constrained ODE-LQ model. This approach summarizes tumor response as class-level radiosensitivity scaling.

To develop a TPS-based BART framework that quantifies response related BED deficits and compensates them using deliverable treatment plans.

METHODS & MATERIALS

Longitudinal GTV assessment and LCMM classification

This study included 96 patients with hypopharyngeal or oropharyngeal squamous cell carcinoma treated with IMRT between 2010 and 2021. We focused on the primary GTV and excluded nodal lesions to reduce heterogeneity in response dynamics. CBCT images were acquired weekly during radiotherapy, with the first CBCT defined as day 0. Each CBCT was rigidly registered to the planning CT. The GTV-primary was delineated at each time point with reference to the planning CT GTV. Tumor volume was normalized to the GTV volume measured on the first treatment day (day 0).

Longitudinal changes in normalized GTV volume were analyzed using latent class mixed modeling (LCMM) [2]. Models with two to four latent classes were evaluated. A two-group solution was selected because models with three or four groups produced small subgroups. This study aimed to characterize robust group level response patterns rather than individual level prediction.

Mechanistic ODE-LQ modeling of tumor response

To interpret the trajectories identified by LCMM, we used a three compartment ODE model with viable, lethally damaged, and removed tumor components. The radiation effect was represented as volume transfer from the viable compartment to the damaged compartment using the LQ dose effect scaled by S.

$$\frac{dV_s}{dt} = \lambda V_s\left(1-\frac{V_s}{K}\right) - S\{\alpha d(t) + \beta d(t)^2\}V_s \quad (1)$$

$$\frac{dV_d}{dt} = S\{\alpha d(t) + \beta d(t)^2\}V_s - \mu_{\mathrm{eff}}(t)V_d \quad (2)$$

$$\frac{dV_r}{dt} = \mu_{\mathrm{eff}}(t)V_d \quad (3)$$

Here, V_s , V_d , and V_r represent viable, lethally damaged, and removed tumor components. The term $S\{\alpha d(t) + \beta d(t)^2\}$ represents the LQ dose effect. S summarizes differences in effective radiation response between groups under fixed 2 Gy fractionation. With α/β constrained near 10 Gy, the remaining model parameters were estimated from the LCMM trajectories.

Mid-course replanning and BART dose compensation

BART dose compensation was evaluated in 13 patients prescribed 70 Gy in 35 fractions. After 40 Gy, the remaining 15 fractions were replanned using our TPS based BART framework [3,4] to compensate for the S -derived BED reduction. The goal was to match the PTV BED distribution of the reference plan. Target compensation was evaluated using PTV BED DVH, and OARs were evaluated using physical dose DVH .

RESULTS & DISCUSSIONS

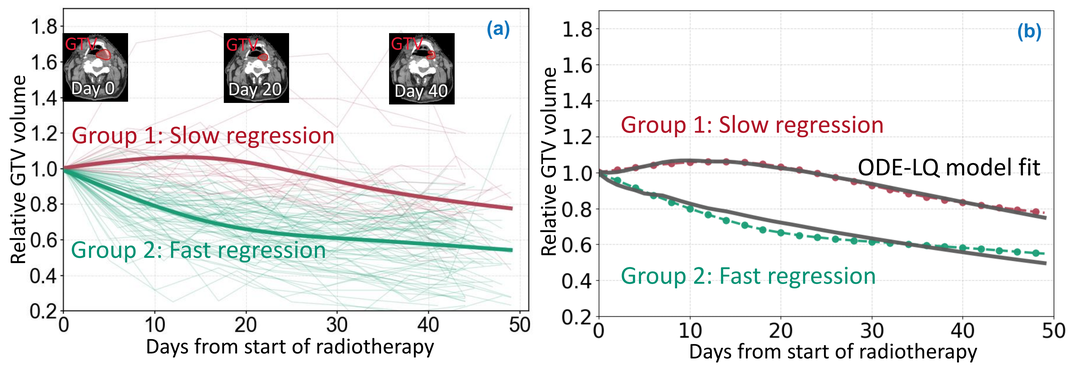

Table 1. ODE model fitting results and estimated parameters from LCMM group trajectories. Parentheses indicate 95% CIs. Parameter definitions: $\boldsymbol{S}$, radiosensitivity scaling; λ, proliferation rate; μ_{eff}, effective clearance rate of damaged tumor; K, carrying capacity.

Group	RMSE	MAE	$\boldsymbol{S}$	λ	μ_{eff}	K
1	0.010	0.008	**0.872** (0.869-0.882)	0.058 (0.057-0.065)	0.013 (0.013-0.014)	1.83 (1.82-1.84)
2	0.035	0.031	1.038 (1.014-1.068)	0.010 (0.001-0.015)	0.013 (0.012-0.015)	2.31 (2.20-2.38)

Figure 2. LCMM grouping and ODE model fitting of GTV trajectories. (a) GTV trajectories of all 96 patients with LCMM group means. (b) ODE model fit to LCMM group trajectories.

Tumor trajectory groups and ODE model fit

LCMM separated the CBCT derived tumor volume trajectories into two regression groups. Group 1 showed slower regression, and Group 2 showed faster regression. The ODE model reproduced the LCMM trajectories with low fitting errors, supporting the use of group level trajectories for stable mechanistic interpretation (Figure 2, Table 1). $\boldsymbol{S}$ was lower in Group 1 than in Group 2, with estimated values of 0.872 and 1.038, respectively. Group 1 also showed a higher proliferation related parameter λ, while μ_{eff} was similar between groups (Figure 2).
Thus, the difference in tumor regression was explained mainly by effective radiation response and proliferation related dynamics. This finding is important for BART because the trajectory difference can be translated into a model-based BED difference. CBCT volume dynamics were therefore not used only for geometric monitoring but were converted into interpretable parameters for biological dose compensation.

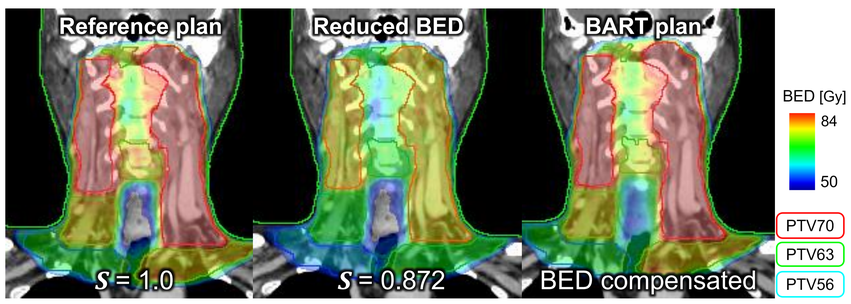

Figure 3. Representative PTV BED distributions before and after BART compensation.

Table 2. PTV BED compensation and OAR physical dose evaluation.

	$\Delta\mathcal{B}_V$(%)	No compensation	BART plan	OAR	Constraint [Gy]	ΔDose **(BART)**
PTV	$B_{98\%}$	-12.5 ± 0.2	$\mathbf{-0.1 \pm 0.8}$	**Parotid**	$D_{mean} < 26$	$+2.6 \pm 1.2$
	$B_{95\%}$	-12.6 ± 0.2	$\mathbf{+0.1 \pm 0.6}$	**Mandible**	$D_{2\%} < 35$	$+4.3 \pm 1.2$
	$B_{50\%}$	-12.6 ± 0.2	$\mathbf{+0.4 \pm 0.4}$	**Spinal cord**	$D_{max} < 46$	$+4.4 \pm 0.9$
	$B_{2\%}$	-12.6 ± 0.1	$\mathbf{+0.7 \pm 0.2}$	**Brainstem**	$D_{max} < 54$	$+3.8 \pm 0.6$

BART compensation and OAR evaluation

Without compensation, the reduced S produced an approximately 13% decrease in PTV BED. BART compensation reduced PTV BED DVH deviations to within $\pm$1% of the reference values (Figure 3, Table 2). OAR physical doses increased after replanning, but all evaluated metrics remained within clinical constraints (Table 2).
These results indicate that response related BED reduction can be translated into a TPS based compensation plan. The value of BART is not uniform dose escalation, but spatial compensation of biological dose reduction estimated from tumor response. This supports the role of BART as a TPS based method for spatially compensating response related BED reduction, rather than applying uniform dose escalation.

CONCLUSIONS

Tumor response derived radiosensitivity scaling quantified BED reduction in the slow regression group. TPS based BART compensated the PTV BED reduction to within $\pm$1% while maintaining OAR doses within clinical constraints. This approach adds biological response information to conventional geometry driven ART.

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