Forecasting Individual Patient Responses to Radiotherapy with a Dynamic Carrying Capacity Model

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Introduction

- Current clinical practice primarily considers tumor stage, primary site, and gross tumor volume when making decisions about radiotherapy (RT) dosage and fractionation.
- This does not consider patient-specific tumor and host factors that may be described by a tumor carrying capacity (K) and the previously described proliferation saturation index[1].
- Traditionally, RT effect has been modeled as direct tumor cell death seen through tumor volume reduction.
- We introduce a new model to investigate effects of RT on the tumor microenvironment that hypothesizes that each RT dose reduces the tumor carrying capacity.

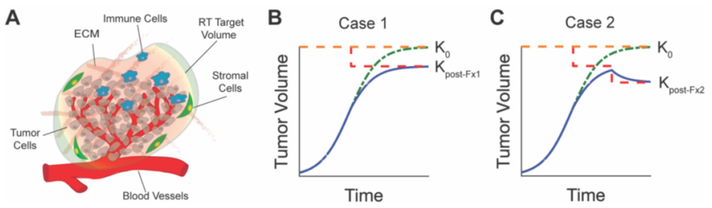

Figure 1. A Depiction of the tumor and its microenvironment, showing non-tumor components that may be caught by the RT target volume. **B-C** Tumor growth is modeled as logistic growth and the effect of RT is modeled as an instantaneous reduction in the carrying capacity. There are two possible cases: **B** Case 1: the carrying capacity after a given RT fraction can be greater than the tumor volume at the time of that dose, leading to slowed tumor growth or **C** Case 2: the carrying capacity after an RT fraction can be less than the tumor volume at the time of that RT dose, leading to tumor volume reduction.

Methods and Models

Logistic growth of tumor volume:

$$\frac{dV}{dt} = \lambda V\left(1 - \frac{V}{K}\right), \quad \lambda \text{ is tumor growth rate [day}^{-1}\text{], V is tumor volume [cc], K is tumor carrying capacity [cc].}$$

Instantaneous reduction in carrying capacity:

$$K_{post\ RT} = K_{pre\ RT} - \delta \cdot K_{pre\ RT}, \quad \delta \text{ is the carrying capacity reduction fraction that ranges between 0 (no reduction) and 1 (100% reduction of K).}$$

Table 1: Description of patient data

Cohort size	17 patients at Moffitt Cancer Center + 22 patients at MD Anderson Cancer Center
Primary Sites	Base of tongue, gum, oral cavity, oraopharynx, soft palate, tongue, tonsil
Tumor stage	T1-T4, no metastatic disease
Treatment approach	66-70 Gy in 2-2.12 Gy daily fractions or with accelerated fractionation. Patients also received concurrent chemo or cetuximab.
Biomarker used to assess model	Tumor volumes derived from treatment planning CT, and CBCT prior to each RT fraction.

Model Calibration

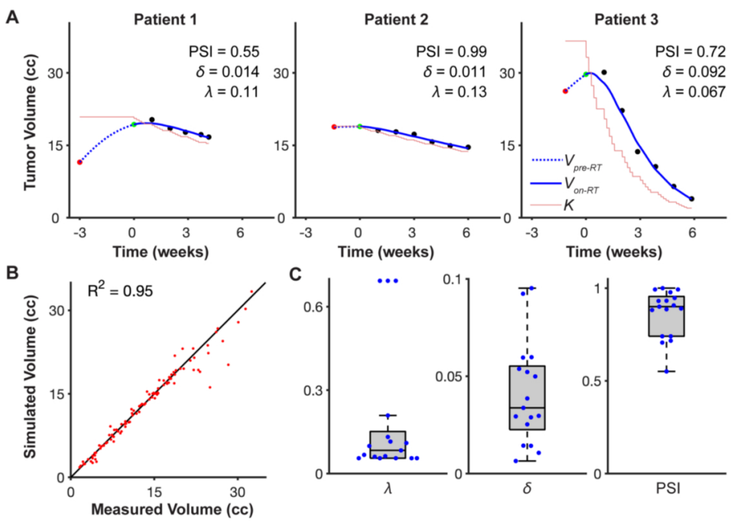

Figure 2. Model fit results for MCC cohort. **A** Representative fitting results for three patients demonstrating the rich variety of response dynamics that the model can capture. The red dots indicate the tumor volume at the time of treatment planning; green dots indicate tumor volumes at the start of RT; black dots indicate weekly tumor volumes during RT; blue curves are the model fits; red dashed lines are the tumor carrying capacity. **B** Correlation of simulated volumes to the measured tumor volumes for all 17 patients. Red dots indicate individual weekly time points and the black line has a slope of 1. The R^2 value shows the degree of correlation to this line and thus the accuracy of the simulations. **C** Box plots showing parameter distributions across all patients. (PSI = V_0/K_0; i.e. how close the initial tumor volume is to the carrying capacity)

Forecasting Pipeline

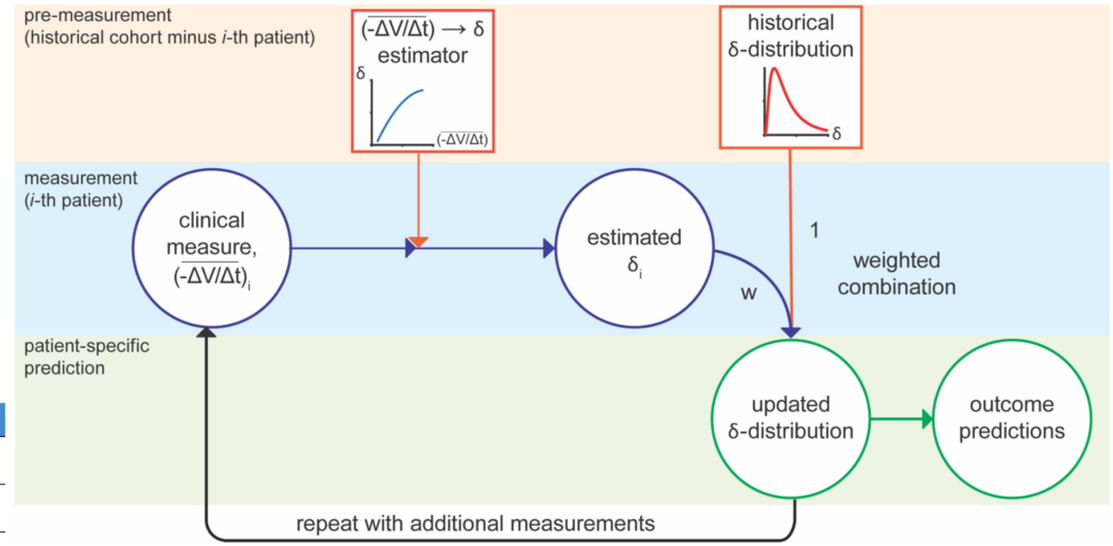

Figure 3. Flowchart representation of the forecasting pipeline. The pipeline is divided into three phases: pre-measurement based on the historical cohort (yellow), measurements for the *i*-th patient (blue), and patient-specific predictions (green). The squares represent information learned from the training cohort; circles represent information measured or calculated for an individual patient. The estimated δi is combined with weight w relative to a weight of 1 at which the historical δ-distribution is considered. The entire prediction pipeline can be repeated with the additional measurements from the patient.

Predicting Outcomes

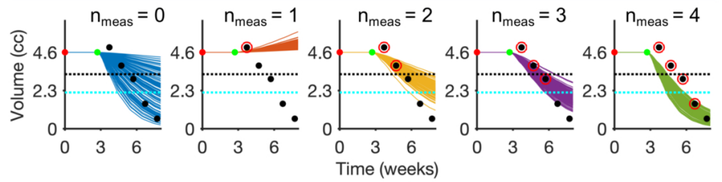

Figure 4. Representative spaghetti plots of tumor volume prediction simulations. 100 prediction simulations for patient 10 including 0–4 weekly volume measurements red circles around the black dots indicate measurements that were considered in making the predictions; black dashed lines indicate the cutoff for prediction of locoregional control; the cyan dashed lines indicate the cutoff for prediction of disease-free survival.

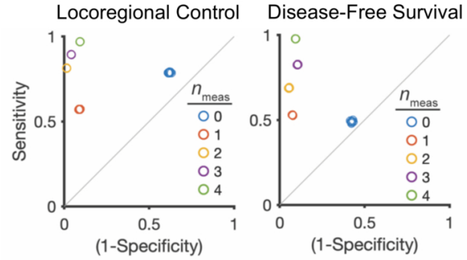

Figure 5. Receiver operator curve plots using 10 simulations (of 500 predictions each) to predict: locoregional control and disease-free survival with 0-4 weekly volume measurements included.

Conclusions

- The model fit data from MCC with a single λ value with high accuracy (R^2 = 0.95). Model analysis revealed that growth rate is not patient specific.
- This model fit the MDACC data with high accuracy (R^2 = 0.98), demonstrating transferability of λ.
- The forecasting method predicts patient-specific outcomes with sensitivity and specificity with the inclusion of just a few on-treatment volume measurements.

Future Directions

- The current patient data is heterogenous. Ongoing trial NCT03656133 at MCC will provide data from a homogenous cohort with controlled treatment conditions, allowing for rigorous analysis of the parameters and predictive power of the models.

References & Acknowledgments

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