Modeling of radiation therapy and radiosensitizing agents in tumor xenografts

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Introduction

We introduce a pharmacodynamic model that describes the tumor volume evolution during and after treatment with radiation and radiosensitizing agents. A key contribution is the inclusion of a long-term radiation effect, which allows the model to describe distinct tumor behaviors including tumor eradication and tumor regrowth with different growth rates. The model also accounts for the effects of combining radiation therapy with radiosensitizing treatment. The model was fitted to data from xenograft experiments using a clinically-relevant administration schedule.

Pharmacodynamic Tumor Model

Tumor volume data were generated in FaDu xenograft mouse models. Animals were divided into the following four groups with N = 9 animals per group: vehicle, radiation (2 Gy), and radiation (2 Gy) and radiosensitizer (25 mg/kg or 100 mg/kg). Animals received treatment five days a week for six weeks.

A pharmacodynamic tumor model was adapted from one of our previously-published models [1,2]. A short-term radiation effect is described by allowing lethally irradiated cells up to one more cell division before apoptosis. Long-term radiation effects are described by an irreversible inhibition of the tumor growth rate. The radiosensitizing agent was assumed to stimulate both processes.

Model Equations

The model is given by the following system of differential equations

\[
\begin{align*}
\frac{dV_1}{dt} &= k_g \exp(-\alpha IR_{Tot}) V_1 - k_k V_1 - \sum F(D_i,C_i) \delta(t - t_i) V_1 \\
\frac{dV_2}{dt} &= k_h V_1 + k_k U_1 + k_k U_2 - k_k V_2 \\
\frac{dV_3}{dt} &= k_k V_1 - k_h V_3 \\
\frac{dU_1}{dt} &= \left( 1 + \alpha C \right) \sum D_i \delta(t - t_i) \\
\frac{dU_2}{dt} &= 2k_g U_1 - k_k U_2
\end{align*}
\]

where \(k_g\) is the growth rate, \(k_k\) the kill rate, \(\alpha\) and \(\beta\) the parameters associated with short- and long-term radiation effects, respectively, and \(a\) and \(b\) are pharmacodynamics parameters associated with the radiosensitizer. The function \(F\) describes the fraction of irradiated cells that are transferred from \(V_1\) to \(U_1\) during each instance of irradiation. \(F\) is given by

\[
F(D,C) = 1 - \exp\left[-(1 + b C) \beta D\right]
\]

Summary

A tumor model was developed that:

- Describes the effects of radiation and radiosensitizer treatment on tumor volume
- Captures long-term tumor dynamics including tumor eradication and tumor regrowth with different rates
- Can be used to predict tumor eradication (Tumor Static Exposure)

Tumor Static Exposure

The calibrated tumor model can be used to predict which radiation doses and radiosensitizer exposures that lead to tumor eradication [1,2]. This occurs when the long-term radiation effect inhibits \(k_k\) to a value below \(k_k\). The net growth rate \(k_g - k_k\) will then be negative and the tumor will shrink. The combinations of total radiation doses and concurrent plasma concentrations of the radiosensitizer that will lead to tumor regression is shown in the figure below (green area).

When radiation therapy is given alone, a total dose of 120 Gy predicted to lead to tumor eradication in a typical individual.

When radiation therapy is preceded by radiosensitizing treatment (100 mg/kg), the total radiation dose needed for tumor eradication is decreased to 30 Gy.

References


Individual Fit

The tumors were modeled using a mixed-effects approach [3]. Between-subject variability was accounted for in initial tumor volume, and both the short- and long-term radiation effects. Examples of individual fits for each treatment arm are shown below.

The estimated tumor doubling time was 5 days. The model predicts that each fraction of 2 Gy kills 15% of the proliferating cells. If radiation is preceded by radiosensitizing treatment (100 mg/kg) 25% of the proliferating cells are killed.