

A model for low-grade glioma tumor growth and response to chemotherapy or radiotherapy

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This work is now published in Clinical Cancer Research: Published OnlineFirst July 3, 2012

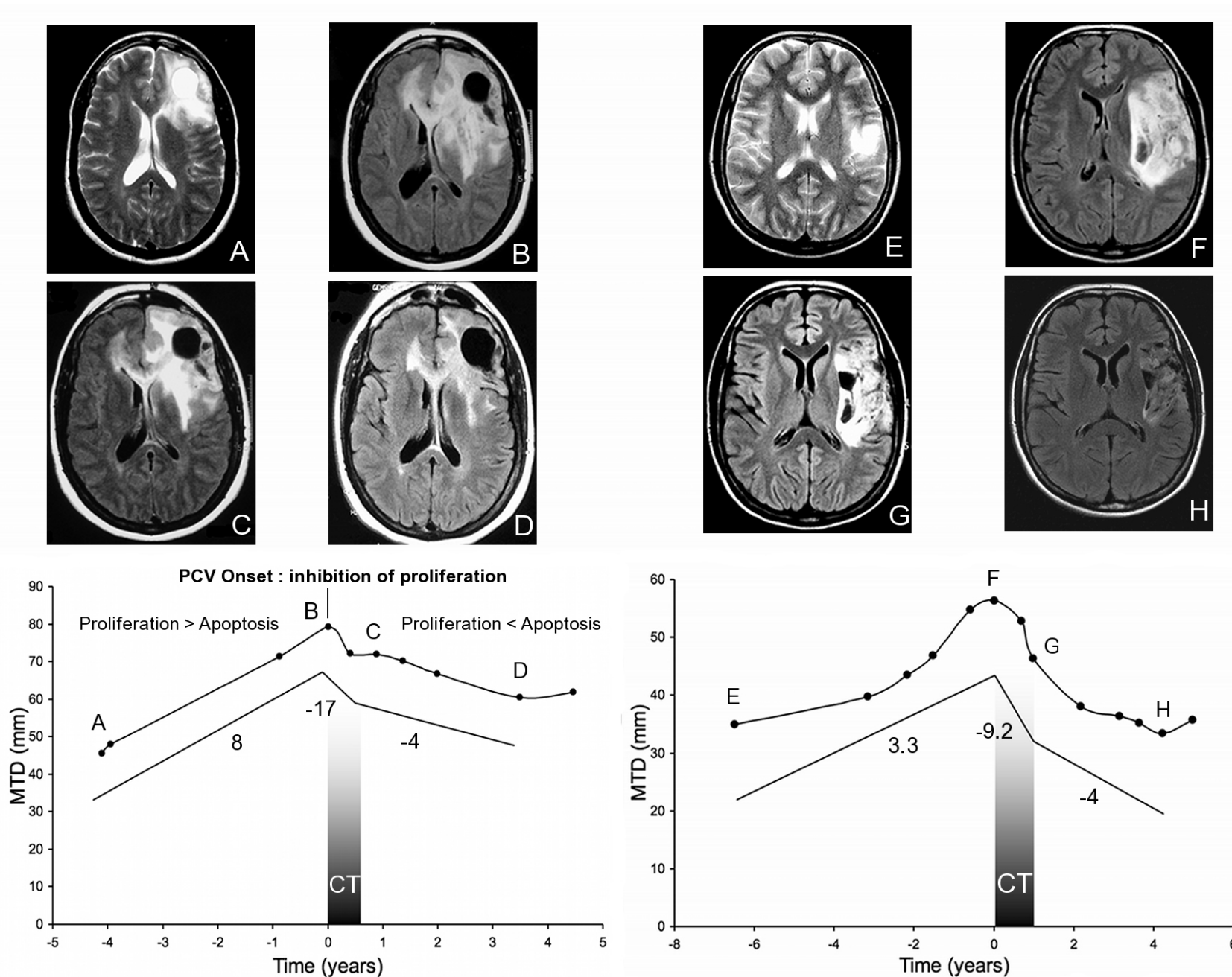
- ✓ We propose a model of tumor growth inhibition that successfully describes the time course of tumor size in patients with low-grade gliomas.
- ✓ We analyze mean tumor dynamics in patients treated with three different forms of first-line therapy – chemotherapy (PCV or temozolomide) or radiotherapy – and show that model performance and parameter estimates are consistent across treatment modalities.
- ✓ Preliminary results suggest that the model can predict treatment response based on pre-treatment tumor size data.

Context

- ✓ Modeling tumor's dynamic response to antitumor treatments is a promising approach towards improving treatment efficacy and accelerating the development of antitumor drugs.
- ✓ Low-grade gliomas (LGGs) are progressive brain tumors characterized by slow and continuous growth preceding anaplastic transformation.
- ✓ Most LGGs remain incurable. Treatment approaches include radiotherapy (RT) and two regimens of chemotherapy : PCV (procarbazine, CCNU, vincristine) and temozolomide (TMZ).

Prolonged action of chemotherapy

In a previous study, it was observed that after termination of PCV chemotherapy, LGGs frequently continue to decrease in volume despite chemotherapy no longer being administered.



Typical MTD curve was characterized by four phases:

- ✓ a slow-growing phase before treatment onset,
- ✓ a decrease in MTD upon treatment initiation,
- ✓ a prolongation (from months to several years) of this decrease after treatment termination,
- ✓ a late final regrowth phase.

One potential cause for this prolonged response is delayed action of chemotherapy on quiescent tumor cells. This hypothesis is consistent with the cell-cycle non-specific mechanism of action of the alkylating agents (procarbazine and especially CCNU) used in the PCV regimen.

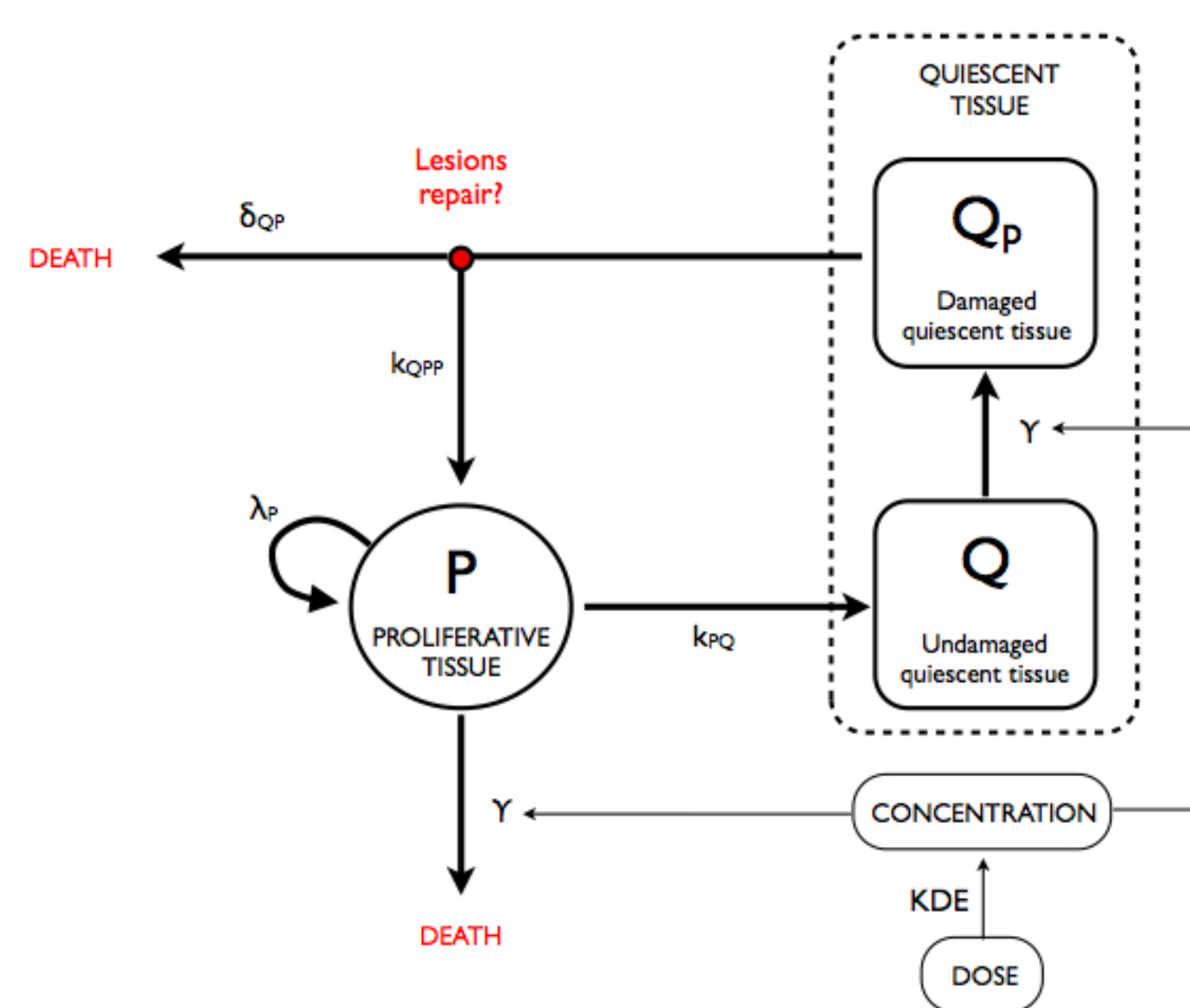
Patients and data collection

In our study, tumor size measurements were expressed as mean tumor diameters (MTDs) in mm and were estimated manually from MRI images.

	Chemotherapy PCV	Chemotherapy TMZ	Radiotherapy RT
Number of patients	21	24	25
Baseline (MTD at treatment)	7 cm	5 cm	5 cm
Protocol details	6 cycles max with intervals of 6 weeks	30 cycles max intervals of 28 days	54 Gy
Median duration of observation period	Almost 7 years	3 years	5 years
Medians of observations before and after treatment	3 and 12	3 and 8	1 and 8

Selected model

- ✓ In the model, the tumor is composed by proliferative (P) and non-proliferative quiescent tissue (Q), expressed in millimeters.
- ✓ The proportion of proliferative tissue transitioning into quiescence (i.e., the rate of quiescence, denoted k_{PQ}) is constant.
- ✓ The treatment directly eliminates proliferative cells by inducing lethal DNA damages while cells progress through the cell cycle.
- ✓ The quiescent cells are also affected by the treatment and become damaged quiescent cells (Q_p).
- ✓ Damaged quiescent cells, when re-entering the cell cycle, can repair their DNA and become proliferative once again (transition from Q_p to P) or can die due to unrepaired damages.



$$\frac{dC}{dt} = -KDE \times C$$

$$\frac{dP}{dt} = \lambda_P \times \left(1 - \frac{P^*}{K}\right) + k_{QpP} \times Q_p - k_{PQ} \times P - \gamma_P \times C \times P$$

$$\frac{dQ}{dt} = k_{PQ} \times P - \gamma_Q \times C \times Q$$

$$\frac{dQ_p}{dt} = \gamma_Q \times C \times Q - k_{QpP} \times Q_p - \delta_{Qp} \times Q_p$$

$$P^* = P + Q + Q_p$$

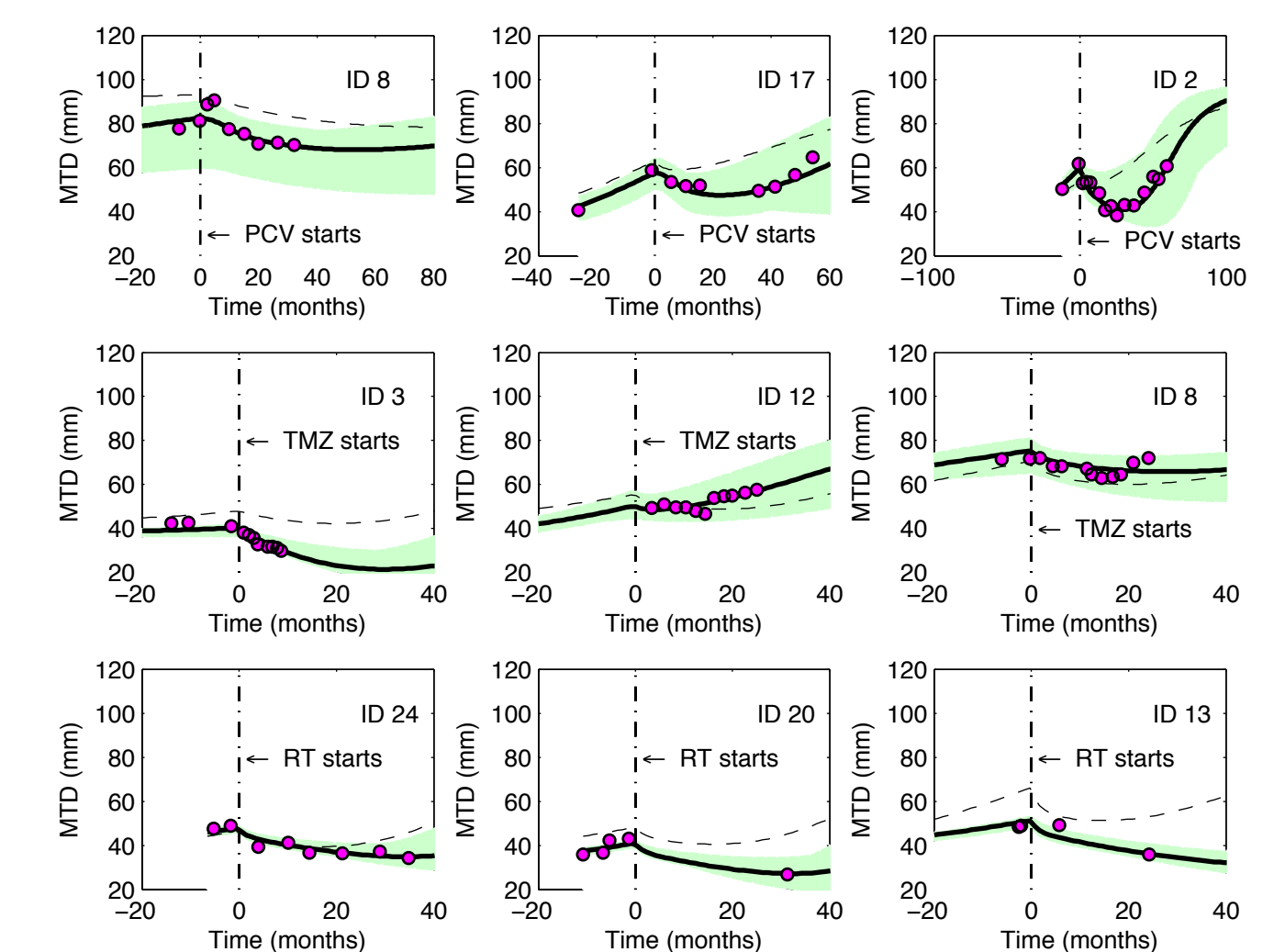
Schematic view of the model and equations. The model parameters were estimated by fitting the model solution $P+Q+Q_p$ to the actual MTD values.

Parameter estimation

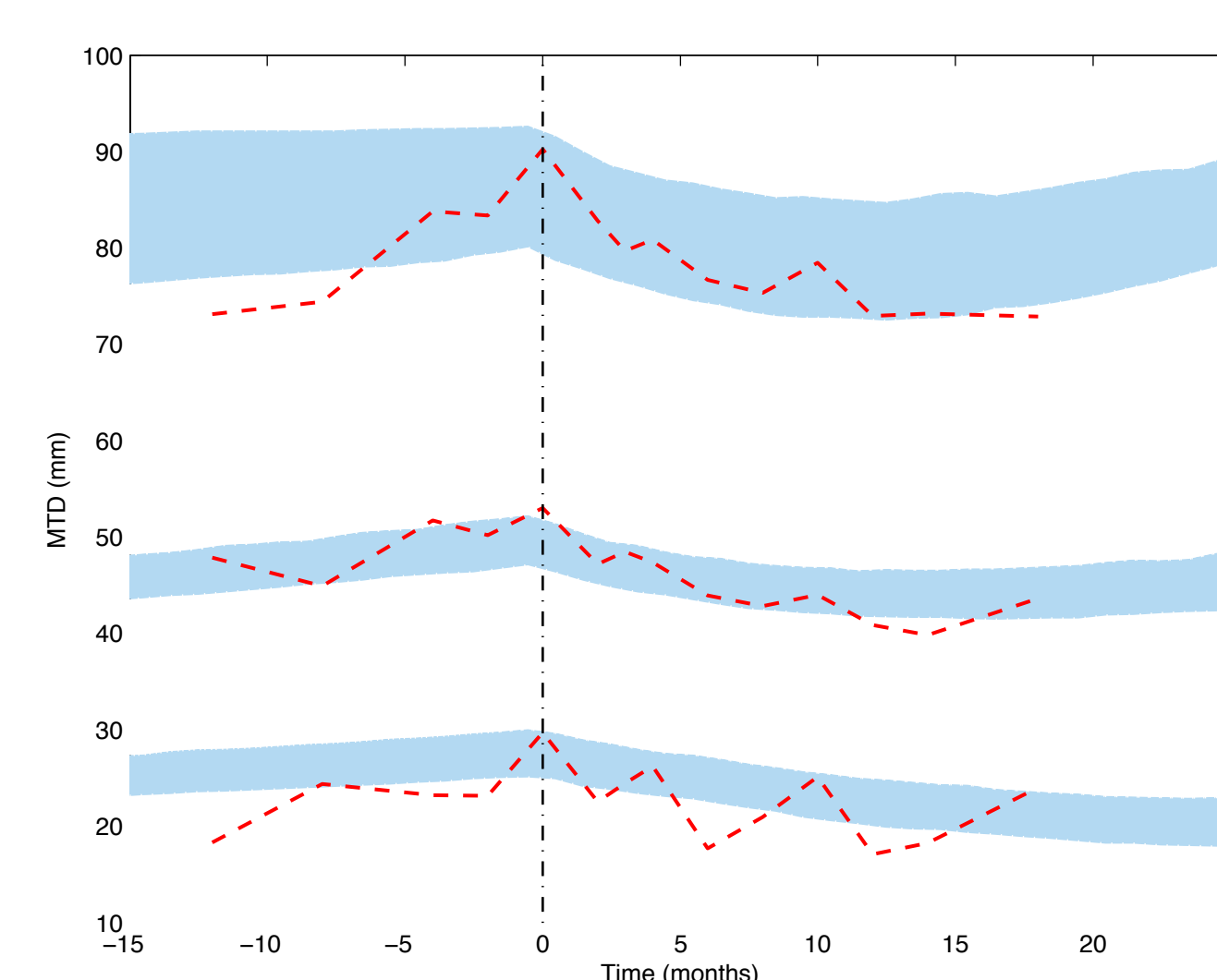
- ✓ The model contains 8 parameters including the 2 initial conditions: ($P_0 = P(t=0)$ and $Q_0 = Q(t=0)$).
- ✓ The three series (PCV, TMZ, RT) were analyzed separately.
- ✓ All parameters and their associated variability were correctly estimated.

	PCV	TMZ	RT
Basic doubling time of the proliferative tissue	8 months	7 months	9 months
Ratio proliferation rate versus quiescent rate	4	5	6
Ratio proliferation rate versus death rate of DNA-damaged cells	3	4	< 0.0001

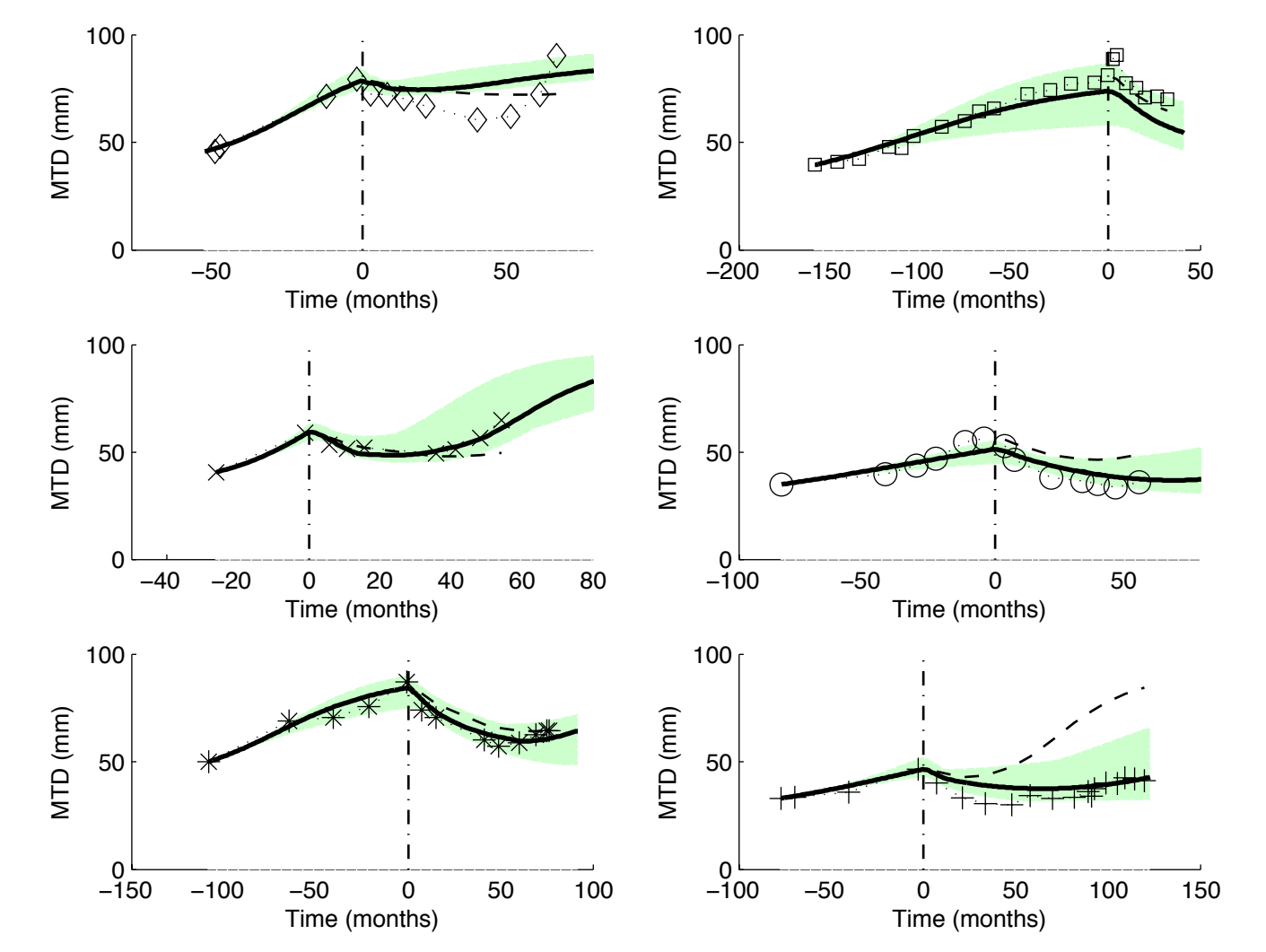
Table: Estimation of meaningful constants derived from the model parameters. Figure: MTD observed (circles), individual predictions (solid line), and population predictions based on mean parameter values (dashed line) for 3 individuals in each study selected on the basis of their typical residual error magnitude. Included is the 90% confidence interval around the individual predictions.



Validation and prediction



We used data from 96 external patients treated with TMZ and compared the 5%, 50% and 95% percentiles of the MTD time course observed (dashed red lines) in this series to the MTD time course as simulated with the model (bleu areas).



On 6 external patients treated with PCV, we predicted the MTD time course by using the population parameter estimated, except for the tumor-specific λ_P parameter, which we estimated for each patient according to his or her individual pre-treatment MTD data.