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A Mathematical Model to Simulate the Progression and Treatment of Brain Metastasis

The present work introduces a novel mathematical model that simulates the progression of brain metastasis as well as the effect of radiotherapy on cancerous and normal tissue. In clinical practice, an optimization of treatment outcome, which includes a maximization of tumor control while minimizing normal tissue toxicity, necessitates not only a quantification of the biological effect on cancerous but also on healthy tissue. Therefore, the present model extends the current mathematical approaches by also modeling the effect of radiotherapy on normal tissue. Ultimately, such models could allow for estimating the biological effect of different treatment schedules and, thus, could contribute to predictions of individualized therapy outcomes.

The progression of brain metastases is described on a macroscopic scale by means of a reaction-diffusion equation. This equation states that tumor cells either proliferate or migrate into surrounding healthy tissue. In addition to random motion cell migration due to adhesive forces is considered. At this, cells will be affected by the forces generated through adhesive binding with other cells. The effects of radiation are described by an extension of the linear-quadratic model. This extension offers in addition to low-dose hypersensitivity a high flexibility for integrating cell repair and varying therapy parameters (e.g. irradiation duration, treatment delays).
The increased intracranial pressure – a consequence of tumor progression – results in a compression and displacement of the surrounding tissue. To account for this expansive nature of the tumor, the tumor cell density is linked to a parametric deformation model.

Simulation of metastatic progression was performed by using a brain atlas with an isotropic resolution of 1 mm. The mathematical model was applied to a patient with two brain metastases from small-cell lung cancer. The metastatic lesions calculated with the model were compared to the lesions measured on contrast-enhanced T1 weighted images at three different time points prior to radiosurgery as well as one time point after radiosurgery. The results show that the progression of both brain metastases can plausibly be recovered in space and time.
The model was also used to quantitatively study the efficacy of irradiation under a variety of treatment schedules and dose distributions. The numerical results illustrate the potential of the proposed model in finding a trade-off between tumor control and normal tissue toxicity.

A novel mathematical approach is presented that allows for simulating the progression of brain metastasis and the effects of irradiation. Typically, radiation-induced cell death is modeled by the linear-quadratic model, which has shown to be limited in describing, for instance, incomplete-repair and high-dose radiation. To overcome these limitations, we introduced an extension to the standard approach that not only allows for incorporating prior knowledge about low-dose-hypersensitivity but also offers a high flexibility for varying therapy parameters. At this, we are able to analyze growth delays under different fractionations and dose distributions. First results for a patient diagnosed with brain metastasis suggest that this model can reproduce the visible part of the lesion as observed on contrast-enhanced T1 weighted images. Incorporation into clinical planning systems could ultimately help radiation oncologists to select the appropriate safety margin for radiosurgery of brain metastasis. Avenues for research in near future include a further validation in a larger series of patients as well as an extension to other types of external beam radiation therapies.