RADIOTHERAPY

# Change in schedule

> an aim to predict a dosing schedule that would improve efficacy

Radiotherapy for glioblastoma mostly remains the same now as it was 50 years ago. Although some changes in schedule (for example, hyperfractionated or hypofractionated dosing) have been attempted, these have not been successful in improving outcomes. Glioblastoma is now understood to be comprised of different molecular subtypes with intratumour heterogeneity; so, Eric Holland, Franziska Michor and colleagues used this information to mathematically model radiation responses in glioblastoma, with an aim to predict a dosing schedule that would improve efficacy.

The authors used a mouse model of glioblastoma that is similar to the human disease and is driven by platelet-derived growth factor B (PDGFB) expression, in which the mice initially respond to radiotherapy but the disease recurs. Cell population responses to radiotherapy were determined by a linear–quadratic model (an accepted model of these responses) that calculated the number of cells that would be present at a given time following a given dose of radiation. The model considered that there were two subpopulations of tumour cells — differentiated radiosensitive cells (DSCs) and stem-like radioresistant cells (SLRCs) — and it was assumed that some DSCs would convert to SLRCs and that some SLRCs would give rise to DSCs. The model also incorporated radiation-induced cell cycle arrest.

An initial set of parameters, which was derived from previously determined data, was used to run an optimization algorithm on the model. From this, the authors predicted the radiation schedule that would minimize the number of tumour cells remaining after treatment. This schedule (optimum-1) was tested in mice in a randomized 'trial' that compared it with a single dose, standard fractionation and a scrambled control that was predicted not to improve efficacy, and optimum-1 was found to significantly improve survival.

This model also predicted that hypofractionation and hyperfractionation schedules would lead to different results compared with standard therapy. However, on the basis of data from both humans and the PDGFB-expressing mice, this prediction was not accurate, and this highlights a weakness of the model. Further model refinement considered that the number of cells acquiring radioresistance depends on the time since the previous dose. This updated model was used to predict another optimum schedule, optimum-2. This schedule significantly improved survival in mice compared with the standard schedule; mice that were treated according to optimum-2 lived longer compared with optimum-1, but the difference was not significant.

Further analyses of the models, as well as flow cytometry analyses of the side-populations (which are enriched for stem cell-like cells) in glioblastoma tissue from treated mice, indicated that the optimized schedules improve survival by enriching for SLRCs. The SLRCs have reduced proliferation compared with DSCs, which might drive the improvement in survival, and although the SLRCs would also need to be eliminated to achieve a 'cure', this indicates that there is a complex relationship between the numbers of stem cell-like cells and clinical outcomes. The model also predicted that if DSCs could not revert to SLRCs, then all of the radiation schedules would have the same efficacy in the mice. Since this was not observed, it indicates that there is a dynamic equilibrium between stem cell-like and differentiated cells in radiation-treated glioblastomas.

There will be several challenges in trying to translate this schedule to humans with glioblastoma. However, mathematical modelling could be a viable way of improving the efficacy of existing therapeutics.

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**ORIGINAL RESEARCH PAPER** Leder, K. *et al.* Mathematical modeling of PDGF-driven glioblastoma reveals optimized radiation dosing schedules. *Cell* **156**, 603–616 (2014)




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