Title of Master's thesis

Fractionated Radiotherapy: Can we do better?

Track

Special Track

Topic / Key words

Ionising Radiation, Hypoxia, Computational Biology, Systems Biology, Dynamical Systems Theory

Supervisor

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External partners

Place(s) of work

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Abstract

The goal of this Master's thesis is to investigate, by means of mathematical modelling, radiation intervals and intensities in fractionated radiotherapy in combination with the administration of angiogenesis inhibitors to improve tumour destruction. Data and mechanism driven models that take care of the dynamics on different scales need to be developed, that is, on the single cell level (e.g., of typical tumour cells and endothelial cells) as well as on the level of a network of coupled single cells. Biological hypotheses, which can be tested in the wet lab, on the best radiation procedure and administration of angiogenesis inhibitors need be established – e.g., by considering hybrid models that include a mixture of continuous-time and discrete-time dynamics.

Requirements

- Interest in clinical application and mathematical modelling
- Advanced knowledge in computational science and dynamical systems theory

Comments

Radiotherapy is a mainstay for current cancer therapy. More than 50% of all patients diagnosed with solid tumours currently receive radiotherapy alone or in combination with surgery and/or chemotherapy. Several significant technological advancements have been important in allowing radiotherapy to achieve its present level of effectiveness. Nevertheless a high radiation resistance of aggressive tumours, e.g., due to tumour hypoxia, still represents a major challenge to improve the therapeutic outcome. Tumour hypoxia determines radiation resistance, rendering tumour cells 2-3 times more radiation resistant.

In cancerous tissue, the tumour environment imposes low oxygen concentrations (hypoxia) on its cells, particularly, on those that are not in the vicinity of blood vessels. Adaption of a growing tumour to these conditions is induced by a selection process towards more aggressive tumour cells, which survive under these conditions, and the induction of a genetic programme, which renders tumour cells more resistant to lower oxygen concentrations. The transcription factor called fittingly Hypoxia-Inducible Factor (HIF) plays a major role in this process promoting the expression of pro-angiogenic factors leading to better survival rates and angiogenesis (growth of blood vessels). Interestingly Ionising Radiation (IR) leads, through a still poorly understood mechanism, to up-regulation of HIF. Additionally, lack of oxygen leads to lower concentrations of reactive oxygen after IR, which leads to better repair of radiation damage and, thus, radiation-resistance. Therefore, while IR destroys the tumour directly it also induces a stress response, which indirectly induces tumour oxygenation.

In conventional radiotherapy IR is applied as a fractionated daily treatment regimen over several weeks with low doses. Fractionated irradiation aims to exploit the phenomenon of (iterative) reoxygenation in which hypoxic cells become reoxygenated and subsequently more radiosensitive. An additional reason for applying a fractionated radiotherapy regimen is also that it reduces the damage to healthy non-cancerous tissue. Because of different regeneration and DNA repair rates, many normal tissues have a survival rate that can be up to 30 times greater than the one of tumour tissue, depending on radiation strength and time between radiation sessions. Thus, choosing the right fraction of the radiation dose and right radiation interval frequency can help shifting the response to radiation towards increased tumour destruction and overcoming intrinsic treatment resistances. This requires a deep understanding of the interplay of the different factors.

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