Tumour vasculature, oxygenation and radiosensitivity

A numerical modelling study

Akademisk avhandling

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I J.H. Lagerlöf, J. Kindblom and P. Bernhardt, "3D modeling of effects of increased oxygenation and activity concentration in tumors treated with radionuclides and antiangiogenic drugs", Medical Physics, Volume 38, Issue 8, Pages 4888-93, 2011

II J.H. Lagerlöf, J. Kindblom, E. Cortez, K. Pietras and P. Bernhardt, "Image-based 3D modeling study of the influence of vessel density and blood hemoglobin concentration on tumor oxygenation and response to irradiation", Medical Physics, Volume 40, Issue 2, Pages 024101:1-7
Listad hos Global Medical Discovery [ISSN 1929-8536]
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III J.H. Lagerlöf, J. Kindblom and P. Bernhardt, "The impact of including spatially longitudinal heterogeneities of vessel oxygen content and vascular fraction in 3D tumour oxygenation models on predicted radiation sensitivity", accepterad för publicering i Medical Physics, februari 2014

IV J.H. Lagerlöf, J. Kindblom and P. Bernhardt, "Oxygen distribution in tumours – a qualitative analysis and modelling study providing a novel Monte Carlo approach", skickad till Medical Physics, februari 2014

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Tumour vasculature, oxygenation and radiosensitivity – a numerical modelling study

Abstract
This thesis aims to investigate theoretically how parameters such as vessel density, blood oxygenation, blood velocity, spatial oxygen variation along vessels, tissue oxygen consumption and their distributions influence the radiosensitivity of tumours.

Numerical calculations are made in MATLAB using voxel-based models. Direct and indirect Monte Carlo based methods are used, e.g. kernels for dose calculations and random-based models for simulation of in oxygen and activity distributions in tumours. Oxygen diffusion is calculated using a Green's function based method and oxygen consumption follows the Michaelis-Menten kinetic model. Cryosectioning and immunostaining of insulinoma from mouse is done for model development. The linear quadratic cell survival model , including the oxygen effect, is used to calculate tumour control probability (TCP) and absorbed doses. Convolutions, with diffusion and dose kernels, are preferably made in frequency space for computational reasons.

By raising the oxygen pressure (pO_2), through antiangiogenic treatment, in tumours and retaining TCP, radiation damage to normal tissues can be strongly reduced. Variation of blood pO_2 affects the position of the pO_2 distribution while altered vessel density affects the distribution shape. The greatest increase in radiosensitivity by increased pO_2 is achieved for 50% relative vessel density. In tumour oxygenation modelling, pO_2 of the blood must vary along the vessel and a random distribution of pO_2 in incoming blood is used to get realistic results.

Combining improved oxygenation and radionuclide uptake shows great potential of improving radionuclide treatment. There is an optimum region of vessel density where the highest increase in radiosensitivity is achieved by increasing blood pO_2. It appears to be possible to determine the cause of hypoxia from the shape of the pO_2 distribution. To make a good estimate of treatment result, it is crucial to know the full pO_2 distribution and not only the mean or the hypoxic fraction. Improving oxygenation of partly necrotic tumours is not always beneficial for radiation treatment. Small spherical tumours are more sensitive than larger ones to the shape of the pO_2 distribution. This is likely because a hypoxic region of a small tumour is more affected by its location relative to the tumour centre, given constant thickness, due to the relatively greater difference in radius and therefore volume.

Keywords: Angiogenesis, Dosimetry, Hypoxia, Modelling, Radionuclide therapy, Radiotherapy, Tumour Control Probability

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