Reoxygenation and Split-Dose Response to Radiation in a Tumour Model with Krogh-Type Vascular Geometry

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Abstract After a single dose of radiation, transient changes caused by cell death are likely to occur in the oxygenation of surviving cells. Since cell radiosensitivity increases with oxygen concentration, reoxygenation is expected to increase the sensitivity of the cell population to a successive irradiation. In previous papers we proposed a model of the response to treatment of tumour cords (cylindrical arrangements of tumour cells growing around a blood vessel of the tumour). The model included the motion of cells and oxygen diffusion and consumption. By assuming parallel and regularly spaced tumour vessels, as in the Krogh model of microcirculation, we extend our previous model to account for the action of irradiation and the damage repair process, and we study the time course of the oxygenation and the cellular response. By means of simulations of the response to a dose split in two equal fractions, we investigate the dependence of tumour response on the time interval between the fractions and on the main parameters of the system. The influence of reoxygenation on a therapeutic index that compares the effect of a split dose on the tumour and on the normal tissue is also investigated.

Keywords Radiotherapy · Reoxygenation · Dose splitting · Krogh model · Tumour cords

1. Introduction

After the delivery of a dose of radiation, important changes that will influence the effect of a subsequent dose occur in the irradiated tumour cell population. The most important processes occurring after irradiation are denoted as the 4R’s of radiotherapy: repair of radiation damage, redistribution of cells among the cell-cycle phases, reoxygenation, and repopulation due to regrowth of surviving cells (Wong and Hill, 1998). Redistribution and reoxygenation are expected to recover and, respectively, to transiently increase
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the pretreatment radiosensitivity (Wong and Hill, 1998). A simple representation of this resensitization that contrasts the effects of damage repair and repopulation has been incorporated in an extension of the so-called LQ model (Thames, 1985) for the response to two dose fractions (Brenner et al., 1995).

We will focus mainly on cell reoxygenation (Vaupel et al., 1984; Goda et al., 1995; Crokart et al., 2005), and will model this phenomenon in the framework of an idealized representation of tumour vascularization, i.e. by adopting the geometry of the Krogh model of microcirculation (Krogh, 1919; Popel, 1989). In this model, the vascular network is assumed to be an array of parallel and regularly spaced vessels, so that the tissue can be partitioned into identical cylinders, each surrounding a central vessel (Krogh cylinders). Observations of experimental tumours suggest that the increased oxygenation level that occurs after irradiation can be caused by an increase in blood perfusion (Sonveaux et al., 2002; Crokart et al., 2005) and/or by a decrease in the oxygen consumption by the tissue (Crokart et al., 2005; Ljungkvist et al., 2006). In our theoretical study, we restrict ourselves to assuming that the decrease in oxygen consumption due to treatment-induced cell death is the only cause of reoxygenation.

In previous papers (Bertuzzi et al., 2003, 2004, 2007) we proposed a mathematical model of the response to single-dose treatments of cylindrical arrangements of tumour cells growing around blood vessels of the tumour (tumour cords). That model included the spatial distribution of cells, cell motion, and oxygen diffusion and consumption. To describe the response to irradiation, the model has been extended in the present paper by including the kinetics of the repair/misrepair process of radiation damage. By means of this model, we have investigated the time course of oxygenation after a single dose and the influence of reoxygenation on the response to two impulsive irradiations separated by a time interval (split-dose response). Experimental evaluations of the split-dose response have been reported, e.g. by Belli et al. (1967), Jostes et al. (1985), O’Hara et al. (1998).

The paper has the following outline. In Section 2, we illustrate the general modeling assumptions concerning the kinetics of radiation damage production and repair. In Section 3, the mathematical model for the tumour cord response is formulated. Section 4 reports the results of model simulation of the single-dose response, and of the split-dose response compared with the response to the single undivided dose. Still in Section 4, the influence of reoxygenation on a therapeutic index, which compares the effect of a split dose on the tumour and on the normal tissue, is investigated. Some concluding remarks are given in Section 5.

2. Kinetics of damage production and repair

Radiation produces a variety of lesions in the cell, with some of the most important repair and misrepair reactions involving the double strand breaks (DSB) of DNA (Sachs et al., 1997). These lesions induce a lethal damage in a fraction of cells that lose the capacity of continuous proliferation and will die at a subsequent time (clonogenically dead cells). Thus, after irradiation, the living tumour cell population will be composed by a subpopulation of viable cells and a subpopulation of live but lethally damaged, clonogenically dead cells. We assume that before irradiation all cells are viable.

Several mathematical models have been proposed to describe the kinetics of radiation damage production and repair (Sachs et al., 1997). We have adopted the model originally