55.

THEORETICAL SIMULATION OF TUMOUR OXYGENATION - PRACTICAL APPLICATIONS

Alexandru Daşu and Iuliana Toma-Daşu*

1. INTRODUCTION

Tissue oxygenation has been recognised many years ago as a major factor that influences the outcome of radiotherapy[1]. It has also been observed that tumours usually have a poor vascular network that results in an impaired supply of oxygen which in turn leads to tissue hypoxia. Furthermore, it has been shown that tumour hypoxia can be divided into two types according to the mechanisms that have led to its appearance. Thus, diffusion limited hypoxia is caused by the limited diffusion of oxygen into tissue due to cellular consumption. Its appearance in human tumours has been reported for the first time by Thomlinson and Gray[2]. Several years later it has been suggested by Brown[3] that transient regions of hypoxia might also appear in tumours due to perfusion-related events such as the temporary closure of blood vessels. The existence of this type of hypoxia, termed perfusion limited hypoxia, has been demonstrated experimentally through mismatch techniques[4-6]. In contrast to the diffusion limited hypoxia that changes very slowly in time, the pattern of perfusion limited hypoxia has a short lifetime ranging from minutes to hours.

Due to the importance of tumour oxygenation, many attempts have been made to characterise it both as practical measurements and as theoretical modelling studies for the quantitative modelling of treatment outcome. However, most experimental methods are invasive and usually do not offer dynamical information. Non-invasive methods on the other hand provide a geometrical resolution that does not allow a detailed quantification of the tumour microenvironment. Theoretical simulation may thus be an alternative method that can provide quantitative data for a whole range of applications. Thus, the results of the simulations may be used to study the influence of the parameters characterising the tissue on the oxygenation pattern. As the results of the theoretical modelling are least affected by experimental artefacts, they can also be used to investigate the accuracy of various experimental techniques for measuring the tissue oxygenation. Furthermore, they can be used as input parameters for other simulations, such as the biological modelling of tumour response for treatment planning.

* Department of Radiation Sciences, Umeå University, 901 87 Umeå, Sweden

2. MATERIALS AND METHODS

We have developed a theoretical model that simulates the tissue oxygenation starting from the distribution of intervessel distances and taking into account the diffusion and cellular consumption of oxygen[7]. A Monte Carlo method was used to generate tissues with parallel blood vessels with distributions of intervascular distances in agreement with the experimental study by Konerding and co-workers[8]. The pO_2 value in the blood vessels was set to a low value (40 mmHg) in agreement with the statement of Vaupel and co-workers[9] that most tumour blood vessels come from the venous side of the vasculature. The tissue oxygenation was calculated for the simulated tissue through a numerical method, starting from the differential equation describing the movement of oxygen given by diffusion and consumption. The result thus described the oxygenation resulting from limitations in the oxygen diffusion and therefore reflected only the diffusion limited hypoxia. The appearance of perfusion limited hypoxia was modelled by randomly closing a fraction of the blood vessels in the tissue and recalculating the oxygenation map. This approach also allowed the simulation of different patterns of hypoxia as may appear at different time points during the treatment. The results of the simulations were expressed as histogram distributions of individual oxygen tensions (pO_2) and they were used to calculate the predicted response of the tissue to a fractionated radiation treatment of 30 fractions of 2 Gy each. For this it was assumed that the same vascular structure exists throughout the whole treatment. This is a reasonable assumption, since on one hand the increase in cell number due to proliferation is accompanied by the creation of new blood vessels through angiogenesis and on the other hand tumour shrinkage is accompanied by vascular damage.

The linear quadratic (LQ) model[10-12] was used to calculate the predicted cell survival. The parameters of the LQ model have been chosen to give an oxic cell survival fraction of 0.5 at 2 Gy while assuming α/β=10 Gy. It was also assumed that the formula proposed by Alper and Howard-Flanders[13] describes the variation of the radiosensitivity with the oxygenation level. Tissue responses were compared in terms of tumour control probabilities (TCP) calculated with a Poisson function from the total cellular survival and the number of clonogenic cells in the tumour.

3. RESULTS AND DISCUSSION

Figure 1 shows the results of a typical simulation of tissue oxygenation. The shape of the log-normal distribution function of the inter-vessel distances used to simulate the tissue is shown in the left-hand panel. The parameters of the distribution (mean intervascular distance of 80 μm and a relative standard deviation of 0.05) are within the range of values that have been encountered in experimental studies of tumour vasculature[8]. It has to be mentioned that all the parameters of the distribution of inter-vessel distances are necessary to describe accurately the tissue oxygenation. The middle panel of Figure 1 shows the resulting tissue oxygenation under the assumption that all the tumour blood vessels are open while the right hand panel shows the results of the simulation under the assumption that some blood vessels have collapsed.

The calculated oxygenation maps, such as those in figure 1, were used to study various aspects of the influence of tissue hypoxia on the predictions of fractionated treatment outcome. In particular, the influence of the temporal variation of the pattern of perfusion limited hypoxia was taken into consideration. The amount of tissue hypoxia can now be measured both at the beginning of the treatment as well as at different time