Accounting for Two Forms of Hypoxia for Predicting Tumour Control Probability in Radiotherapy: An In Silico Study

Emely Lindblom, Iuliana Toma-Dasu, and Alexandru Dasu

Abstract

The progress in functional imaging and dose delivery has opened the possibility of targeting tumour hypoxia with radiotherapy. Advanced approaches apply quantitative information on tumour oxygenation retrieved from imaging in dose prescription. These do not, however, take into account the potential difference in radiosensitivity of chronically and acutely hypoxic cells. It was the aim of this study to evaluate the implications of assuming the same or different sensitivities for the hypoxic cells. An in silico 3D-model of a hypoxic tumour with heterogeneous oxygenation was used to model the probabilities of tumour control with different radiotherapy regimens. The results show that by taking into account the potential lower radioresistance of chronically hypoxic cells deprived of oxygen and nutrients, the total dose required to achieve a certain level of control is substantially reduced for a given fractionation scheme in comparison to the case when chronically and acutely hypoxic cells are assumed to have similar features. The results also suggest that the presence of chronic hypoxia could explain the success of radiotherapy for some hypoxic tumours. Given the implications for clinical dose escalation trials, further exploration of the influence of the different forms of hypoxia on treatment outcome is therefore warranted.

1 Introduction

Hypoxia, a microenvironmental feature common in many solid tumours, has been associated with treatment resistance and increased potential for metastatic spread. Indeed, clinical studies showed that poor oxygenation correlates with poor prognosis for radiation therapy [1, 2]. Advances in functional imaging and radiation delivery techniques have paved the way for new approaches aiming to improve treatment success rates by targeting hypoxia, ranging from empirical dose escalations to complex dose prescription algorithms based on quantitative information on tumour hypoxia [3–5]. Nevertheless, a number of issues raise concerns with respect

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to the effectiveness of the proposed targeting approaches, including the magnitude of dose escalation, the heterogeneity of hypoxic regions, the dynamics of tumour hypoxia and the radiosensitivity of the hypoxic cells [6, 7]. Therefore, the effectiveness of the proposed approaches is yet to be validated in clinical studies. However, some of these aspects could also be tested in modelling studies accounting for the main features and processes of interest for radiotherapy. Indeed, theoretical modelling has been suggested as a powerful tool to complement clinical studies by investigating the effects of factors that could not be easily separated in the experimental setting [8, 9].

Tumour hypoxia is the result of inadequate vasculature characterised by immature vessels and long intercapillary distances. Several processes are responsible for the appearance of hypoxia, but cells could be generically grouped into chronically hypoxic (CH), caused by diffusion limitations in the tissue, and acutely hypoxic (AH), caused by transient perfusion limitations of the blood vessels [10, 11]. These types of hypoxia are usually referred to as having the same cellular response. However, it has been suggested that prolonged oxygen and nutrient deprivation characterising chronic hypoxia leads to the depletion of cell energy levels impairing the repair processes, while the short-term oxygen depletion characterising acute hypoxia leads to radioresistance [6, 12, 13]. Consequently, hypoxic cells might have different radiosensitivities depending on their origin, which could influence the effectiveness of therapeutic approaches targeting hypoxic tumours. These effects have previously been investigated with simple compartment models of oxic, acutely hypoxic and chronically hypoxic cells [6, 12]. Realistic three-dimensional tumour models taking into account the spatial heterogeneity of hypoxic regions have been developed in recent years and used for in silico studies of tumour response [14–16]. It is the aim of this study to further develop these models to account not only for the dose-modifying effect of the oxygen partial pressure, but also for differences in radiosensitivities for different kinds of hypoxic cells. Furthermore, this study aims at investigating the impact these differences might have on the probability of controlling tumours with clinically relevant radiotherapy schedules.

2 Methods

Simulations were performed on a three-dimensional in silico tumour with 20 mm diameter and heterogeneous oxygenation. The tumour was assumed to have severe chronic hypoxia at its core, gradually improving towards the periphery (Fig. 1). Two cases were simulated for the core, one in which it was 8 mm in diameter (‘small core’, black circle in Fig. 1) and one with 12 mm (‘large core’, grey circle in Fig. 1).

Cell survival in each voxel was calculated using either the linear quadratic (LQ) model with oxygen modifying factors or a combination of the LQ model and the LQ model with inducible repair to account for the difference in sensitivity of the assumed acutely and chronically hypoxic cells. Thus, in the former case, cell survival is given by the expression in Eq. 1, where α and β are LQ parameters and OMF_α and OMF_β are oxygen modifying factors depending on local oxygen tension [4].

$$SF_{LQ} = \exp\left(-\frac{\alpha}{OMF_\alpha}\cdot d - \frac{\beta}{OMF_\beta}\cdot d^2\right) \quad (1)$$

In the latter case, assuming different radiosensitivities for chronic and acute hypoxia, the expression in Eq. 2 was used to calculate the cell survival in the core, and the expressions in Eq. 3 were assumed for the outer rim of the in silico tumour, where α_S and D_C are parameters describing the inducible repair as described by Denekamp and Dasu [6] and α_R is the same as α in Eq. 1.

$$SF_{core} = \exp\left(-\frac{\alpha_S}{OMF_\alpha}\cdot d - \frac{\beta}{OMF_\beta}\cdot d^2\right) \quad (2)$$

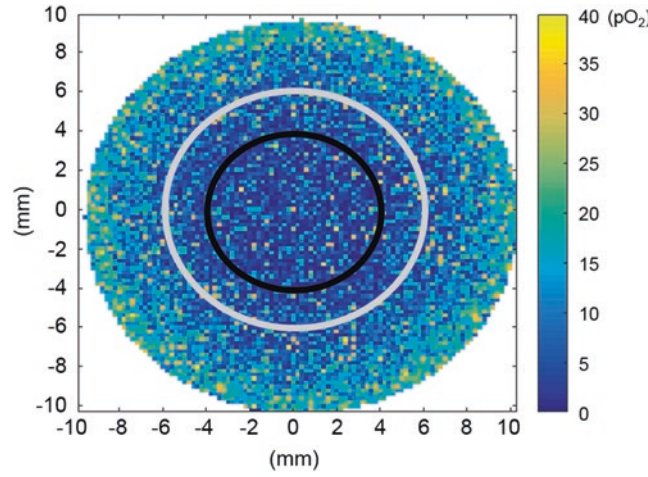

Fig. 1 Cross-section through the simulated tumour with a small (black) and a large (grey) chronically hypoxic core and an overall hypoxic fraction less than 5 mmHg of 22%. The colour scale indicates the partial oxygen pressure in mmHg

$$SF_{rim} = \begin{cases} \exp\left\{-\alpha_R \cdot \left[1+\left(\frac{\alpha_S}{\alpha_R}-1\right)\cdot e^{-\frac{d}{D_C}}\right]\cdot d - \beta \cdot d^2\right\} & for\ pO_2 \geq 30\,mmHg \\ \exp\left\{-\frac{\alpha_R}{OMF_\alpha}\cdot\left[1+\left(\frac{\alpha_S}{\alpha_R}-1\right)\cdot e^{-\frac{d}{D_C\cdot OMF_{D_C}}}\right]\cdot d - \frac{\beta}{OMF_\beta}\cdot d^2\right\} & for\ pO_2 < 30\,mmHg \end{cases} \quad (3)$$

Radiotherapy treatments with a homogeneous dose delivered in 3, 5 and 30 fractions were considered for the simulations. The total tumour control probability (TCP) was calculated as the product of voxel-based TCP determined from cell survival given by Eqs. 1, 2 and 3, assuming a homogeneously distributed population of clonogenic cells at the beginning of the treatment. The following modelling parameters were used for simulations: $\alpha = \alpha_R = 0.33\ Gy^{-1}$, $\alpha_S = 0.66\ Gy^{-1}$, $\alpha_R/\beta = 10$ Gy, $\beta = 0.033\ Gy^{-2}$, $D_C = 0.27$ Gy, $OMF_{max} = 3$ and $N = 10^6$ cells, N being the initial number of clonogenic cells at the beginning of the treatment.

3 Results

The simulations showed that assuming different response characteristics for cells characterised as acutely and chronically hypoxic leads to dramatically different results compared with the case in which the same modification in radiosensitivity for a given oxygen partial pressure is assumed. Thus, when the radiosensitivity of chronically and acutely hypoxic cells is considered to be the same for a given pO_2, very high doses are needed to achieve tumour control, as illustrated by the curves labelled 'LQ' in Fig. 2. For example, the dose needed for 50% TCP (TD_{50}) in the case of a small chronically hypoxic core (Fig. 2) is 94 Gy if the total dose is delivered using a standard fractionation scheme involving 30 fractions. Even in case of hypofractionated schedules employing much higher doses per fraction than the conventional ones, the corresponding TD_{50} is 76 and 79 Gy in 3 and 5 fractions, respectively.

In contrast, assuming different radiosensitivities in the core and in the rim, leads to substantially lower doses. Thus, the TD_{50} values for the tumour with a small chronically hypoxic core are 53, 59 and 85 Gy, respectively, in 3, 5 and 30

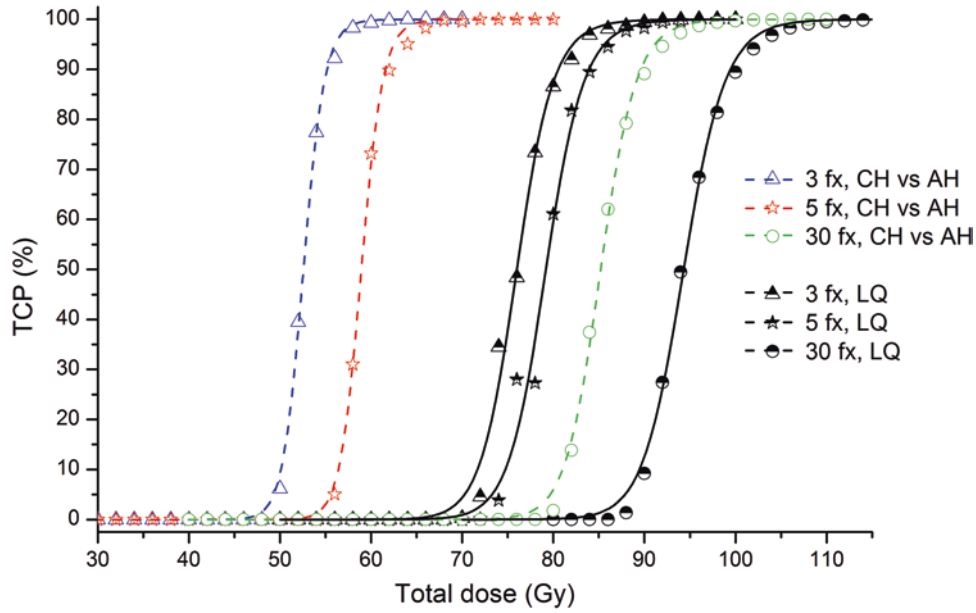

Fig. 2 Tumour control probabilities for the tumour with a small core of chronically hypoxic cells as function of the total dose delivered in 3, 5 or 30 fractions

fractions schedules. Similarly, the TD_{50} values for the tumour with a large chronically hypoxic core are 47, 53 and 79 Gy, respectively, for the three fractionation regimes. The reduction of the doses for the tumour with a larger chronically hypoxic core (Fig. 3) indicates the complexity of the relationship between radioresistance induced by the oxygen effect and the biochemically induced sensitisation caused by the reduced repair capacity of the chronically hypoxic cells. In turn, these results suggest that dose escalation studies might not lead to a substantial improvement of the success rates for those tumours with a significant proportion of chronically hypoxic cells.

It also has to be noted that when assuming different responses in the core and in the rim the dose levels required to achieve a reasonable tumour control are comparable to clinically used dose levels, in contrast to the case when the classical LQ approach has been used. Indeed, the predicted doses for controlling the tumour with a relatively low level of hypoxia (22%) if only the oxygen effect is assumed together with the LQ model are much higher than the known tolerance of the normal tissues. This indicates that the biochemically-modulated response of chronically hypoxic cells may be a possible explanation for the success of radiotherapy for some hypoxic tumours.

4 Conclusions

The results stress the importance of differentiating between the responses of various hypoxic subspecies when building in silico models accounting for tumour hypoxia. They also suggest that the degree of improvement that could be expected from hypoxia-targeted dose escalation strategies may be modulated by the proportion of chronically hypoxic cells. Given the implications for clinical dose escalation trials, further exploration of the influence of the different forms of hypoxia on treatment outcome is therefore warranted.

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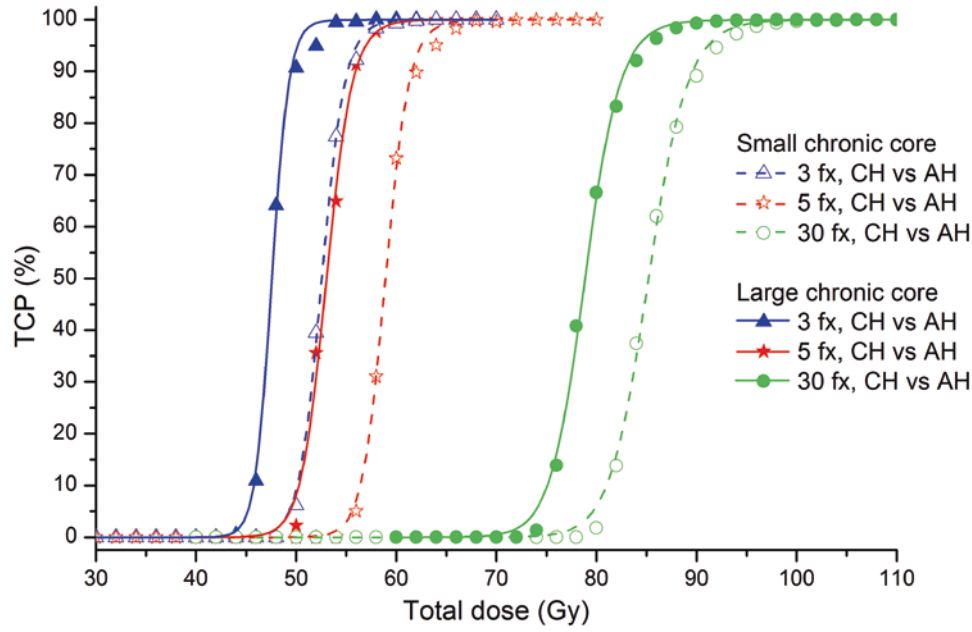

Fig. 3 Tumour control probabilities for the tumour with a large core of chronically hypoxic cells as function of the total dose delivered in 3, 5 or 30 fractions. For an easy comparison, the tumour control probabilities for the tumour with the small core are also shown

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