A model to describe potential effects of chemotherapy on critical radiobiological treatments

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Abstract. Although chemotherapy and radiotherapy can annihilate tumors on their own, they are also used in coadjuvancy: improving local effects of radiotherapy using chemotherapy as a radiosensitizer. The effects of radiotherapy are well described by current radiobiological models. The goal of this work is to describe a discrete radiotherapy model, that has been previously used describe high radiation dose response as well as unusual radio-responses of some types of tumors (e.g. prostate cancer), to obtain a model of chemotherapy-radiotherapy that can describe how the outcome of their combination is a more efficient removal of the tumor. Our hypothesis is that, although both treatments have different mechanisms, both affect similar key points of cell metabolism and regulation, that lead to cellular death. Hence, we will consider a discrete model where chemotherapy may affect a fraction of the same targets destroyed by radiotherapy. Although radiotherapy reaches all cells equally, chemotherapy diffuses through a tumor attaining lower concentration in its center and higher in its surface. With our simulations we study the enhanced effect of combined therapy treatment and how it depends on the tissue critical parameters (the parameters of the non-extensive radiobiological model), the number of “targets” aimed at by chemotherapy, and the concentration and diffusion rate of the drug inside the tumor. The results show that an equivalent chemo-radio-dose can be computed that allows the prediction of the lower radiation dose that causes the same effect than a radio-only treatment.

1. Introduction
Chemo- and radiotherapy are the two most often used treatments to deal with cancer tumors. Although these two treatments can remove tumors on their own, they are also used in coadjuvancy: chemotherapy, administered globally, may improve the effects of local radiotherapy; this synergistic effect is actually exploited in the clinic, where patients who received combined therapy had a significant increase in survival [1]. This radiotherapy enhancement, known as radiosensitisation by chemotherapy, has been investigated in vitro using mammalian normal and cancer cells [2]. These studies show that this interaction is more effective in cell lines which are relatively sensitive to chemotherapy.

The effect of radiotherapy is well modeled by linear-quadratic (LQ) models currently in use that predict cell survival fractions for low and fractionated doses [3]. However, for higher doses, such as those used in hypofractionated therapy, better predictions are obtained using a model derived from non-extensive Tsallis entropy [4]. In a previous paper [5] the former model was discretized and new predictions emerged, describing unusual behaviors of some types of tumors (e.g. prostate cancer) under radiotherapy, not well predicted by LQ model without introducing further hypotheses.
Experimental results describe radiosensitization numerically as a change in LQ parameters [2]. Two different behaviors can be observed depending on the type of cells and the chemopharm used in the culture: one in which chemotherapy largely enhances the effects of radiotherapy and one in which its effect is less significant. And, in the first case, there are cases in which the enhancement does depend on the chemopharm dosage and cases in which it does not. We hypothesize that all these behaviors can be reproduced within the framework of our former radiotherapy discrete model based on random damage of units in the cells that increase their risk of failure, that is, of random death. This could provide a way to generalize to chemo-radiotherapy the non-extensive formulae that described fractioned radiotherapy based on the Tsallis entropy model [6, 7].

Hence, our hypothesis is that, although both chem- and radiotherapy have different mechanisms, both affect similar key points of cell metabolism and regulation, that may lead equally to cellular death. The goal of this paper is to model radiosensitization effects using the radiotherapy model in [5].

2. Methodology

We will consider a discrete model that starts with a population of \( N \) cells, each with identical \( T_0 \) units. Upon being hit by a damage event, each cell has a death risk inversely proportional to the number of remaining intact units \( T \) so that

\[
\frac{\delta N}{N} = \gamma \frac{\delta T}{T}
\]

being \( \delta T = 1 \), the target that will be faced after the event. In [5] this model was introduced considering damage by radiation, so that taking the continuum limit the survival fraction \( F_r \) after a dose \( D \) (proportional to the average number of damage events per cell) could be obtained as [4]

\[
F_r = \left(1 - \frac{D}{D_0}\right)^\gamma
\]

As the number of damaged units, \( T_0 - T \), is proportional to the dose given \( D \), thus the critical dose \( D_0 \) is proportional to the number of units \( T_0 \) in the intact cell.

We model chemotherapy following the same rules, although considering the possibility that only a number \( T_q \) of the initial \( T_0 \) units can be affected by a given chemopharm, and that the rate at which units are removed may depend on the local concentration \( C(r) \) of the compound, which may change across the tumor due to diffusion or angiogenesis [8]. We consider a radial exponential distribution of the form

\[
C(r) = \frac{1}{K} \exp(-r \log K)
\]

where \( K \) stands for the ratio of the concentrations on the boundary (where we assume \( C(R) = 1 \)) and at the center of the tumor \( (C(0) = 1/K) \).

The simulation of chemo-sensitized radiotherapy will be carried out following these steps:

- chemotherapy sensitization: chemotherapy is simulated for the given \( \gamma \) and \( T_0 \) of the tumor cells and the \( C(r) \) chemopharm distribution within the tumor, defined by \( K \). The simulation is run starting from the intact tumor until the number of cells contained in it reaches a fraction \( F_q \) characteristic of the intensity of chemotherapy treatment.

- radiotherapy cycles: radiotherapy is simulated on the cells remaining after chemotherapy. The simulation is run continuously and the number of living cells is recorded after given dosages. In order to have a dimensionless dosage unit, it is taken as that number of events required to halve the number of cells in the intact tumor (i.e. prior to chemotherapy).

Hence, we will study the consequences that chemotherapy model parameters \( T_q, K \) and \( F_q \) may have on the radiotherapy dose-survival functions of a given tumor (described by \( \gamma \) and \( T_0 \)).
Figure 1. Simulated radiotherapy survival fractions after radiosensitization with a chemopharm, for homogenous tumours ($\gamma = 5$, $T_0 = 1000$, $K = 1$) with different fractions of chemosensitive units: $T_q/T_0 = 0.1, 0.2, 0.3, 0.4, 0.5, 0.8, 1$. Survival fractions of radio-only therapy are also shown.

3. Results

Let us first examine the effect of $T_q$, the number of units chemotherapy can harm in the cell, on radiotherapy dose-survival curves. Figure 1 shows the effects on a tumor totally permeable to the chemopharm ($K = 1$) under a chemotherapy reduction effects of $F_q = 0.10$. It can be seen that larger reductions (small $F_q$) do depend on $T_q$, whereas smaller reductions become independent of $T_q$.

The effect of the chemopharm distribution along the tumor is shown in Figure 2 for different values of $K = 1, 10, 100$: the larger the tumor permeability to chemopharm, the more acute the effect of radiotherapy.

Finally, the intensity of chemotherapy, measured from its reduction effect $F_q$, also increases the effectiveness of radiotherapy, according to Figure 3. As in the former cases, isoeffect doses can be obtained as shifts in the critical dose, that can be interpreted as an equivalent chemo-radio-dose administered through chemotherapy.

4. Discussion

A consequence of describing the two therapies through a unified chemo-radiotherapy model is that two apparently unrelated mechanisms can be described in the common language of therapy session combinations [6, 7], helping to interpret (and predict) the radiosensitizing effects of some chemopharms. This is in agreement with the fitted curves in Figures 4a,b: these curves are just the corresponding radiotherapy-only curves transformed to a rescaled dose. The experimental situation would be similar to that represented in Figures 3 for increasing concentrations of the chemopharm, causing a decrease of $F_q = 0.10, 0.25, 0.50$ of the initial tumor volume (after shrinkage). In terms of the model, a fraction of units equal to

$$\frac{\Delta T}{T_0} = 1 - F_q^{1/\gamma}$$  \hspace{1cm} (4)
\begin{align*}
F_s &= \left(1 - \frac{D}{D_0 - D_q}\right)^\gamma \\
\end{align*}

where
\begin{align*}
D_q &= D_0 \frac{\Delta T}{T_0}
\end{align*}

which is in good agreement with the simulations and provides for the data in [2] values of $D_q/D_0 = 0.17$ (Figure 4a, where the dose of the radiotherapy-only curve has been rescaled by 0.83 to adjust the cisplatin-radiosensitized curve) and $D_q/D_0 = 0.31$ (Figure 4b, where dose has

**Figure 2.** Simulated radiotherapy survival fractions after radiosensitization for tumours ($\gamma = 5$, $T_q/T_0 = 1$, $F_q = 1$) with varying chemopharm perfusion: $K = 1, 10, 100$. Survival fractions of radio-only therapy are also shown.

**Figure 3.** Simulated radiotherapy survival fractions after radiosensitization of tumors with different initial radiosensitivities ($\gamma = 5$ and 10, $T_q/T_0 = 1$, $K = 1$) and different chemotherapy intensities: $F_q = 0.1, 0.25, 0.5$. Survival fractions of radio-only therapy are also shown.
Figure 4. Experimental data of radiotherapy survival fractions extracted from [2]: (left) after treatment with cisplatin 1 µM during one hour, (right) emcitabine 100 nM during 24 h. Also shown are the radiotherapy only survival fraction and the dose-rescaled version of this curve that best matches the radiosensitized survival data (in accordance with, Eq. (5)).

been rescaled by 0.69 to match the gemcitabine-radiosensitized curve). That is, according to our model, those would be the chemopharm equivalent radio-doses of the cisplatin 1 µM acting during one hour, and gemcitabine 100 nM during 24 h.

Under these assumptions (homogeneous distribution of the chemopharm across the tumor), the chemopharm equivalent radio-dose $D_q$ will be given only by its effect on the tumor size. E.g. given a reduction fraction $F_q$ of the tumoral cells attained at a unit concentration ($C = 1$). However, according to our hypotheses this behavior can be limited by two other factors: the number of chemosensitive units $T_q$ and the chemopharm distribution. The former must only be taken into account for very intensive chemotherapy. Figure 2 shows that above a given number of chemosensitive units (around 36% of the total in that particular case) chemotherapy effect is no longer dependent of $T_q$: there are enough radio-sensitive units to be damaged during the chemotherapy treatment, thus radiotherapy starts from a tumor that has a number of intact units given only by $F_q$. For tumors with less radio-sensitive units, radiosensitization will be imposed by that number $T_q$, for a given $F_q$.

On the other hand, when tumor perfusion is not homogeneous, an outer shell will be more affected by the chemopharm than the inner core, about $K$ times more affected. That means that for a low dose of chemopharm about $K$ times more units will be damaged in the outer cells than in the inner ones. For intense chemotherapy, the outer shell can be totally removed, while the inner core will have about $1/K$ times less unit damages than would a similar homogenous tumor. According to our model, the radiosensitized radiotherapy curves would behave as

$$F_s \simeq \left(1 - \frac{D}{D_0 - D_q/K}\right)^\gamma$$

(7)

Although this expression qualitatively explains why the curves having larger $K$ in figure 2 get closer to the radiotherapy-only curve (the rightmost one), the expression is not straightforwardly applicable: the effective values of $D_q/K$ that fit the simulation data are much larger than the ones expected from $F_q$ alone; that is, radiosensitization is much larger than expected from chemopharm perfusion in the tumor. This can be explained by the rough approximation made in (7) and the assumption that all the outer shell is removed by chemotherapy, which is not true for less aggressive chemotherapies.
5. Conclusions

The simple discrete model described above seamlessly combines chemotherapy and radiotherapy in one single model, so that an equivalent chemo-radio-dose can be defined. This allows a simple derivation of the chemo+radiotherapy survival fraction and predicts the influence of other factors on radiosensitization, such as chemosensitivity or chemopharm perfusion (that is, its radial concentration profile) inside a tumor.

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6. References

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