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On the Importance of Prompt Oxygen Changes for Hypofractionated Radiation Treatments

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Abstract

This discussion is motivated by observations of prompt oxygen changes occurring prior to significant number of cancer cells dying (permanently stopping their metabolic activity) from therapeutic agents like large doses of ionizing radiation. Such changes must be from changes in the vasculature that supplies the tissue or from the metabolic changes in the tissue itself. An adapted linear-quadratic treatment is used to estimate the cell survival variation magnitudes from repair and reoxygenation from a two-fraction treatment in which the second fraction would happen prior to significant cell death from the first fraction, in the large fraction limit. It is clear the effects of oxygen changes are likely to be the most significant factor for hypofractionation because of large radiation doses. It is a larger effect than repair. Optimal dose timing should be determined by the peak oxygen timing. A call is made to prioritize near real time measurements of oxygen dynamics in tumors undergoing hypofractionated treatments in order to make these treatments adaptable and patient-specific.

I. Introduction

Tumor responses to radiation have classically been dependent upon the four “Rs” of radiobiology: redistribution, repopulation, repair, and reoxygenation that describe how tumors and tumor microenvironment adapt to therapy. The time course of these factors varies by tumor type, but typically occurs on the order of 10’s of hours from cell cycle effects (redistribution, repopulation, reoxygenation) or a few hours or less (repair, *prompt reoxygenation*). Immediate or prompt changes in oxygenation can occur through changes in blood vessels and/or metabolism and may be controlled by tumor and patient-specific factors. Changes occurring in only a few hours are occurring before significant cell death. The term “reoxygenation” here is used in the context of the four “Rs” but in a more general sense as prompt oxygen changes that can be positive or negative. The term “cell death” is used in most of this paper to describe the inability to resume oxygen consumption. This definition is approximated, for the sake of uncertainty estimation, by the lack of survival as it is used in most survival models like the linear-quadratic model employed here. For example, if a cell cannot succeed in dividing 5 or 6 times, then it will not lead to the resumption of significant oxygen consumption.

Several groups have provided evidence of a prompt oxygen response following radiation. For example, Crockart and colleagues found that oxygen in the interstitial space peaks 3–4 hours after a 10 Gy dose of radiation and remains elevated for 24 hours (Crockart *et al* 2005). Similarly, Bussink demonstrated that hypoxia decreases and perfusion increases immediately following a 10 Gy dose of radiation (Bussink *et al* 2000). They suggest that an immediate inflammatory response and a decrease in oxygen consumption contribute to the loss of hypoxia and increase perfusion.

These prompt alterations in tumor oxygenation have potentially profound implications upon severely hypofractionated radiotherapy regimens that are becoming more frequent (Alongi and Scorsetti 2012). In particular, delivery of a limited number of radiation fractions over a 1–2 week schedule is commonly performed for stereotactic treatments. We sought to determine the theoretical worst-case scenario, for the uncertainty, for effective dose delivery based upon radiation-induced changes in tumor oxygenation by utilizing a variant of the linear quadratic model system. To simplify the modeling required and allow us to draw straightforward conclusions, herein we present modeled data regarding a two-fraction dose delivery scheme in which a second dose at this oxygen peak may be efficacious.

II. Methods & Materials

The goal is to explore the implications for uncertainty in cell survival due to effects prior to cell death for a model two-dose hypofractionated treatment. The dose per fraction is potentially large, much greater than 2 Gy. The tumor cell survival, S , for a Dose, $D = D_1 + D_2$ in a two fraction hypofractionated treatment is provided to lowest order by the linear-quadratic equation with radiosensitivity parameters α and β . The factor β dominates at large dose beyond α/β that a severely hypofractionated therapy would require. The linear-quadratic equation can be written as follows as a function of the partial pressure, p :

$$\ln S(p) = -(\alpha_a/[OER(p)])D - (\beta_a/[OER(p)]^2)GD^2, \quad (1)$$

where the second term traditionally contains *timing* information for repair in G , the Lea-Catcheside factor. The local partial pressure of oxygen in the interstitium will provide an oxygen enhancement factor (OER) according to the treatment in Wenzl and Wilkens (2011). A similar tactic is taken by Carlson *et al* (2006). They have (essentially) $\alpha_h = \alpha_a/[OER(p)]$ and $\beta_h = \beta_a/[OER(p)]^2$. The quantities α_h and β_h represent the hypoxic limit values, and the quantities α_a and β_a represent the aerobic limit values. We also use $\alpha_a = 0.121 \text{ Gy}^{-1}$ and $\beta_a = 0.0367 \text{ Gy}^{-2}$, values used in Carlson *et al* (2006). It should be noted that the effectively same OER factor could be formulated in other ways such as the hypoxia reduction factor, the dose modifying factor, oxygen modifying factor, etc. However, the use of any other factor would not change any conclusion reached here.

The factor G is calculated for two prompt doses separated by a time T as follows (Sachs *et al* 1997):

$$G = \frac{D_1^2 + D_2^2 + 2D_1D_2e^{-\lambda T}}{(D_1 + D_2)^2}. \quad (2)$$

In G , the “repair rate” factor is λ . Since sublethal DNA damage repair occurs on the order of 0.5 hours from *in vitro* studies (Carlson *et al* 2006) to 4 hours clinically (Bentzen *et al* 1999), it needs to be considered, but there is evidence that it is independent of oxygen tension (Carlson *et al* 2006). However, to be conservative, we consider limiting cases for T so that G has its maximum value of 1 and its minimum value of 0.5 when $D_1 = D_2$. Luckily, it is observed that $\lambda \propto [OER(p)]$ (Carlson *et al* 2006), and so these effects can easily be plotted in simple combination. Of note, it has been observed that *acute* hypoxia is the most important factor for radiosensitivity (Chan *et al* 2008) in a particular situation where chronic hypoxia was also present during or before the irradiation. While this study therefore does differ from clinical conditions in some obvious ways, it does point to the potential for prompt effects having more importance than conceived of conventionally.

By incorporating repair explicitly into G, we will not assume complete repair between fractions as is often done when the fractions are 24 hours apart. In addition, prior to prompt OER variations added, the curve will include two doses implicitly but with no information assumed as to the partition between these doses – only time between them as indicated by T. At longer separation times, T, complete repair would occur implicitly in G. The oxygen changes will cause OER changes from prompt effects that result from the first dose such as from vascular dilation/contraction changes and metabolic changes but not cell death. These variations will not start from zero dose, but from the first dose, D_1 . For the calculation presented, $D_1=10$ Gy is assumed. The repair will be implicit in a curve that includes both doses, and the OER changes affected survival will plot only from the second dose. We will use the full range possible for both repair and OER and look for which leads to larger variations and what factors affect these variations.

These calculations used the product Matlab (The Mathworks, Inc., Natick, MA, USA).

III. Results

We can see from Fig. 1 that if we accept the possibility of a full range of OER values, then *the uncertainty from OER variations could be very large and could dominate over repair uncertainties*. The repair uncertainty considers a full range of G values for both prompt (within a day and even an hour) and not prompt (a few days) to which an OER variation can be compared. That figure displays a two dose treatment with a full range of possibilities for both repair and prompt OER changes; both happen prior to cell death and are assumed to be independent. It therefore is a worst case scenario, but it shows the potential for a large error if one does not know the oxygen tension at the time of second dose. In Fig. 1a, a typical relationship between OER and the oxygen tension is displayed. In Fig. 1b, the lowest and the highest G values are used, but for the $G=0.5$ case, the curve changes as a result of the prompt oxygen changes due to the first dose for maximum range possible. Both doses are implicit in G, but the prompt oxygen changes are due to the first dose but manifest in the second dose only. Fig. 1c is reverse of Fig. 1b in terms of where the oxygen variation is shown. The larger the second dose, D_2 , the stronger the OER term becomes. It is possible that the OER variation is also a strong function of the first dose, D_1 .

Inserting an OER dependence, Eq. 1 can be written as the following in a similar way to Wenzl and Wilkens (2011) and Carlson *et al* (2006):

$$\ln S \approx -\alpha_a/(OER)D - \beta_a/(OER)^2 GD^2. \quad (3)$$

By taking the derivative in the *high dose per fraction limit*, we can relate changes in the relative cell survival to absolute changes in the OER value as follows for severely hypofractionated treatments:

$$\partial S/S \approx \partial(OER) \cdot [2G\beta_a/(OER)^3] \cdot D^2. \quad (4)$$

It is clear that the *high dose per fraction limit* will increase the sensitivity of the cell survival uncertainties S/S to uncertainties of (OER) . The dose in Eq. 4 is really the second dose, D_2 . The variations in the OER, (OER) , are likely a function of the first dose, D_1 . We acknowledge complications in the linear-quadratic equation at high doses pointed out by Astrahan (2008) among others, but for the sake of simplicity for an uncertainty analysis, we leave these details out of our calculations.

IV. Discussion

Using an adaptation of the classical linear-quadratic equation, we have demonstrated the importance of tumor oxygenation on surviving fraction and the potential effect of not optimizing stereotactic body radiotherapy (SBRT) to be delivered at optimal oxygenation. For example, merely by delivering SBRT at low oxygen levels many orders of magnitude difference in cell kill can be seen. This magnitude of difference would lead to large potential variability in tumor control probability, but these calculations assume uniform oxygenation of all the tumor cells. In vivo of course, there is a distribution of oxygenation that would undoubtedly reduce the magnitude of the uncertainty shown in Fig. 1, but the extent of this reduction is unknown. The repair curves are also likely not as far apart either in Fig. 1 in that the G factor is likely not potentially at either extreme of 1/2 or 1. Nonetheless, we and others have suggested that alterations in tumor oxygenation can be induced by radiation, potentially leading to an initial increase in oxygenation (Crokart *et al* 2005, Bussink *et al* 2000, Fujii *et al* 2008). The consequence of these effects on scheduling of SBRT doses, the time T in our calculations for example, has not been well explored, but may have important clinical consequences.

It is known that hypoxia is an excellent prognostic factor for local-regional control after radiation (Nordsmark and Overgaard 2004). A sensitivity to hypoxia for a few large doses has also been calculated for equivalent Biological Effective Dose (BED) by Carlson *et al* (2011) – the survival at equivalent BED is dominated by hypoxia for regimens utilizing fewer than 15 fractions. We can expect that metabolic changes are at least a part of these fast changes from radiation, since changes in reduced nicotinamide adenine dinucleotide (NADH) with overshoots are observed (Schaue *et al* 2012).

The implication is that intrinsic radiosensitivity (the fifth “R” of radiotherapy) could also be obtained by observing these prompt effects. There is evidence that acutely hypoxic cells (low PO₂ for less than a few hours) are the type possessing the greatest radioresistance (Chan *et al* 2008). In addition, it has been discussed that intermediate hypoxia (PO₂ in the range of about 1–10 mmHg) dominates the response to fractionated radiotherapy (Wouters and Brown 1997). If one looks at effects from prompt reoxygenation, then one could separate important radioresistance dynamics between acute and chronic hypoxia, as well as preferentially affect the intermediate hypoxic zone, since no significant cell death would have occurred on this time scale. This targeted approach to acute hypoxia has previously been called-for by the research community (Janssen *et al* 2005). For either hypofractionation or hyperfractionation, the issue of timing between doses, especially for accelerated fractionation of head and neck cancer radiotherapy, is important to study in the clinic (Saunders 1999).

Squamous cell head and neck tumors are frequently treated with altered fractionation schemes (Brizel 2008, Sanghera *et al* 2007, Saunders 1999). These schemes are often accelerated. With improved technology for Intensity Modulated RadioTherapy (IMRT), hypofractionation could start to compete with hyperfractionation because larger doses are possible for the same rate of normal tissue toxicity. It was found that overcoming repopulation with an accelerated schedule in these tumors was beneficial (Brizel 2008). However, missing from most studies are prompt measurements of hypoxia and oxygen dynamics in response to radiation before cell death and repopulation become significant. Such information opens a door which may lead to temporal dose modulation for patient-specific adaptation of radiotherapy. Care must also be taken to understand that temporal fluctuations may also occur without any therapy triggers (Dewhirst 2009), and these can affect therapy nonetheless.

There have been many studies trying to modulate the dose accurately in space, since cold spots in a tumor can lead to a loss in local tumor control (Tomé and Fowler 2002). The tailoring of a radiotherapy dose to the heterogeneity of meaningful sub-tumor volume characteristics, such as tumor hypoxia has been studied but without a clear procedure for the correct dose prescription based on the images (Bentzen 2005, Flynn *et al* 2008, Kissick *et al* 2010, Bowen *et al* 2009, and McCall *et al* 2010). IMRT can very effectively tailor spatial aspects of the treatment to specific patients, tumor locations, and tumor volumes. However, although tumor hypoxia is recognized as one of the most important factors that determine the dynamics of tumor growth and response to treatments (Harris 2002), at present little emphasis is placed on adapting to it when planning or delivering radiation treatments.

If the oxygen changes can go in any direction, then at the very least, we need to consider the full range possible and calculate the uncertainty from these effects that happen prior to cell death (repair and prompt reoxygenation changes, see Fig. 1). It therefore behooves us to characterize reoxygenation mechanisms and timing other than from cell death, and consider a wide variety of times between doses for optimal cell kill.

V. Conclusion

A two-dose linear-quadratic calculation is performed with a Lea-Catcheside factor to account for the range of repair between the doses. Inside of that, assuming independence between oxygen tension and DNA repair, an oxygen variation is included, but only for the second dose, assuming that a significant change may occur from the first dose. Better oxygen measuring devices are needed that can provide a useful temporal measure of the oxygen response from the first dose and its dynamics, since these will have a large impact on the effectiveness of the second dose. All indications from the literature are that modulating the dose temporally, and based on oxygen dynamics could be very efficacious in the development of patient-specific adaptive radiotherapy. The clinical implication is that optimizing the timing between doses, possible short times between doses, could open new doors for better high dose hypofractionated treatments. This advance requires that we are able to observe potentially prompt changes in oxygen, changes that occur prior to significant cell death. A call is therefore made for more research in this direction.

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Fig. 1.

(a) The Oxygen Enhancement Ratio (OER) in relation to the interstitial oxygen pressure is plotted, based on Carlson et al (2006). In (b and c), the linear-quadratic equation is modified by a range of OER caused by the first dose of 10 Gy and affecting the second dose, and is plotted. Complete repair between two fraction is not assumed, and the Lea-Catcheside factor for a two dose treatment, G , is used. The full ranges of G and oxygen tensions (0.01 to 100 mmHg) are used. Notice that the range of cell kill is dominated by OER variations and that the larger the second dose, the more variation one will see resulting from the OER changes induced by the first dose. The time between them as indicated by T , and it should be compared to repair rate factor $\lambda = 0.5\text{hr}^{-1}$.