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BIOLOGY CONTRIBUTION

VALIDATION OF TEMPORAL OPTIMIZATION EFFECTS FOR A SINGLE FRACTION OF RADIATION *IN VITRO*

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Purpose: To experimentally validate how temporal modification of the applied dose pattern within a single fraction of radiation therapy affects cell survival.

Method and Materials: Using the linear-quadratic model, we have previously demonstrated that the greatest difference in cell survival results from comparing a temporal dose pattern delivering the highest doses during the middle of a fraction and the lowest at the beginning and end ("Triangle") to one with the lowest doses at the middle and the highest at the beginning and end ("V-shaped"). Also, these differences would be greatest in situations with low α/β and large dose/fraction and fraction length. Two low (WiDr, PC-3) and one high (SQ-20B) α/β cell lines were irradiated in six-well plates with 900 cGy over 20 min (900 cGy/20 min), one each with a Triangle and V-shaped dose pattern. WiDr cells were subjected to the same experiments with first 180 cGy/20 min, then 900 cGy/5 min. Cell survival was assessed using the clonogenic assay.

Results: At 900 cGy/20 min, irradiation with a V-shaped pattern resulted in an increased survival compared with use of a Triangle pattern of 21.2% for WiDr ($p < 0.01$), 18.6% for PC-3 ($p < 0.025$), and 4.7% for SQ-20B cells ($p > 0.05$). For WiDr cells at 180 cGy/20 min, this increase reduced to 2.7% ($p > 0.05$) and to −0.8% ($p > 0.05$) at 900 cGy/5 min.

Conclusions: These results verify the assertions of the modeling study *in vitro*, and imply that the temporal pattern of applied dose should be considered in treatment planning and delivery. © 2009 Elsevier Inc.

Temporal optimization, Linear-quadratic model, IMRT, Hypofractionation, *In vitro* experiments.

INTRODUCTION

The increasing popularity and complexity of several forms of external beam radiation therapy (EBRT), such as hypofractionated intensity-modulated radiation therapy (IMRT) and stereotactic radiosurgery, have given rise to single-fraction treatment times of lengthening duration (1–3). The emergence of these longer treatment delivery times has driven an interest in elucidating the impact of temporal effects in EBRT, especially as they relate to the radiobiology of the underlying tissue (1, 4–9). Several studies have thus begun to recognize that the interaction between increasing radiation therapy (RT) treatment times and cell repair, and hence cell survival, may have clinically relevant implications with regard to tumor control and normal tissue sparing (2, 3, 10–14).

Temporal effects relating to RT are generally analyzed in terms of cell survival using the linear quadratic (LQ) model (15–17). The LQ model is dependent on two time-related factors that correlate to radiobiological effects: the duration of radiation application (''fraction duration''), and the functional form of *how* the dose is applied over time (''temporal pattern of applied dose''). Although the former of these has been studied in some detail (1, 5, 8–14), there have been only a few investigations into the temporal pattern of applied dose (3, 18, 19).

One of these was a theoretical study that we performed, which used dose patterns with variable, intermittent doses, characteristic of points within IMRT plans, to determine techniques for temporal manipulation of the dose arrangement to maximize or minimize cell kill (18). The study also analyzed the effect of several variables associated with a single fraction

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of IMRT that can interact with variations in the temporal pattern of applied dose to affect cell kill. Results from the modeling study thus provided both an algorithm through which a random temporal sequence of doses could be rearranged to maximize or minimize cell kill, as well as guidelines to determine the clinical situations for which optimizing the temporal dose patterns would yield the greatest impact. However, before these techniques could be used in clinical treatment planning, their reflection of reality must be established. The goal of this study is to experimentally validate *in vitro* the assertions and constructs suggested by the modeling study.

Theory

For a single fraction of radiation, the LQ model relates the fraction of surviving cells (S) to total dose (D) by:

$$S = \exp - \left(\alpha D + \beta G(t) D^2\right) \tag{1}$$

where α and β relate to the tissue's susceptibility to acutely lethal and potentially repairable radiation damage, respectively. G(t), the dose protraction factor, accounts for the time variables involved in RT. In its most general form, G(t) is given, at a time t, by (20):

$$G(t) = \frac{2}{D^2}\int_0^t dw\ I(w) \int_0^w dv\ I(v) e^{-\mu(w-v)} \tag{2}$$

where D is the dose per fraction (dose/fx), I(k) is the dose rate at time k, $\mu = \ln 2/T_{1/2}$, where $T_{1/2}$ is a tissue specific repair half-time, and w and v are time variables. The limits of integration of the outer integral in Eq. 2 can be viewed as the beginning and end of the time span defined by the fraction duration (T_f). The double integral and exponential term in Eq. 2 also render the dose protraction factor dependent on the temporal pattern of applied dose. Physically, the dose protraction factor accounts for the cell repair that occurs during the time between the applications of any two acute or ''instantaneous'' doses. Any functional form of dose application can be considered a series of acute doses, and G(t) considers all pairs of instantaneous doses that comprise the functional form, taking into account their distribution in time.

Modeling study

The theoretical study assumed a simple IMRT model composed of alternating periods of radiation (''fields'') and no radiation, yielding a dose pattern that approximates multi-field IMRT. A database of multiple-field clinically—based IMRT plans was then generated. Analyzing only a single voxel, G(t) was calculated for all temporal permutations of the fields for each plan in the database. Through this analysis, a consistent temporal dose pattern was found which maximized cell kill: a ''Triangle'' dose pattern, with the highest dose fields clustered in the middle of a treatment fraction and the lowest doses distributed between the beginning and end (Fig. 1a). Similarly, a ''V-shaped'' pattern, in which the lowest dose fields were clustered at the center and the highest dose fields were distributed between the beginning and end of a treatment fraction, consistently minimized cell kill (Fig. 1b). These patterns were manifest for all numbers of radiation fields per plan and fraction durations analyzed.

The effect of changes in irradiated tissue type (in terms of α/β ratio), T_f, and dose/fx, three of the major variables associated with a single fraction of IMRT that can interact with variations in the temporal pattern of applied dose to affect cell kill, were then analyzed. The impact of the temporal arrangement of applied dose on cell kill was found to be greatest in situations with low α/β ratio, longer T_f, and higher doses/fx. The modeling study held α constant, meaning there was also an implicit dependence on β. As the temporal factors couple to the β term in the LQ model (Eq. 1), the impact of the temporal pattern of dose will be stronger with higher β. However, in terms of overall cell survival, a cell line more susceptible to repairable relative to irreparable damage (thus low α/β) is also important.

METHODS AND MATERIALS

In vitro experiments

In vitro experiments were performed to validate the conclusions of the modeling study using the clonogenic assay for cell survival. Three cell lines with distinct radiobiological parameters were irradiated using two different temporal patterns of applied dose (Triangle

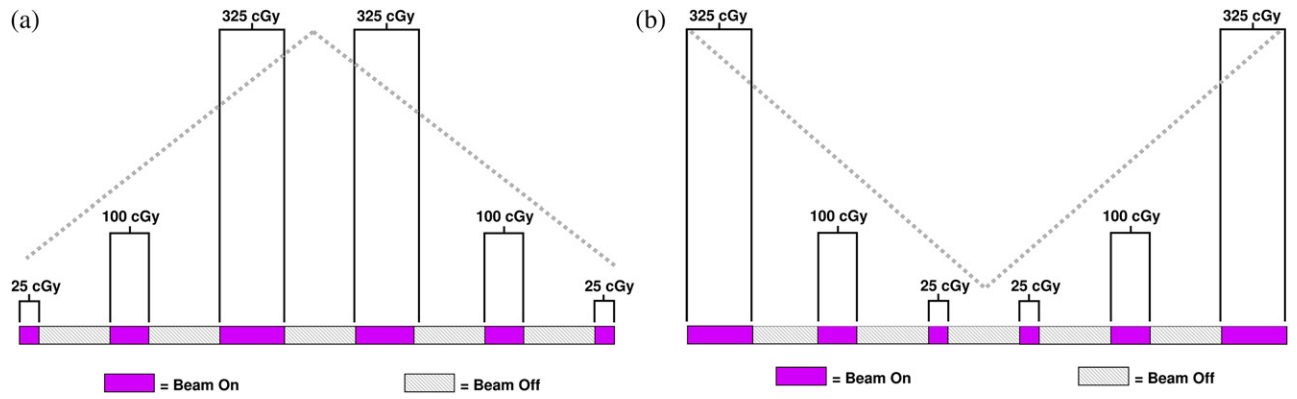

Fig. 1. (a) Schematic diagram of the six-field 900 cGy dose pattern used to irradiate cells. Fields are arranged in a ''Triangle'' pattern (dashed line) yielding maximum cell kill. Horizontal axis represents time. (b) Same as (a), except a representation of the ''V-shaped'' dose pattern (dashed line) to yield minimum cell kill. The exact same fields are used in both (a) and (b), and the duration of delivery is the same; only the order in which the fields were delivered was changed.