Intra-fraction dose delivery timing during stereotactic radiotherapy can influence the radiobiological effect

Martin J. Murphy and Peck-Sun Lin
Department of Radiation Oncology, Virginia Commonwealth University, Richmond, Virginia 23298

Cihat Ozhasoglu
Department of Radiation Oncology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania

(Received 4 August 2006; revised 20 October 2006; accepted for publication 21 November 2006; published 17 January 2007)

The sequence of incremental dose delivery during a radiotherapy fraction can potentially influence the radiobiological effect. This would be most noticeable during the long fractions characteristic of hypo-fractionated stereotactic radiotherapy and radiosurgery. We demonstrate here the spatio-temporal variation of dose delivery by the CyberKnife to a lung tumor and propose strategies to reduce and/or correct for any resultant dose-time cytotoxic effects. © 2007 American Association of Physicists in Medicine. [DOI: 10.1118/1.2409750]

INTRODUCTION

In radiation therapy there are three significant timescales for irradiation—the daily fractionation schedule, the duration of each individual fraction, and the intra-fraction sequence for delivering individual radiation fields. Theory and experiment indicate that the temporal pattern of cell irradiation influences the competition between clonogen proliferation, cell kill, and sub-lethal repair. This in turn influences overall cell survival rates and hence tumor control probability (TCP). This has for a long time influenced the design of optimal daily fractionation schemes.

Researchers have also drawn attention to the possible effects of long individual fractions on the cell survival rate. Both in vivo radiobiological experiments1–4 and calculations based on the linear-quadratic model5 have shown greater cell survival rates for long (15–60 min) compared to short (2–5 min) fractional delivery times. In particular, Benedict et al. observed a 40% increase in malignant glioma cell survival when the dose delivery schedule for a single-fraction 12 Gy irradiation was altered from 5 min (2.4 Gy/min) of continuous irradiation to 60 min (0.2 Gy/min) of intermittent irradiation. Survival rates increased three-fold when the intermittent irradiation was stretched over 110 min. Generally, it is observed that as the average dose rate drops below 2 Gy/min the cell kill rate begins to drop significantly.4 Such effects have prompted recommendations to adjust the treatment planning and delivery processes to compensate for the protracted delivery schedules that are characteristic of intensity-modulated radiation therapy (IMRT), hypo-fractionated radiotherapy, and radiosurgery (cf. Benedict et al.).

Less attention has been paid to the temporal pattern of radiation as it is delivered during a prolonged fraction. As a typical IMRT delivery progresses from one field to the next the fractional dose to any particular tumor cell is delivered in nonuniform incremental steps separated by variable pauses. This intra-fraction modulation in dose delivery can also influence the radiobiological effect. For example, Lin et al. have demonstrated variable cell survival as a function of incremental dose magnitudes and sequences. They show that when a dose of 2 Gy is delivered in a sequence of two small increments followed by a large increment the cell survival probability is significantly (up to 10–20%) smaller than when the dose is delivered as a large increment followed by two small increments. They also point out that variable time intervals between the intra-fraction dose increments can result in variable cytotoxicity. This temporal complexity amounts to a “mini-fractionation” effect resulting in statistically significant differences in survival for cells that receive the same total fractional dose. Similar effects have been modeled analytically by Altman et al., who used the linear-quadratic model to estimate cell survival in a single irradiated voxel as a function of the dose delivery sequence during IMRT.

The effects observed by Benedict and by Lin and Wu and modeled by Altman are attributable to accelerated repair of radiation-damaged cells, which begins immediately upon irradiation and continues for 2–4 h. During this time interval the repair rate is initially very fast and nonlinear, then tapers off. Furthermore, cell response to radiation damage is nonlinear and has a threshold: Larger doses (>0.5 Gy) induce more radio-resistance than smaller doses (<0.5 Gy) while sufficiently small doses do not trigger repair at all.8,9 (The threshold dose at which repair begins is the transition dose.) According to this explanation, one delivers the radiation in a sequence consisting of a large initial increment followed by a long (e.g., >5 min) pause and then followed by small increments, the later small doses cannot adequately compensate for the repair stimulated by the initial large dose, rendering them less effective. On the other hand, a sequence of small doses can trigger little or no repair, making any intervening pauses inconsequential to the TCP. For hyper-radiosensitive tumor cells that have transition doses higher than surrounding normal tissue, a pulsed-low-dose schedule can potentially improve the therapeutic ratio by increasing TCP while allowing normal tissue time to repair.10,11

These dose-time effects have so far only been observed in vitro and modeled in computational simulations. However,
if they carry over to in vivo tumors, then one should expect intra-fraction dose timing to affect treatment outcome at some level. In this note we demonstrate that the kind of complex intra-fraction dose delivery schedules investigated in the in vitro studies actually occur during IMRT and radiosurgery. In particular, we show that the temporal dose delivery pattern can also be spatially irregular, potentially leading to a differentiated TCP within the volume of the tumor. We suggest that, if these dose-time effects are real, then one can develop simple strategies to analyze the partial-fractionation schedules and then improve the TCP by altering and/or compensating for the temporal sequence of irradiation. We illustrate these ideas with an example of dose delivery by the CyberKnife (Accuray Incorporated, Sunnyvale CA). The CyberKnife is frequently used for hyper-fractionated stereotactic radiotherapy and radiosurgery of the type analyzed by Benedict et al.

A radiosurgery fraction delivered by the CyberKnife can take 30–90 min. This places the dose delivery process in the time frame during which the effects of protracted delivery and accelerated repair are most pronounced. The stop-and-shoot method of delivery can result in an average dose rate of about 1 Gy/min, which is in the range where cell survival is dependent on dose timing. Furthermore, different voxels can receive a dose in different sequential increments spaced by pauses of variable length, resulting in a complex spatio-temporal pattern of dose buildup. Under these circumstances the treatment plan could potentially be optimized further by considering not only the spatial but also the temporal distribution of radiation. This kind of refinement was proposed by Benedict et al. to deal with intermittent dose delivery during conventional radiosurgery.

The in vitro experiments of Lin et al. suggest that large dose increments trigger faster repair than small increments while sufficiently small doses do not trigger any repair. If these effects carry over to in vivo tumors then, given a choice, one would want to have small dose increments followed by large increments rather than vice versa. Likewise one would want short pauses (e.g., < 1 to 2 min) after large increments, to minimize repair. (Long pauses after small dose increments are less important.) Finally, what one does at the beginning of the fraction would be more important than what one does near the end. Therefore small increments would best be delivered first to maximize their effectiveness. Long (>5 min) pauses should preferentially occur near the end of the fraction. (Ideally, increments delivered after long pauses could be delayed until the next fraction to maximize their effect.) This amounts to “front-loading” the dose delivery sequence.

Under these circumstances there would be four possible strategies to improve CyberKnife TCP: (1) Start the delivery process at beams that deliver small doses or are followed by short pauses; (2) re-order the beam sequence to reduce long pauses in the buildup of the dose; (3) re-arrange the fractionation scheme to find those beams that irradiate a voxel after a considerable pause and deliver them on a later day; (4) adjust the dose delivered by the different beams to compensate for variable TCP due to increments and pauses in dose buildup in the tumor.

The CyberKnife beam delivery sequence has already been developed to minimize the time spent moving from beam to beam. Re-ordering the individual beams to reduce extended pauses is a complex problem that would almost always result in a substantially longer fraction. However, there is no cost in selecting the first beam of the sequence.

Allocating different beams to different daily fractions is also a complex problem that works against one of the reasons for fractionation, which is to reduce the normal tissue complication probability (NTCP). The CyberKnife uses small pencil beams that overlap only at or very near the tumor. Far from the tumor the normal tissue dose tends to be delivered mainly by one beam. Conventionally, the dose is divided into N fractions by dividing each beam weight by N. This reduces daily normal tissue dose by N. If instead one delivered an entire beam in one fraction rather than N fractions then the total daily dose to the tumor might stay roughly the same but normal tissue dose far from the tumor could go up N times for that fraction.

We, therefore, propose that the biological effects of partial fractionation would be reduced most easily by identifying the best beam at which to start the fraction. The remaining effects can be at least partly compensated by adjusting the dose delivered to each voxel using time-dose correction factors as suggested by Benedict et al. We illustrate this with an example.

METHOD AND MATERIALS

The CyberKnife delivers overlapping pencil beams to the tumor from a three-dimensional (3D) configuration of directions. For optimal conformity the beam diameter is typically less than the cross-sectional area of the tumor. One hundred or more beams are delivered sequentially with nonisocentric pointing to achieve full coverage and high conformity. In a typical treatment the linear accelerator is positioned at a point in space (called a “node”) and then the beam is aimed at a sequence of points within the tumor. The accelerator then moves to another node and repeats the process. This causes parts of the tumor to be irradiated at different times and in different increments.

Our example is a three-fraction plan that prescribed 60 Gy to the 80% isodose line for a 6.5 cm³ lung tumor. The largest dimension of the tumor was approximately 30 mm. The plan utilized a 15 mm diameter collimator that delivered anywhere from 6 to 242 MU (approximately 1.25–50 cGy at the tumor) per beam from 184 distinct directions. Each fraction lasted approximately one and a half hours.

Using the planned beam directions, beam sequence, and dose-per-beam, and assuming that the CyberKnife delivers 400 MU/min and takes about 5 s to move from one beam node to the next, we calculated the integral dose to each voxel of the tumor as a function of time. We then identified for each voxel the number and length of significant (>4 min) pauses in the buildup of dose. This was done two
ways: (1) We recorded the longest pause between dose depositions; (2) we summed the total pauses during the fraction. In each case we binned the pauses in four-minute intervals. This analysis revealed the partial fractionation schedules for each voxel.

To demonstrate the potential for variable cytotoxicity from one voxel to the next we made a simple repair model based on the general observation that the repair rate for dose increments $>0.5$ Gy is much greater than the repair rate for increments $<0.5$ Gy, and that the repair rate increases with increasing increment size. We combined this with the observation of Benedict et al. that during intermittent dose delivery there is on average a loss of about 2 cGy of dose effectiveness for each minute of pause between increments. From this we made a model of loss of dose effectiveness for pauses following doses of various incremental magnitudes. This model is summarized below:

<table>
<thead>
<tr>
<th>Dose increment</th>
<th>Loss of dose effectiveness during subsequent pause</th>
</tr>
</thead>
<tbody>
<tr>
<td>$&lt;0.4$ Gy</td>
<td>0.0 cGy/min</td>
</tr>
<tr>
<td>0.4–0.6 Gy</td>
<td>1.0 cGy/min</td>
</tr>
<tr>
<td>0.6–0.8 Gy</td>
<td>1.75 cGy/min</td>
</tr>
<tr>
<td>0.8–1.0 Gy</td>
<td>2.5 cGy/min</td>
</tr>
<tr>
<td>$&gt;1.0$ Gy</td>
<td>3.0 cGy/min</td>
</tr>
</tbody>
</table>

By integrating the pauses following each dose increment in each voxel, we calculated a total loss in dose effectiveness per voxel during the fraction, expressed as a fractional reduction of the delivered dose. This shows how much one would have to increase the dose at each voxel to compensate for the simulated time-dose effects during delivery.

To demonstrate a method to adjust beam weights to compensate the variable cytotoxicity of different delivery sequences to different voxels, we determined the unit matrix $[M]$ that mapped each beam to the voxels that it transited. We then increased the total delivered dose in each voxel by the amount $\delta D_j$ calculated to compensate time-dependent differences in cytotoxicity. This defined the new, perturbed dose distribution that we wished to deliver. We calculated the required perturbations $\delta B_i$ to the original beam weights by solving

$$\min \varepsilon^2 = \|\delta D - [M]\delta B\|.$$  

(1)

Although this over-simplifies the dose re-calculation by neglecting radiation attenuation and scatter effects, it is only a perturbation to the original calculation, which included all of those details. (This perturbation can be refined further.)

The number of voxels in Eq. (1) is much greater than the number of beams. Therefore, the beam perturbations that minimize $\varepsilon^2$ can be solved by the method of singular value decomposition (SVD) as follows:

(1) Get the SVD of $[M]=UWV^T$, where $W$ is the diagonal matrix of singular values;
(2) get $\delta B = \Sigma([U_i \cdot \delta D]/w_i)V_i$, where $U_i$ and $V_i$ are the column vectors of the respective SVD matrices $[U]$ and $[V]$ and $w_i$ are the diagonal elements of $[W]$.

This yields a corrected treatment plan that partly compensates for the variable effectiveness of the voxel-by-voxel dose buildup.

RESULTS

Figure 1 shows the buildup of dose over time for two selected voxels, illustrating the problematic issues in the dose delivery sequence. The dose delivery rate is not uniform. One voxel (A) receives a 1.5 Gy dose increment at the beginning of the fraction, followed by a 20 min pause, and then followed by a sequence of small dose increments. This voxel will experience the most adverse effects of accelerated repair. The second voxel (B) receives a series of small incremental doses separated by significantly shorter pauses. Voxel B accumulates the dose faster than A in the first half of the fraction, thus front-loading the dose delivery. When the simple model of dose-time-dependent repair is calculated for these two voxels, voxel B has its effectiveness reduced to 98% of the prescribed dose while A is reduced in effectiveness to 89% of the prescription by the long pauses early in the delivery.

Figure 2 illustrates for one slice the longest pause in incremental dose delivery to each voxel. These ranges from less than five to more than twenty minutes. This clearly shows the spatial variability in dose delivery timing. The longest pauses are clustered near one extremity of the tumor. The greatest reduction in dose effectiveness (87–92% of the planned dose) tends to be concentrated in this part of the tumor as well, resulting in a local region that would potentially experience less cytotoxicity than the planned dose distribution would suggest. These spatial variations provide the basis for perturbing the beam weights via Eq. (1) to compensate for the diminished cytotoxic effect.

DISCUSSION

In vitro studies have shown that below 2 Gy/min the cytotoxicity becomes dose-rate-dependent. In the present example the average dose rate over the entire fraction was...
1 Gy/min. Individual CyberKnife beams delivered anywhere from 0.03 to 1.2 Gy per increment, which brackets the 0.5 Gy dose at which the cell repair rate is observed to change rapidly. The dose increments were separated by pauses of anywhere from a few seconds to fifteen minutes. This puts the CyberKnife intra-fraction dose timing squarely in the range of parameters where one might expect dose-time effects in the TCP.

Our very simple model for repair as a function of dose delivery timing suggests that the intra-fraction timing of our example treatment plan might reduce the cytotoxic effectiveness per voxel by up to 15%. However, this model is not based on any particular radiobiological model, nor is it meant to be physically realistic. It is merely a heuristic device to demonstrate how the variable voxel irradiation schedules that occur during a CyberKnife treatment can translate into a spatially-variable reduction in dose effectiveness within the treated volume.

Figure 1 suggests that the variation in cytotoxicity due to the pattern of increments and long pauses could be reduced simply by reversing the order of the nodes, thereby front-loading the delivery for voxel A with small closely spaced dose increments and placing the long pause at the end of the fraction. This strategy is supported by the calculations of Altman et al., who reach a similar conclusion. However, this will still leave variations in dose buildup, which we suggest can be compensated by adjusting individual beam weights.

Why worry about these effects? Treatment plan optimization for IMRT can invest significant computing resources to achieve uncertainties of 1 to 2% in the predicted dose. However, cytotoxicity for a given total dose could potentially vary by considerably more than a few percent due to temporally variable intra-fraction delivery effects. We have shown a clear example of significant spatio-temporal variability in CyberKnife dose delivery and demonstrated a simple strategy for re-ordering and re-weighting the beams to partly compensate for the corresponding variability in tumor cell survival. Although our proposed plan adjustments will not eliminate variations in TCP altogether they can reduce it at essentially no cost. We hope that this example will stimulate further discussion and study of these temporal effects in CyberKnife therapy, IMRT, and GammaKnife radiosurgery.

Fig. 2. The spatial distribution of longest significant (>5 min) pauses in the buildup of dose within the tumor volume. The color scale runs from <4 min (blue) to >20 min (red) in 5 min color increments.