Optimal drug release schedule for in-situ radiosensitization of image
guided permanent prostate implants

Robert A. Cormack, Paul L. Nguyen\textsuperscript{a}, Anthony V. D’Amico\textsuperscript{a}, Sri Sridhar\textsuperscript{b}, Mike Makrigiorgos\textsuperscript{a}
\textsuperscript{a}Department of Radiation Oncology, Dana-Farber Cancer Center/ Brigham and
Women’s Hospital, Boston, MA 02115 USA
\textsuperscript{b}Electronic Materials Research Institute and Department of Physics,
Northeastern University, Boston, MA 02115 USA

ABSTRACT

Planned in-situ radiosensitization may improve the therapeutic ratio of image guided \textsuperscript{125}I prostate brachytherapy. Spacers used in permanent implants may be manufactured from a radiosensitizer-releasing polymer to deliver protracted localized sensitization of the prostate. Such devices will have a limited drug-loading capacity, and the drug release schedule that optimizes outcome, under such a constraint, is not known. This work determines the optimal elution schedules for \textsuperscript{125}I prostate brachytherapy. The interaction between brachytherapy dose distributions and drug distribution around drug eluting spacers is modeled using a linear-quadratic (LQ) model of cell kill. Clinical brachytherapy plans were used to calculate the biologic effective dose (BED) for planned radiation dose distributions while adding the spatial distributions of radiosensitizer while varying the temporal release schedule subject to a constraint on the drug capacity of the eluting spacers. Results: The greatest increase in BED is achieved by schedules with the greatest sensitization early in the implant. Making brachytherapy spacers from radiosensitizer eluting polymer transforms inert parts of the implant process into a means of enhancing the effect of the brachytherapy radiation. Such an approach may increase the therapeutic ratio of prostate brachytherapy or offer a means of locally boosting the radiation effect without increasing the radiation dose to surrounding tissues.

Keywords: Brachytherapy, prostate, radiosensitization, modeling

1. INTRODUCTION

Prostate cancer is a common malignancy in males in the United States and Canada. For patients with disease confined to the gland, localized treatments such as surgery or brachytherapy are appropriate. Prostate brachytherapy uses transrectal ultrasound (TRUS) imaging\textsuperscript{1,2} or interventional MRI\textsuperscript{3} to plan and guide the implant process and is one of the earliest examples of image guided radiation therapy (IGRT). Permanent \textsuperscript{125}I prostate brachytherapy uses transperineal needles to place on the order of 80 radioactive sources within the prostate to deliver radiation to the gland. Attempts to improve the dosimetric outcome of the procedure include end of procedure imaging to confirm source placement\textsuperscript{4}, and real-time adaptive treatment planning during the implant procedure.\textsuperscript{5} The dose delivered to the prostate is limited by the resulting dose to the urethra and rectum which are interposed and adjacent structures. IGRT procedures rely on imaging to improve the therapeutic ratio by producing more conformal dose distributions that reduce dose to normal structures.

Another approach to increase the therapeutic ratio is to increase the effectiveness of the radiation by sensitizing the target tissue.\textsuperscript{6,7} In order to achieve high spatial accuracy, TRUS guided permanent brachytherapy procedures may use spacers to ensure that the sources are placed according to the planned configuration. These spacers are generally biodegradable, and provide on therapeutic purpose other than ensuring uniform spacing of the radioactive sources. It has been suggested that the spacers could be loaded with radiosensitizers to provide localized enhancement of the radiation effect using drug releasing surface coatings\textsuperscript{8,9}. The ability to sensitize a significant portion of the gland depends on the number of implanted drug eluting spacers and the diffusion parameters of the released drug and suggests the need for biologically conformal treatments\textsuperscript{10} and biologic in-situ image guided radiation therapy.\textsuperscript{11}

The diffusion parameters can be modified by a number of ways\textsuperscript{12} including the use of nanoparticles\textsuperscript{13}. Nanospheres are able to release drugs over a range of time scales depending on the composition of the particles\textsuperscript{14}. With the ability to
control drug release schedule, the optimal schedule for permanent 125I prostate brachytherapy remains to be determined. A simple analysis of the relation between radiation dose rate and time variable radiosensitization\textsuperscript{15} suggest shorter periods of more intense radiosensitization produce a greater biologic effect than longer periods of less sensitization. Such an analysis has not been carried out for the spatially and temporally variable dose and drug distributions that would arise from an implant using drug eluting spacers. This work investigates how the optimal schedule for localized radiosensitization depends on the concentrations that are achievable.

2. METHODS AND MATERIALS

This work models the biologic effect of permanent prostate implant that include timed release of localized radiosensitizer. The distribution of the sources and spacers are extracted from treatment plans of clinically delivered prostate implants. Biologic effect is calculated based the widely used linear quadratic (LQ) model of radiation damage\textsuperscript{16} and the magnitude of the radiosensitization effect is taken from reported radiosensitization\textsuperscript{6} effects. The radiation dose distribution is calculated from the source configuration while the drug distribution is calculated from the location of the spacers assuming diffusion parameters capable of sensitizing a significant portion of the gland as determined by earlier work.\textsuperscript{11}

2.1 Patient Information

![Figure 1 Schematic of a prostate implant. A coronal view of a prostate represented as the oval. The arrow represents a transperineal needle used to deposit a line of radioactive sources and spacers. The location of radioactive sources is extracted from the treatment plans and indicated by a filled rectangle. The locations of spacers are calculated from the planned location of all needles used in the implant and indicated as unfilled rectangles.](image-url)
As part of an IRB approved medical record review, the brachytherapy treatment plan of five patients were analyzed to extract the contoured patient anatomy, planned needle locations and the source loading patterns for each needle. MATLAB\(^1\) scripts were used to extract the relevant information from DICOM RT files saved by the SPOT PRO\(^2\) treatment planning system. Anatomy contours were used to tag voxels belonging to the following structures: prostate, rectum and urethra. Voxels were 0.05 x 0.05 x 0.25 cm in dimension. Source locations were extracted from the plan files. Spacer locations were calculated based on the location of the most superior source in each needle assuming spacers were placed every 0.5 cm along the needle path until the path was no longer within the prostate as shown in Figure 1. This allows both sources and spacers to be at the same location, but this was seen as a reasonable simplifying assumption. All patients were prescribed a brachytherapy dose of 144 Gy.

### 2.2 Radiation and Drug Distributions

Source and spacer locations were used to calculate the radiation dose and drug concentration delivered to each prostate labeled as prostate. Radiation dose calculations used the point source approximation of the Task Group 43 of American Association of Physicists in Medicine (AAPM)\(^17\):

\[
\hat{D}(r) = \left( \frac{S_k \Lambda}{r^2} \right) g(r) \phi_{an}(r)
\]

Where \(r\) is the distance from the source to calculation point, \(S_k\) is the air kerma strength of the source, \(\Lambda\) is the dose rate constant, \(g(r)\) is radial dose function of the source, and \(\phi_{an}(r)\) is the anisotropy factor. The time dependence of the radiation dose was determined by the 59.4 day half-life of 125I and given by \(\hat{D}(r, t) = \hat{D}_0(r) \exp(-\lambda t)\). The radiation dose at a point \(\hat{p}\) is given by summing the contribution from all radiation sources: \(\hat{D}(\hat{p}) = \sum_i \hat{D}(r_i, t)\) where \(r_i\) is the distance from the \(i\)th radiation source to the point \(\hat{p}\). The drug distribution was calculated from an analytic steady state solution to the diffusion equation for a spherical diffusion source\(^18\). Drug concentration is given by

\[
C(r) = \frac{A_0 a}{r} \exp(-\phi_b(r - a))
\]

Where \(r\) is the distance from the diffusion source to the calculation point, \(a\) is the radius of the diffusion source, \(A_0\) is the drug concentration at the surface of the diffusion source and \(\phi_b\) is the diffusion elimination ratio. The drug concentration at a point \(\hat{p}\) is given by summing the contribution from all drug sources: \(C_{\hat{p}}(\hat{p}) = \sum_j C(r_j)\) where \(r_j\) is the distance from the \(j\)th drug source to the point \(\hat{p}\). Spacers in brachytherapy procedures have dimensions of 0.8x5mm. A value of \(a=2\)mm was used for all calculations.

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\(^1\) Mathworks, Natick Ma, USA
\(^2\) Nucletron Corp, Veenendaal, The Netherlands
Figure 2 Cell survival curves. Cell survival curves express the fraction of cells that survive as a function of radiation delivered. The curves are characterized in terms of two parameters that characterize radiosensitivity: \(\alpha, \beta\). The parameters \(\alpha, \beta\) may be determined by fitting survival curves results of cell survival experiments, or inferred from clinical outcomes. The bold line shows a survival curve for \(\alpha=0.3 \text{ Gy}^{-1}, \beta=0.03 \text{Gy}^{-2}\). The dashed curve represents the survival curve for radiosensitized cells. The sensitization evaluated at SF=0.1 is \(S= 5.1/3.6=1.4\).

In previous work, we have demonstrated that polymer coatings can release a radiosensitizer over the course of 1-4 weeks with the time constant of the release determined by the composition of the polymer. In this work, the drug concentration was modeled as variable duration extending for up to 7 weeks. The concentration as a function of distance and time is given by \(C(\tilde{p}, t) = C_0(\tilde{p}) w(t)\) where \(w(t)\) is proportional to the amount of drug released at time \(t\). The limited drug capacity of a diffusion source is incorporated by constraining the integral of \(w(t)\).

2.3 Radiosensitization

Radiosensitizers are drugs that enhance the cell killing effect of radiation. Radiation’s cell killing effect is described by a linear quadratic model where the surviving fraction (SF) of cells can be expressed as

\[
SF = \exp\left\{-\alpha D - \beta D^2\right\} \tag{3}
\]

where \(D\) is the radiation dose and \(\alpha\) and \(\beta\) are constants related to the susceptibility of cells to radiation damage\(^6\). Radiation sensitization is quantified in terms of a sensitization factor \(S\), as shown in Figure 2, which is the ratio of the doses needed to achieve equivalent cell kill effects for reference and sensitized cells: \(S = \frac{D_{\text{ref}}}{D_{\text{sens}}}\). The sensitization factor of taxol has been reported as high as 1.4\(^6\). Radiosensitization varies with drug concentration and there is a concentration above which no additional sensitization is achieved which is referred to as \(C_{\text{sat}}\). With this terminology, the sensitization arising from a spatially variable drug concentration \(C(\tilde{p})\) is expressed as
\[
S(\tilde{p}, t) = S_{\text{max}} \frac{C(\tilde{p}, t)}{C_{\text{sat}}} \\
S_{\text{max}} = \begin{cases} 
C(\tilde{p}, t) < C_{\text{sat}} \\
C(\tilde{p}, t) \geq C_{\text{sat}} 
\end{cases} 
\]

(4)

The effective radiation dose distribution is given by:

\[
\hat{D}(\tilde{p}, t) = S(C_0(\tilde{p})w(t))\hat{D}_0(\tilde{p})\exp(-\lambda t) 
\]

(5)

2.4 Biologic Effect

To compare the effectiveness of different drug release schedules, the biologic effect is calculated from the average of the survival fraction for each voxel. The survival fraction of the voxel is calculated from integrating equation 3 over the duration of the time period of interest using the effective dose of equation 5 for all prostate voxels having a radiation dose equal to or greater than the prescription dose. To reduce the possibility of results being dependant on the values of \(\alpha\) and \(\beta\), the calculations were carried out for parameter values of \((\alpha=0.3 \text{ Gy}^{-1}, \beta=0.03 \text{ Gy}^{-2})\), \((\alpha=0.3 \text{ Gy}^{-1}, \beta=0.1 \text{ Gy}^{-2})\) and \((\alpha=0.3 \text{ Gy}^{-1}, \beta=0.3 \text{ Gy}^{-2})\).

3. RESULTS

The characteristics of the treatment plans analyzed are summarized in Table 1. The prostate volumes range from 23 to 74 cc and span the range of gland sizes treated in our clinic. All treatments were delivered with 0.41 mCi sources. The range of prostate volumes, combined with using a single activity for all patients resulted in plans using from 34 to 81 sources. The number of drug sources varied from 36 to 111.

All patients were prescribed 144 Gy to the prostate. It should be noted that anterior regions of the prostate in the vicinity of the urethra do not necessarily receive full prescription dose. Figure 3a shows the contoured structures on an axial slice around midgland. The prostate, urethra and anterior rectal wall are shown. The dose distribution is shown in Figure 3b which shows a low dose region in the vicinity of the urethra.

<table>
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<tr>
<th>Patient</th>
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<th>Spacers</th>
<th>(C_{\text{min}})</th>
<th>(C_{\text{max}})</th>
<th>Volume (cc)</th>
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<td>87</td>
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<tr>
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<td>111</td>
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<tr>
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<tr>
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<td>66</td>
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<td>5.4</td>
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</tbody>
</table>

Table 1 Characteristics of implants analyzed and resulting bounds of drug concentrations for a value of \(\phi_b=0.3\). Implant parameters were extracted from treatment plans used in clinical practice. Plans studied spanned the range prostates treated.

Figure 3c shows a representation of the drug distribution resulting from assuming the brachytherapy spacers are drug eluters. The effect of this sensitization is shown in Figure 3d showing the regions of high drug concentration resulting in an increase in the effective dose of up to 40%. The biological effective dose is for the sensitized implant is calculated from the effective dose represented by figure 3d. The shape of the drug distribution depends on the diffusion elimination ratio of the drug or drug carrier while the amplitude of the distribution is determined by the rate of the drug or drug carrier from the brachtherapy spacer.
This work is concerned with the relative effectiveness of different temporal sensitization schedules. Average survival fraction, as calculated by the LQ model, is used as a metric to compare the biologic effectiveness of different drug release schedules. Survival fractions are sensitive to the values of the LQ parameters and the parameters are not well determined. To minimize the likelihood of results being parameter dependent, survival fractions are calculated for multiple combinations of alpha and beta. The effect of the time release schedule is determined by comparing survival fractions calculated for different sets of time weighting coefficients while holding the LQ parameters constant.

The magnitude of the cell kill is dependent on the drug distribution as well as the concentration above which no further sensitization is achieved. The magnitude of the drug distribution is determined by the release rate of the brachytherapy spacers while the relative drug distribution is determined by the diffusion-elimination ratio of the drug or drug carriers. Drug distributions were calculated for a values of $\phi_b$ ranging from 3 to 0.03 which correspond to small regions of sensitization to sensitization of large regions of the gland. Survival fractions were calculated for values of $C_{sat}$ ranging from 3 to 0.3. Large values of $C_{sat}$ correspond to drug distributions where greater concentrations result in increases in sensitization while low values of $C_{sat}$ correspond to drug concentrations largely above the saturation concentration. The value of $C_{sat}$ is held constant for comparison of time release schedules.
The release of drug was assumed to be constant ranging from 1 week to 7 weeks. One week of sensitization would correspond to $w(t)=1$ for $t<1$ week and $w(t)=0$ for $t>1$ week while a 7 week sensitization was modeled as $w(t)=1/7$ for all 7 weeks. Average survival fractions for differing release schedules were normalized to the survival fraction of 1 week sensitization. Two limiting behaviors were observed. For drug distributions in the linear range, shorter sensitizations result in lower average survival fraction as shown in Figure 4 as the low concentration plot. In this situation, it would be preferable to take advantage of sensitization when the radiation dose is greatest. For drug concentrations in the saturated range, extended sensitizations have the greatest effect as shown in the lower curve which was monotonically decreasing. In this situation, the maximum sensitization is already achieved and extended sensitization is the dominant way to increase the effectiveness of the radiation. The dashed plot shows the intermediate situation where the release of the drug over the course of 1 week results in predominantly saturated concentrations slightly greater than $C_{sat}$. As a result, we see a decrease in average survival fraction with longer release. However the lower concentrations associated with extended release longer than 3 weeks, due to the constraint of fixed drug capacity, cause the drug distribution to enter the linear range and leads to increasing cell survival. The optimal duration of sensitization is largely independent of modeling parameters but is strongly dependent on the achievable drug concentrations suggesting the need to plan drug distributions in the same manner that radiation dose is planned.

4. CONCLUSION

Biologic in-situ image guided radiation brachytherapy offers the potential to improve the therapeutic ratio by planned localized radiosensitization of the prostate. The magnitude of the target sensitization and normal tissue sparing is dependent on the diffusion and elimination properties of the drug or drug carrier. The sensitization schedule that causes the greatest decrease in average cell survival is dependent on the achievable drug concentrations in comparison with the saturation concentration that produces the maximal sensitization. Further work is needed to improve our understanding of the distributions of drug or drug carrying nanoparticles around diffusion sources in tissue as well as the retention of drug when delivered from an interstitial source. The dependence of the sensitization on drug concentration suggest the need for planned drug source deployment and treatment planning systems that can calculate biologic effects in addition to dose distributions.
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REFERENCES

8 Gultepe E, Hagesha D, Casse BD et al., Small 6, 213-6 (2010).