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PHYSICS CONTRIBUTION

BIOLOGICAL *IN SITU* DOSE PAINTING FOR IMAGE-GUIDED RADIATION THERAPY USING DRUG-LOADED IMPLANTABLE DEVICES

ROBERT A. CORMACK, PH.D.,* SRINIVAS SRIDHAR, PH.D.,† W. WARREN SUH, M.D., M.P.H.,* ANTHONY V. D'AMICO, M.D., PH.D.,* AND G. MIKE MAKRIGIORGOS, PH.D.*

*Department of Radiation Oncology, Dana Farber Cancer Institute, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; and †Electronics Materials Research Institute, Northeastern University, and Department of Physics, Northeastern University, Boston, Massachusetts

Purpose: Implantable devices routinely used for increasing spatial accuracy in modern image-guided radiation treatments (IGRT), such as fiducials or brachytherapy spacers, encompass the potential for *in situ* release of biologically active drugs, providing an opportunity to enhance the therapeutic ratio. We model this new approach for two types of treatment.

Methods and Materials: Radiopaque fiducials used in IGRT, or prostate brachytherapy spacers ("eluters"), were assumed to be loaded with radiosensitizer for *in situ* drug slow release. An analytic function describing the concentration of radiosensitizer versus distance from eluters, depending on diffusion–elimination properties of the drug in tissue, was developed. Tumor coverage by the drug was modeled for tumors typical of lung stereotactic body radiation therapy treatments for various eluter dimensions and drug properties. Six prostate ^{125}I brachytherapy cases were analyzed by assuming implantation of drug-loaded spacers. Radiosensitizer-induced subvolume boost was simulated from which biologically effective doses for typical radiosensitizers were calculated in one example.

Results: Drug distributions from three-dimensional arrangements of drug eluters versus eluter size and drug properties were tabulated. Four radiosensitizer-loaded fiducials provide adequate radiosensitization for ~4-cm-diameter lung tumors, thus potentially boosting biologically equivalent doses in centrally located stereotactic body treated lesions. Similarly, multiple drug-loaded spacers provide prostate brachytherapy with flexible shaping of "biologically equivalent doses" to fit requirements difficult to meet by using radiation alone, *e.g.*, boosting a high-risk region juxtaposed to the urethra while respecting normal tissue tolerance of both the urethra and the rectum.

Conclusions: Drug loading of implantable devices routinely used in IGRT provides new opportunities for therapy modulation via biological *in situ* dose painting. © **2010 Elsevier Inc.**

Image-guided radiation therapy, Fiducials, Brachytherapy seeds, Lung SBRT treatment.

INTRODUCTION

Despite advances in the precision, accuracy, and mode of therapy delivery, the effective use of present day radiation therapy modalities (intensity-modulated radiation therapy, image-guided radiation therapy [IGRT], brachytherapy, protons) remains limited by the radiation dose to normal structures surrounding the target region. Image-guided lung stereotactic body treatment achieves over 90% rates of tumor control for early-stage peripheral lesions. However, treatment of centrally located lung lesions to full dose (20×3 Gy) is associated with unacceptable toxicities (1), thus excluding a substantial fraction of patients from the benefits of new technology. Prostate cancer is another example where image-guided brachytherapy has made substantial progress (2, 3) but remains limited by normal tissue tolerance of adjacent and interposed structures. The means to augment the biological action of radiation therapy in tumors without additional toxicity to surrounding normal tissues would be useful for improving the therapeutic ratio.

In order to achieve high spatial accuracy, modern radiation therapy practice routinely utilizes implantation of fiducials (external beam therapy) or source spacers (brachytherapy) into the tumor (4). These implantable devices are an essential technical component of the delivery of radiation but are inert and provide no direct therapeutic function. We propose that the routine introduction of these implantable devices in tumors provides opportunities for delivering *in situ* therapy or radiosensitization during IGRT as part of the established routine procedures. For example, coating radiopaque fiducials with polymers allowing slow release of radiosensitizers

Reprint requests to: G. Mike Makrigiorgos, Ph.D., Division of Medical Physics and Biophysics, Department of Radiation Oncology, DFCI-BWH Hospitals, 75 Francis Street, Boston, MA 02115. Tel: (617) 525-7122; Fax: (617) 582-6037; E-mail: mmakrigiorgos@lroc.harvard.edu

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or cytotoxic compounds would allow fiducials to act as dual-functioning devices, providing both image guidance and *in situ* bioactive drug release. Such coatings have been described on titanium and aluminum (5) surfaces and on stents used in cardiology practice (6, 7). Similarly, spacers used to separate ^{125}I sources in prostate brachytherapy procedures can be replaced by polymeric rods (8, 9) acting as both spacers and drug-release molecules to provide additional flexibility in shaping biological dose distributions that avoid normal structures while boosting dose to the target. Since implantation of these devices is already part of current radiation therapy practice, use of drug-loaded fiducials and spacers would not cause any added risk or discomfort to patients during the implantation procedure.

We present a modeling study of drug distributions that would result from dual-action fiducials or dual-action brachytherapy spacers, assuming these are implanted in geometries commonly used during lung or prostate radiation treatments. We provide phenomenological modeling of drug concentration vs. effective diffusion distance that is independent of a particular choice of drug or tumor tissue type. The generalized approach describes the required balance between drug diffusion, elimination, and eluter size in order to achieve a desired drug distribution in the target volume. As we do not focus on a specific drug or radiosensitizer, agent-specific biological aspects of drug radiation interaction are not explicitly accounted for in this investigation. Instead, by assuming typical radiosensitization enhancements encountered in radiation oncology practice, we compare the ability to deliver a local increase in effective dose by either brachytherapy alone or by brachytherapy plus *in situ*-delivered radiosensitizer. Assisting IGRT treatment via the proposed biological *in situ* IGRT (BIS-IGRT) dose painting can be generalized beyond radiosensitizers to utilize a variety of molecularly targeted biological agents and to provide a practical means to translate recent developments in biological targeting agents to clinical radiation oncology practice.

METHODS AND MATERIALS

Analytic function for modeling drug diffusion from a chemical source

The concentration of drug versus the distance from a drug-eluting source can be modeled by the diffusion equation (10). Assuming a uniform diffusing medium around a spherical eluter, the diffusion equation may be expressed in spherical coordinates as

$$\frac{\partial A}{\partial t} = D\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial A}{\partial r}\right) \quad (1)$$

where r is radius, t represents time, A is drug concentration, and D is the diffusion constant. To model the distribution of drug around a drug-eluting object in tissue, accounting also for drug removal, Eq. 1 can be modified to include a term representing elimination of the drug:

$$\frac{\partial A}{\partial t} = D\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial A}{\partial r}\right) - kA \quad (2)$$

where k is a measure of the rate of elimination of the agent from the system by any means. For a first approximation, we have assumed constant rates of drug release from the eluter and drug elimination in tissue. Under these conditions, it can be shown that a time-independent function that satisfies Eq. 2 is

$$A = \frac{A_o a}{r}\exp(-\phi_b(r-a)) \quad (3)$$

where a is the radius of the eluter, $\varphi_b = (k/D)^{1/2}$ is the elimination–diffusion modulus, and $r > a$. The parameter φ_b depends on the properties of the drug and medium chosen. Figure 1 illustrates a plot of Eq. 3 as a function of the distance from the center of a drug eluter, for two values of eluter radius and two values of φ_b. A lower value of φ_b increases the depth of penetration of the drug. Lower values of φ_b can be achieved either by increasing the diffusion length (D) or by decreasing the elimination constant (k). To provide a rough comparison with the attenuation of radiation with distance from a point radioactive source, the inverse square curve is also plotted. Values of the diffusion–elimination modulus φ_b plotted in Fig. 1 encompass the range of φ_b values (0.4–1.3 mm^{-1}), inferred from experimentally measured distribution of taxol as a function of distance from the eluter surface in the monkey brain (11, 12).

The diffusion distance of a drug in tissue can be modified in various ways, including adding of micelles (13) to change local hydrophilicity or lipophilicity or by using dextrans to increase convection. We (5) and others (14) have also shown that the drug can be loaded on nanoparticles which are then incorporated in the eluter. This approach does not change the chemical properties of the drug but takes advantage of the nanoparticle properties to change the effective rate of elimination and thus φ_b. Transport of nanoparticles and biomolecules in tumors is determined by the enhanced permeability and retention effect (15). The enhanced permeability facilitates drug delivery, while the retention, prolonged for weeks or months, can be therapeutically beneficial (15). Data for real-time tracking of quantum dot complexes of nanometer size in tumors (16) show that nanoparticle extravasation in the bloodstream displays both fast and slow movement, with speeds ranging from 100 to 600 μm/s. Large nanostructures such as liposomes, with diameters of 100 to 400 nm, appear to have even lower mobility (17). In summary, given multiple means to adjust the tissue diffusion properties of the drug, in this work φ_b and eluter radius are assumed to be parameters that can be modulated, and thus they are treated as variables.

Few eluters: fiducial markers

Commercially available cylindrical markers used in image-guided lung stereotactic body radiation therapy (SBRT) range from 0.8 to 1.2 mm in diameter and from 3 to 20 mm in length. However, for simplicity throughout this work, we simulated spherical eluters and used the radially symmetrical Eq. 3. To represent the range of fiducial sizes, we simulated small and large eluters (radii of 0.5 and 2 mm, respectively). We modeled four drug-loaded markers within a spherically shaped tumor with the eluters located at the vertices of a tetrahedron centered in the tumor, with the vertices being 5 mm from the tumor surface. The drug distribution is the sum of the distributions from each eluter, and the magnitude of the distribution is determined by A_0, the drug concentration at the surface of the eluter. The distance at which the drug concentration drops by a factor of 10 is often used as a measure of effective tissue penetration by the drug (12, 13). Accordingly, the volume of tumor with a drug concentration in excess of $A_0/10$ is taken as the metric to quantify the fraction of tumor that is sensitized by the drug. The sensitized fraction of tumor volume (I) is calculated for multiple values of φ_b and eluter radius.