Three-Dimensional Radiobiological Dosimetry (3D-RD): Application of Radiobiological Modeling to Patient-Specific, 3-D Imaging-based Internal Dosimetry

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Abstract

Phantom-based and patient-specific imaging-based dosimetry methodologies have traditionally yielded mean organ absorbed doses or spatial dose distributions over tumors and normal organs. In this work, radiobiological modeling is introduced to convert the spatial distribution of absorbed dose into biologically effective dose and equivalent uniform dose parameters. The methodology is illustrated using data from a thyroid cancer patient treated with radioiodine. METHODS: Three registered SPECT/CT scans were used to generate 3-D images of radionuclide kinetics (clearance rate) and cumulated activity. The cumulated activity image and corresponding CT were provided as input into an EGSnrc-based Monte Carlo calculation; the cumulated activity image defined the distribution of decays while an attenuation image derived from CT was used to define the corresponding spatial tissue density and composition distribution. The rate images were used to convert the spatial absorbed dose distribution to a Biologically Effective Dose (BED) distribution which was then used to estimate a single Equivalent Uniform Dose (EUD) for segmented volumes of interest. EUD was also calculated from the absorbed dose distribution directly. RESULTS: Validation using simple models and also comparison of the dose-volume histogram to a previously analyzed clinical case is shown as well as the mean absorbed dose, mean biologically effective dose, and equivalent uniform dose for an illustrative clinical case of a pediatric thyroid cancer patient with diffuse lung metastases. The mean absorbed dose, mean BED and EUD for tumor was 57.7, 58.5 and 25.0 Gy, respectively. Corresponding values for normal lung tissue were 9.5, 9.8 and 8.3 Gy, respectively. CONCLUSION The analysis demonstrates the impact of radiobiological modeling on response prediction. The 57% reduction in the equivalent dose value for the tumor reflects a high level of dose non-uniformity in the tumor and a corresponding reduced likelihood of achieving a tumor response. Such analyses are expected to be useful in treatment planning for radionuclide therapy.

Key Words: dosimetry, radiobiology, 3D-ID, patient-specific dosimetry, treatment planning

Introduction

The tools and methodologies for performing radionuclide dosimetry for therapeutic nuclear medicine applications have evolved over the past two decades such that current research is focused on patient-specific 3-D image or voxel-based approaches (*1*,*2*). In this work, we describe an extension of this methodology that incorporates radiobiological modeling to account for the spatial distribution of absorbed dose and also the effect of dose-rate on biological response. The methodology is incorporated into a software package, called 3D-RD for 3D-Radiobiological Dosimetry.

Patient-specific, 3D-image based internal dosimetry is a dosimetry methodology in which the patient's own anatomy and spatial distribution of radioactivity over time are factored into an absorbed dose calculation that provides as output the spatial distribution of absorbed dose (*3*-*9*). This is accomplished by accepting as input a CT image of the patient and one or more SPECT or PET images. The CT image is used to provide density and composition of each voxel for use in a Monte Carlo calculation; CT images are also used to define organs or regions of interest for computing spatially averaged doses. A longitudinal series of PET or SPECT images are used to perform a voxel-wise time integration and obtain the cumulated activity or total number of disintegrations on a per voxel basis. If multiple SPECT or PET studies are not available, a single SPECT or PET can be combined with a series of planar images. By assuming that the relative spatial distribution of activity does not change over time, it is possible to apply the kinetics obtained from longitudinal planar imaging over a tumor or normal organ volume to the single SPECT or PET image, thereby obtaining the required 3-D image of cumulated activity. The results of such a patient-specific 3-D imaging-based calculation can be represented as a 3-D parametric image of absorbed dose, as dose –volume histograms over user-defined regions of interest or as the mean, and range of absorbed doses over such regions(*10*).

The objective of such patient-specific, voxel-based absorbed dose calculations is to better predict biological effect. The highly patient-specific methodology outlined above is a step in this direction; a further step towards this goal would couple the output described above with radiobiological models that account for the spatial absorbed dose distribution and the rate at which it is delivered. The former can be described by the

radiobiological model-derived quantity, the equivalent uniform dose (EUD, defined on a per structure basis); the latter by the biologically effective dose (BED, defined on a per voxel basis).

The uniformity (or lack thereof) of absorbed dose distributions and their biological implications have been examined extensively, primarily in animal studies, (*11-16*). Dose-volume histograms have been used to summarize the large amount of data present in 3-D distributions of absorbed dose in radionuclide dosimetry studies (*17*). The EUD model takes this one step farther by introducing the radiobiological parameters, α and β, the sensitivity per unit dose and per unit dose squared, respectively, in the linear-quadratic dose-response model. The EUD model converts the spatially varying absorbed dose distribution into an equivalent uniform absorbed dose value that would yield a biological response similar to that expected from the original dose distribution. This provides a single value that may be used to compare different dose distributions; the value also reflects the likelihood that the magnitude and spatial distribution of the absorbed dose is sufficient for tumor kill (*15*).

That dose rate influences response has been known since at least the early seventies (*18*). The BED formalism (*19,20*), initially termed Extrapolated Response Dose, was developed to compare different fractionation protocols for external radiotherapy. BED may be thought of as the actual physical dose adjusted to reflect the expected biological effect if it were delivered at a reference dose-rate. As in the case of EUD, by relating effects to a reference value, this makes it possible to compare doses delivered under different conditions. In the case of EUD the reference value relates to spatial distribution and is chosen to be a uniform distribution. In the case of BED the reference value relates to dose rate and is chosen to approach zero (total dose delivered in an infinite number of infinitesimally small fractions).

In radionuclide therapy, the dose rate is temporally variant and a number of investigators have examined the implications of this on tumor control and normal tissue toxicity (*21-26*). To date, almost all clinical studies have considered total absorbed dose, the majority of which is delivered at an exponentially decreasing dose rate, while the benchmark for projecting potential toxicity and justifying initial phase I activity and absorbed dose levels has been the experience with normal organ tolerance in external beam radiotherapy, the majority of which is delivered at high dose-rate in daily 2-Gy

fractions over a period of 30 to 40 days. The simplest and more generally applied (exponential repair) BED model was implemented in this work.

The implications of radiobiological modeling and response prediction are examined using a simple spherical representation of target and normal organ tissue. The methodology is also applied to a clinical case that illustrates the features and potential clinical importance of the approach.

Materials and Methods

The previously developed 3-D imaging-based patient-specific dosimetry methodology (*8,10,27*) has been extended to better incorporate Monte Carlo calculations, which are needed in cases of variable tissue density, and also to include radiobiological modeling by incorporating the BED and EUD formalisms. The resulting 2nd generation dosimetry package, referred to as 3D-RD for 3D-Radiobiological Dosimetry, was applied in a patient study to illustrate its features and impact on patient dosimetry.

3-Dimensional Imaging Based Dosimetry

3-D Imaging-based Dosimetry entails the following steps: 1. Input a series of longitudinal 3-D SPECT/CT or PET/CT images. 2. Register the images across time by using both the SPECT or PET data set and the corresponding CT set (*28*). 3. Obtain the cumulated activity for each voxel either by fitting an exponential function to each voxel and integrating analytically over time or by performing a numerical integration over time for each voxel (*29,30*). 4. Use the CT image voxel values to assign density and composition (i.e., water, air and bone) (*5,31*). 5. Use the 3-D cumulated activity image and the matched density and composition image to perform a Monte Carlo calculation to estimate the absorbed dose by tallying energy deposition in each voxel (*5*). 6. Present the absorbed dose distribution as a set of images, isodose contour plots or as dose volume histograms for user-identified tumor or normal organ volumes.

To introduce radiobiological modeling, the process described above was modified so that step 3 is preceded by an estimate of clearance rate in each voxel. This information, coupled with assignment of the radiobiological parameters, α, β, μ, the radiosensitivity per unit dose, radiosensitivity per unit dose squared and the repair rate assuming an exponential repair process, respectively (*32*), is used to generate a BED

value for each voxel, and subsequently an EUD value for a particular user-defined volume.

In external radiotherapy, the expression for BED is:

$$BED = Nd\left(1+\frac{d}{\alpha/\beta}\right) \quad (1).$$

This equation applies for N fractions of an absorbed dose, d, delivered over a time interval that is negligible relative to the repair time for radiation damage (*i.e.*, at high dose rate) where the interval between fractions is long enough to allow for complete repair of repairable damage induced by the dose d; repopulation of cells is not considered in this formulation. The parameters, α and β are the coefficients for radiation damage proportional to dose (single event is lethal) and dose squared (two events required for lethal damage), respectively. A more general formulation of equation 1 is:

$$BED(T) = D_T(T)\cdot RE(T) \quad (2),$$

where $BED(T)$ is the biologically effective dose delivered over a time T, $D_T(T)$ is the total dose delivered over this time and $RE(T)$ is the relative effectiveness per unit dose at time, T. The general expression for $RE(T)$ assuming a time-dependent dose rate described by $\dot{D}(t)$ is given by:

$$RE(T) = 1+\frac{2}{D_T(T)\left(\frac{\alpha}{\beta}\right)}\times\int_0^T dt\cdot\dot{D}(t)\int_0^t dw\cdot\dot{D}(w)e^{-\mu(t-w)} \quad (3).$$

The second integration over the time-parameter, w, represents the repair of potentially lethal damage occurring while the dose is delivered, i.e., assuming an incomplete repair model (*33*). If we assume that the dose rate for radionuclide therapy, $\dot{D}(t)$, at a given time, t, can be expressed as an exponential expression:

$$\dot{D}(t) = \dot{D}_0 e^{-\lambda t} \quad (4),$$

where $\dot{D}_0$ is the initial dose rate and λ is the effective clearance rate (= ln(2)/t_e; t_e=effective clearance half-life of the radiopharmaceutical), then, in the limit, as T approaches infinity, the integral in equation 3 reduces to:

$$\frac{\dot{D}_0^{\,2}}{2\lambda(\mu-\lambda)} \quad (5).$$

Substituting this expression and replacing $D_T(T)$ with D, the total dose delivered, and using $\dot{D}_0 = \lambda D$, which may be derived from equation 4, we get:

$$BED = D + \frac{\beta D^2}{\alpha}\left(\frac{\ln(2)}{\mu \cdot t_e + \ln(2)}\right) \quad (6).$$

In this expression, the effective clearance rate, λ, is represented by $\ln(2)/t_e$. The derivation follows closely that described by Dale, *et. al*, (*32*,*34*).

In cases where the kinetics in a particular voxel are not well fitted by a single decreasing exponential alternative formalisms have been developed that account for an increase in the radioactivity concentration followed by exponential clearance (*35*). Since the number of imaging time-points typically collected in dosimetry studies would not resolve a dual parameter model (*.i.e.*, uptake and clearance rate) the current methodology assumes that the total dose contributed by the rising portion of a tissue or tumor time-activity curve is a small fraction of the total absorbed dose delivered.

Equation 6 depends upon the tissue-specific intrinsic parameters, α, β and μ. These three parameters are set constant throughout a user-defined organ or tumor volume. The voxel specific parameters are the total dose in a given voxel and the effective clearance half-life assigned to the voxel. Given a voxel at coordinates (i,j,k), D^{ijk} and t_e^{ijk} are the dose and effective clearance half-life for the voxel. The imaging-based formulation of expression 6 that is incorporated into 3D-RD is then:

$$BED^{ijk} = D^{ijk} + \frac{\beta D^{ijk\,2}}{\alpha}\left(\frac{\ln(2)}{\mu \cdot t_e^{\,ijk} + \ln(2)}\right) \quad (7).$$

The user inputs values of α, β and μ for a particular volume and D^{ijk} and t_e^{ijk} are obtained directly from the 3-D dose calculation and rate image, respectively. This approach requires organ or tumor segmentation that corresponds to the different α, β and μ values. The dose values are obtained by Monte Carlo calculation as described previously, and the effective clearance half-lives are obtained by fitting the data to a single exponential function, as has been previously described (*10*,*36*). Once a spatial distribution of BED values has been obtained a dose-volume histogram of these values can be generated. Normalizing so that the total area under the BED (differential) DVH curve is one, converts the BED DVH to a probability distribution of BED values denoted, P(ψ), where ψ takes on all possible values of BED. Then, following the derivation for EUD from

(*15*), the EUD is obtained as:

$$EUD = -\frac{1}{\alpha}\ln\left(\int_0^\infty P(\psi)e^{-\alpha\psi}d\psi\right) \quad (8).$$

The EUD of the absorbed dose distribution, as opposed to the BED distribution, can also be obtained using equation 8, but using a normalized DVH of absorbed dose values rather than BED values. Expression 8 may be derived by determining the absorbed dose required to yield a surviving fraction equal to that arising from the probability distribution of dose values (absorbed dose or BED) given by the normalized DVH.

It is important to note that a rigorous application of equation 7 would require estimation of the absorbed dose at each time point; the resulting set of absorbed dose values for each voxel would then be used to estimate t_e^{ijk}. In using activity-based rate images to obtain the t_e^{ijk}, instead of the absorbed dose at each time point, the implicit assumption is being made that the local, voxel self- absorbed dose contribution is substantially greater than the cross-voxel contribution. This assumption avoids the need to estimate absorbed dose at multiple time-points, thereby substantially reducing the time required to perform the calculation. A methodology is being developed to address this issue and will be described in a separate report.

Radiobiological Parameters

The illustrative simplified examples and also the clinical implementation involve dose estimation to lungs and to a thyroid tumor. Values of α and β for lung were obtained from Van Dyk, et al. (*37*,*38*), and for thyroid cancer were obtained from Gaussen et al. (*39*) and Challeton et al. (*40*) , respectively. The constant of repair, μ, for each tissue was taken from Bodey et. al.(*41*). The parameter values are listed in table 1.

Clearance Rate Effects

A sphere was generated in a 56^3 matrix such that each voxel represents a volume of $(0.15\text{cm})^3$. All elements with a centroid greater than 1 cm and less than or equal to $(2.0\text{cm})^{1/3}$ from the matrix center (at 28,28,28) were given a clearance rate value (λ) corresponding to a half life of 2 hours.. Those elements with a center position less than or

equal to 1.0 cm from the center voxel were assigned a λ value equivalent to a 4 hour half life. In this way an outer shell (with 2 hour half life) was separated from an inner sphere (with 4 hour half life) (Fig. 1). This allowed both regions to have nearly equivalent volumes. The procedure was used to generate a matrix representing a sphere with a uniform absorbed dose distribution despite having non uniform clearance rate. This is accomplished by varying the initial activity such that the cumulative activity of both regions is identical. These two matrices were input into 3D-RD for the BED and EUD calculations. Input of a dose distribution rather than an activity distribution was necessary to make comparison with an analytical calculation possible. The partial-volume effects of a voxelized vs. idealized sphere were avoided by using the shell and sphere volumes obtained from the voxelized sphere rather than from a mathematical sphere. The impact of sphere voxelization on voxel-based MC calculations has been previously examined (*42*).

Absorbed Dose Distribution Effects

To demonstrate the impact of dose distribution on EUD, the following model was evaluated (Fig. 2). First, a uniform density sphere (1.04 g/cc in both regions) was evaluated with a uniform absorbed dose distribution of 10 Gy. Second, the uniform sphere was divided into two equal volume regions. The inner sphere was assigned zero absorbed dose while the outer shell was assigned an absorbed dose of 20 Gy. The effective half-life was 2 hours in both regions. Again the whole sphere average dose was 10 Gy.

Density Effects

To illustrate the effect of density differences, a sphere with radius 1.26 cm was created that had unit cumulated activity throughout, but a density of 2 g/cc in a central spherical region with radius 1 cm and 1 g/cc in the surrounding spherical shell (Fig. 3). The input parameters were chosen to yield a mean dose over the whole sphere of 10 Gy. Since, for a constant spatial distribution of energy deposition, the absorbed dose is a function of the density, the absorbed dose in the center is less than the absorbed dose of the shell. The distribution was selected so that the average over the two regions was 10 Gy. 3D-RD was used to generate a spatial distribution of absorbed dose values which

were then used to estimate EUD over the whole sphere.

Application to a Patient Study

The 3D-RD dosimetry methodology was applied to an 11 year old female thyroid cancer patient who has been previously described in a publication on MCNP-based 3D-ID dosimetry (*42*).

Imaging

SPECT/CT images were obtained at 27, 74, and 147 hours post injection of a 37MBq (1.0mCi) tracer ^{131}I dose. All three SPECT/CT images focused on the chest of the patient and close attention was directed at aligning the patient identically for each image. The images were acquired with a GE Millennium VG Hawkeye system with a 1.59 cm thick crystal. All images shown were displayed using the software package, MIAU (*28*).

An OS-EM based reconstruction scheme was used to improve quantization of the activity map (*43*). A total of 10 iterations with 24 subsets per iteration was used. This reconstruction accounts for effects including attenuation, patient scatter, and collimator response. Collimator response includes septal penetration and scatter. The SPECT image counts were converted to units of activity by accounting for the detector efficiency and acquisition time. This quantification procedure, combined with image alignment, made it possible to follow the kinetics of each voxel. Using the CTs, which were acquired with each SPECT, each subsequent SPECT and CT image was aligned to the 27 hour 3-D image set. A voxel by voxel fit to an exponential expression was then applied to the aligned data set (*27*) to obtain the clearance half-time for each voxel.

To obtain mean absorbed dose, mean BED and EUD, as well as absorbed dose and BED-volume-histograms, voxels were assigned to either tumor or normal lung parenchyma using an activity threshold of 21% of highest activity value; this approach is the same as that used in reference (*42*).

Results

A spherical model was used to validate and illustrate the concepts of BED and EUD.

Clearance Rate Effects

Assuming that the sphere was lung tissue and applying the radiobiological parameters listed in table 1, the BED value in the slower clearing region, corresponding to the inner sphere with an activity clearance half-life of 4 hours, was 13.14 Gy. The faster clearing region (outer shell, 2 hr half-life) yielded a BED value of 15.69 Gy. The same model using the radiobiological values for tumor gave 10.09 Gy and 11.61 Gy for the slower clearing and faster clearing regions, respectively. The mean absorbed dose (AD) value for all these regions was 10 Gy.

Absorbed Dose Distribution Effects

The EUD value over the whole sphere when a uniform activity distribution was assumed recovered the mean absorbed dose of 10 Gy. A non-uniform absorbed dose distribution was applied such that the inner sphere was assigned an absorbed dose of zero, and an outer shell of equal volume, an absorbed dose of 20 Gy, In this case, the mean absorbed dose is 10 Gy, but the EUD was 1.83 Gy. The substantially lower EUD value is no longer a quantity that may be obtained strictly on physics principles, but rather is dependent on the applied biological model. The true absorbed dose has been adjusted to reflect the negligible probability of sterilizing all cells in a tumor volume when half of the tumor volume receives an absorbed dose of zero.

Density Effects

In the sphere with non-unform density (inner sphere density of 2 g/cc, outer shell of equal volume (1 g/cc)) and an average absorbed dose of 10 Gy, the EUD over the whole sphere was 6.83 Gy. The EUD value is lower than the absorbed dose value to reflect the dose non-uniformity in spatial absorbed dose (inner sphere = 5 Gy, outer shell = 15 Gy) arising from the density differences.

Application to a Patient Study

A 3D-RD calculation was performed for the clinical case described in the methods. A dosimetric analysis for this patient, without the radiobiological modeling described in this work has been previously published using the Monte Carlo code MCNP as opposed to EGSnrc which was used in this work (*42*). The clinical example illustrates all of the elements investigated using the simple spherical geometry. As shown on the CT scan (Fig. 4a), there is a highly variable density distribution in the lungs due to the tumor infiltration of normal lung parenchyma. Coupled with the low lung density, this gives a density and tissue composition that includes air, lung parenchyma and tumor (which was modeled as soft tissue). As shown on figures 4b and 4c, the activity and clearance kinetics of ^{131}I are also variable over the lung volume. These two data sets were used to calculate the cumulated activity images shown in figure 4d.

A comparison between the EGS-based 3D-RD calculation and the previously published MCNP-based calculation (*42*) was performed. Figure 5 depicts the DVH of the absorbed dose distribution obtained with 3D-RD superimposed on the same plot as the previously published DVH. Good overall agreement between the two DVHs is observed and the mean absorbed doses, expressed as absorbed dose per unit cumulated activity in the lung volume are in good agreement, 3.01 x 10^{-5} and 2.88 x 10^{-5} mGy/MBq-s per voxel, for the published, MCNP-based, and 3D-RD values, respectively.

Figures 6 and 7 depict the results obtained with the radiobiological modeling capabilities of 3D-RD. Figure 6 depicts a parametric image of BED values. Within this image the spotty areas of highest dose are areas where high activity and low density overlap. In Figure 7a, normalized (so that the area under the curve is equal to 1) DVH and BED DVH (BVH) are shown for tumor voxels. The near superimposition of DVH and BVH suggests that dose rate will have a minimal impact on tumor response in this case. Figure 7b depicts the normalized BVH for normal lung parenchyma. The DVH and BVH are given in Gy and reflect the predicted doses resulting from the administered therapeutic activity of 1.32 GBq (35.6 mCi) of ^{131}I. These plots may be used to derive EUD values. It is important to note that the volume histograms must reflect the actual absorbed dose delivered and not the dose per unit administered activity. This is because

the EUD is a nonlinear function of absorbed dose. The model relies on estimation of a tumor control probability to yield the equivalent uniform dose. If the data used to estimate EUD are expressed as dose per administered activity the EUD value will be incorrect. Mean absorbed dose, mean BED, and EUD are summarized in table 2. The EUD value for tumor, which accounts for the effect of a non-uniform dose distribution, was approximately 43% of the mean absorbed dose. This reduction brings the absorbed dose to a range that is not likely to lead to a complete response. The analysis demonstrates the impact of dose non-uniformity on the potential efficacy of a treatment.

Discussion

The previously developed, patient-specific dosimetry package, 3D-ID, is being re-written to better integrate Monte Carlo calculations and also to incorporate radiobiological modeling. The new package, 3D-RD for 3D-Radiobiological Dosimetry, provides the radiobiological dose parameters, biologically equivalent dose (BED) and Equivalent Uniform Dose (EUD). The former adjusts the physical absorbed dose to reflect the impact of dose-rate on tissue response, the latter accounts for the spatial distribution of dose in adjusting the physical absorbed dose value.

The concept (and value) of EUD is illustrated by considering a tumor in which one-half of the volume receives a dose of 200 Gy and the other half 0 Gy. Even though the average over the tumor volume is 100 Gy, such an absorbed dose distribution would lead to treatment failure since the tumor half not exposed to radiation would regrow. In this case the equivalent absorbed dose delivered uniformly throughout the tumor volume (i.e., the EUD) would be close to zero in order to be consistent with the expected biological effect of the dose distribution described above.

Although we have applied the EUD model to the lungs, EUD is not a valid measure of normal organ toxicity since normal organs have a structural organization. Two hundred Gy to even a small portion of the spine can lead to paralysis; in contrast, 200 Gy to a large portion of the liver might be inconsequential since the liver can regenerate. Normal organ EUD should not be related to the potential normal organ toxicity, but rather, the difference between EUD and mean absorbed dose over a normal organ volume should be seen as a reflecting the spatial absorbed dose distribution within

a normal organ.

The importance of BED has been recently highlighted by the use of engineered, lower molecular weight targeting agents (peptides and single-chain constructs) and also by multi-step targeting approaches (*44-48*). The targeting and excretion kinetics of these agents differ substantially, and, as suggested by pre-clinical and clinical evidence (*21,49-53*), the dose-rate is an important parameter in understanding normal organ toxicity and tumor response. The BED model has also been used in combination with external beam radiotherapy/radionuclide therapy studies (*54,55*).

Calculation of EUD and BED requires knowledge of the radiosensitivity and repair kinetic parameters. In the calculations presented in this work, a single set of thyroid cancer-specific or normal lung-specific parameter values were applied to all tumor- and normal lung-associated voxels, respectively. In the tumor, the assumption was made that all elements of the tumor were clonogenic. As is well-recognized, the radiosensitivity is likely to vary in different tumor regions (e.g., hypoxic vs. normoxic). Clonogenicity and DNA damage repair rate, will also be variable throughout the tumor (i.e., dormant vs rapidly proliferating regions). Nevertheless, BED and EUD are still potentially useful in comparing different tumor absorbed dose distributions in a patient trial population. In the case of normal organs, the same concerns apply, especially regarding radiosensitivity and repair-rate. In both cases, using the voxel-by-voxel implementation demonstrated in this work, it would be possible to sub-divide a particular organ or tumor region if radiobiological parameters were available for the organ or tumor sub-regions. For example, using ^{18}F-misonidazole PET imaging one could identify hypoxic tumor regions that might be radioresistant (*56,57*)

Conclusion

Radiobiological modeling has been implemented in a patient-specific, imaging-based dosimetry software package, 3D-RD (3D-Radiobiological Dosimetry). The software package was used to demonstrate the implications of accounting for the absorbed dose rate and uniformity to thyroid tumor and to normal lung tissue and was also used in a clinical case to demonstrate application of the methodology.

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TABLES

Table 1 – Radiobiological parameters used in the clinical 3D-RD calculation.

	α (Gy^{-1})	β (Gy^{-2})	μ (h^{-1})
Lung	.0172	.00521	1.5
Tumor	.365	.028	1.3

Table 2. – Summary of results from the clinical 3D-RD calculation.

	Tumor (Gy)	Lungs (Gy)
Mean Absorbed Dose	57.7	9.5
Mean BED	58.5	9.8
EUD	25.0	8.3

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Figure Legends

Figure 1. A uniform density sphere with an effective half –life of 2 hours in the outer green region and 4 hours within the red region. Green and red region have equal volume in this example. Initial activity in each region is selected so that total number of decays are equal in both regions.

Figure 2. A. Density distribution (uniform) for the uniform (B) and non-uniform (C) activity distribution models; in the non-uniform distribution, The same total activity from 3B is now concentrated into half the volume (the outer shell).

Figure 3. A. Spherical non-uniform density model where inner sphere is twice unit density (2.0 g/cc) and outer shell is at unit density (1.0 g/cc). B. Uniform activity distribution for the density model in figure 2A. C. Cross sectional slice of 3D-RD output for spherical non-uniform density model.

Figure 4. A. Clinical CT of patient showing non-uniform density distribution in lungs. B. Clinical SPECT of patient showing non-uniform activity distribution. C. Rate map generated from 3 longitudinally aligned SPECT images; regions with effective half-life > physical half-life of ^{131}I, reflect tumor uptake. D. Cumulative activity generated from rate map and SPECT.

Figure 5. Comparison between Song et al. MCNP based dose volume histogram over lung and tumor regions and the results from EGS using the same inputs. Mean value of MCNP method is 3.01×10^{-5} mGy/MBq-s while EGS Mean is 2.88×10^{-5} mGy/Mbq-s per pixel.

Figure 6. BED map resulting from 3D-RD using full patient specific data. While the values of AD and BED are different, their relative changes from voxel to voxel are so similar that it is nearly impossible to visually differentiate the two.

Figure 7. Differential absorbed dose (solid line) and BED-volume-histogram (dashed line) of (A) tumor and differential BED-volume-histogram of (B) lung resulting from full patient specific 3D-RD calculation.