Estimation of survival curve using microdosimetric kinetic model and Geant4-DNA in targeted radionuclide therapy

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Microdosimetric kinetic model is used for an estimation of survival curves of cell lines in particle therapy, which is based on specific energy (energy deposition in microscopic region). In NIRS Japan, targeted radionuclide therapy using alpha or Auger isotopes is investigated aimed at clinical treatment. The isotopes are transported to cell nucleus by an anti-body. Then, we calculated specific energies using a Monte Carlo simulation Geant4-DNA and estimated survival curves for ^{211}At (α) and ^{111}In (Auger), respectively. In addition, we compared survivals in the cases of isotope remains at cell membrane and is transported to nucleus. In the cases of ^{211}At at nucleus with 20 Bq/cc, surviving fraction was down to about 0.3 after 10 hours of administration. For ^{111}In with 2 Bq/cc, surviving fraction of 0.6 was estimated after 120 hours of administration. However isotopes at membrane were minimally-effective to cell killing. Thus, efficiency of transformation to nucleus will be critical for RI targeted therapy. The present study will be helpful for designing radiopharamceuticals and treatment planning.

Targeted radionuclide therapy

Targeted radionuclide therapy using alpha or Auger electron emitters is one of promising radiation therapy. HER2 (human epidermal growth factor receptor family) is overexpressing in breast cancer cell. Trastuzumab (Herceptin) is a molecular target anti-body to HER2. Thus, labeling isotopes such as ^{211}At (α) and ^{111}In (Auger) to Trastuzumab, cancer cells are killed by radiation. In addition, labeling nuclear transport signal to Trastuzumab (Trastuzumab-NLS) is more effective to cell killing by delivering isotopes to nucleus. Currently, investigations on targeted radionuclide therapy with ^{211}At and ^{111}In has been performed at National institute of radiological sciences (NIRS)

Microdosimetric kinetic model

The microdosimetric kinetic model was proposed by Hawkins [1]. The model predicts surviving fraction of cells based on dose absorbed by a subcellular structure referred to as a "domain" for any kind of radiation. The model has been applied to treatment planning of carbon therapy in Japan. The domains in sphere shape with 0.32 μm radii are distributed in the nucleus. When population of cells is exposed to ionizing radiation of macroscopic dose *D*, the dose absorbed by any individual domain, the specific energy *z*, is a random variable from domain to domain. Ionizing radiation is assumed to cause two types of primary lesion, type I and II. These creation rates are proportion to specific energy *z* and proportionality constants are λ_d and k_d, respectively. A type I lesion is lethal. If a type I lesion is created in a domain, the cell is always killed. A type II lesion may undergo one of four transformations as follows,

1. Convert to a lethal unrepairable lesion with first-order rate constant *a*
2. Pairwise combination with another type II lesion in the same domain to form a lethal lesion with second order rate constant b_d
3. Repaired with first order rate constant *c*
4. Persist for a length of time t_r, after which it becomes lethal lesion

These specifications are expressed in the following rate equations:

$$\frac{dx_I}{dt} = \dot{x}_I = \lambda_d \dot{z} + a x_{II} + b_d x_{II}^2 \quad (1)$$

$$\frac{dx_{II}}{dt} = \dot{x}_{II} = k_d \dot{z} - (a+c) x_{II} - 2 b_d x_{II}^2 \quad (2)$$

Where x_{II} and x_I are the mean number of type II and I lesion per domain that have absorbed *z*. According to [1], the term $2b_d x^2_{II}$ is negligible compared to $(a+c)x_{II}$ for less than about 125Gy macroscopic dose *D*. Equation (1) can be approximated to

$$\frac{dx_{II}}{dt} = \dot{x}_{II} \cong k_d \dot{z} - (a+c) x_{II} \,. \quad (3)$$

The numbers of type I and II lesion are

$$x_I = \left[\lambda_d + \frac{a k_d}{(a+c)} + \frac{c k_d}{(a+c)} e^{-(a+c)t} \right] z + \frac{b_d k_d^2}{2(a+c)} (1 - e^{2(a+c)t}) z^2 \,, \quad (4)$$

$$x_{II}(t) = k_d z e^{-(a+c)t} \,. \quad (5)$$

The number of type I lesion follows Poission distribution. The probability of the domains surviving without a type I lesion is given by

$$\begin{aligned} s_d &= e^{-x_I} \\ \ln s_d &= \ln e^{-x_I} = -x_I = -Az - Bz^2 \end{aligned} \quad (6)$$

where,

$$A = \lambda_d + \frac{ak_d}{(a+c)} + \frac{ck_d}{(a+c)} e^{-(a+c)t}, \quad (7)$$

$$B = \frac{b_d k_d}{2(a+c)} \left(1 - e^{-2(a+c)t}\right). \quad (8)$$

Surviving of a domain expressed by a linear quadratic equation similar to LQ model. The expected value of *ln S*, where S is surviving fraction of cell, is given by

$$\ln S = p\left\langle \ln s_d \right\rangle = -p < x_I > , \quad (9)$$

where p is number of domain. We calculated z by a Monte Carlo simulation described following section and obtained x_I. The model parameter values are listed in table 1, which are available from [2]. These parameters are derived from some experiments with HSG cell line.

Table 1. Parameter values of the model available from [2]

a (h^{-1})	c (h^{-1})	t_r (h)	b_d (h^{-1})	k_d (Gy^{-1})	λ_d (Gy^{-1})	p
0.022	2.165	2.284	0.3975	1.934×10^{-2}	1.934×10^{-4}	1840

Monte Carlo simulation, Geant4-DNA

In order to calculate specific energy z, Geant4-DNA [3] was used. The Geant4 general purpose particle-matter Monte Carlo simulation toolkit is being extended with processes for the modeling of early biological damage induced by ionizing radiation at the DNA scale. We constructed cell geometries with 9-13 μm radius of cell, 5 μm radius of nucleus, 0.32 μm radius domain and 5 nm thickness of membrane. These cells were densely distributed according to [4]. Alpha emitter of ^{211}At and Auger electron emitter of ^{111}In were decayed in a nucleus and cell membrane uniformly. The simulation geometries are shown in figure 1.

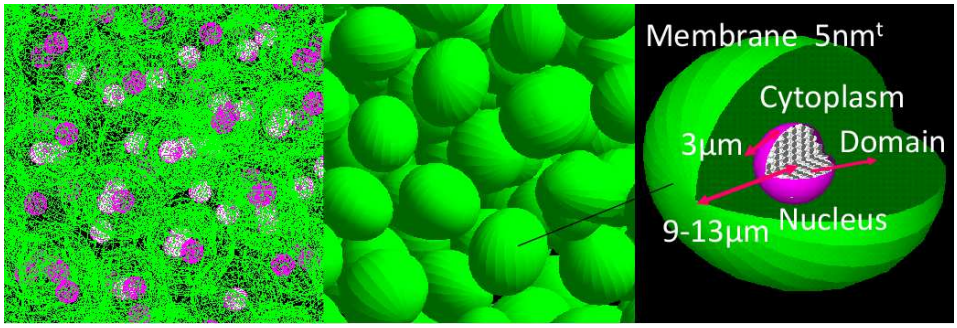

Figure 1. A simulation geometry in Geant4-DNA. Cells were densely distributed. Radii of cell,

nucleus and domain were 9-13 μm, 3 μm and 0.32 μm, respectively.

Results

The comparison of surviving fraction of ^{211}At and ^{111}In is shown in figure 2, where isotopes are located in nucleus. Activities of ^{211}At and ^{111}In are 20 and 2 Bq/cc, respectively. Numbers of isotope are almost equivalent. In the case of the concentration of ^{211}At, surviving fraction is down to about 0.3 after 10 hours of administration. For ^{111}In with 2 Bq/cc, surviving fraction of 0.6 was estimated after 120 hours of administration. Figure 3 shows comparisons of surviving fractions of ^{211}At (a) or ^{111}In (b) distributed at nucleus and membrane.

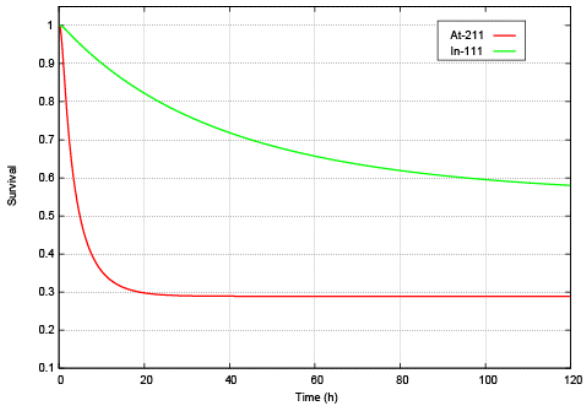

Figure 2. Surviving fractions as function of time in cases of ^{211}At and ^{111}In were distributed in nucleus with activity of 20 Bq/cc and 2 Bq/cc, respectively.

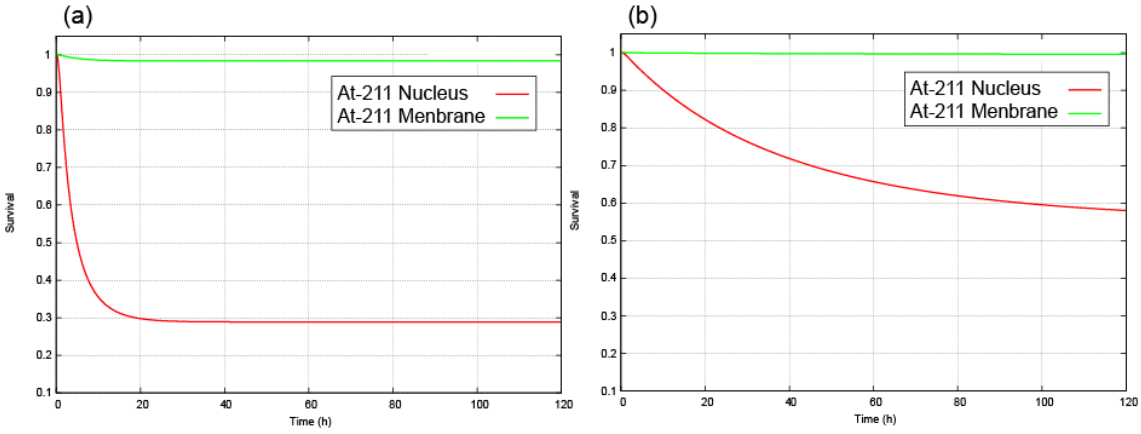

Figure 3. Comparisons of surviving fractions between isotopes were distributed in nucleus and membrane for ^{211}At (a) and ^{111}In (b).

Discussions and Conclusions

In the case of comparable numbers of isotope are delivered to nucleus for ^{211}At and ^{111}In, ^{211}At is significantly efficient to cell killing. However, we need higher concentration in tumors to obtain highly lethal rate. In addition, to deliver isotopes to nucleus is critically important for cell killing. In the present work, we demonstrated estimation of surviving fractions in targeted radionuclide therapy using MK model and Geant4-DNA. This work will be useful for determine amount of dosage and estimating not only tumor control but also surviving fraction of normal cell. However, we need to validate the estimation by comparing experimental survival curves. Also, we need to measure delivering efficiency to nucleus and parameter values of the model for normal cells.

References

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