SIMULATION PLATFORM FOR RADIONUCLIDE THERAPY (RNT) AND EXTERNAL BEAM RADIOTHERAPY (EBRT) IN VITRO STUDIES

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Introduction: It is well known that radiation delivered at high dose-rates (HDR) is biologically more effective than the same total/accumulated dose delivered at a low dose-rate (LDR)[1]. Since the dose rate in radionuclide therapy (RNT) is not constant but exponentially decreasing, the kinetics of DNA double-strand break (DSB) induction, repair and misrepair play an important role in therapeutic outcome[1]. Therefore, the aim of this study was to establish a simulation platform for RNT and external beam radiotherapy (EBRT) *in vitro* studies to investigate the differences in delivering dose by HDR/LDR RNT and HDR EBRT. In this study, the radionuclide ^{90}Y ($t_{½}$=64 h) was considered in the RNT simulations.

Materials and Methods: Monte Carlo simulations were performed with the GATE.7.1[2] software toolkit. A monolayer of 5000 non-overlapping spherical cells were randomly simulated at the bottom of a 200 μL cylindrical well (figure 1.a-b) to mimic the actual cell culture geometry (figure 1.e-f). All the cells were modelled as spheres with diameter of 15 μm. Each cell contains a simulated nucleus with diameter of 5μm shown in figure 2c. Cells and well were uniformly filled with water.

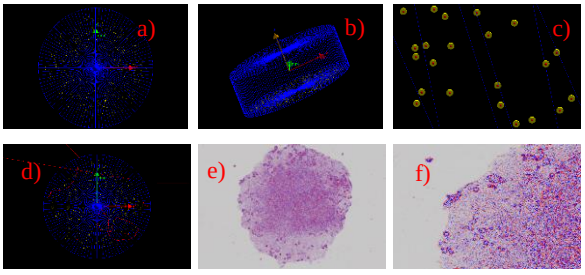

Figure 1. Geometry set-up in GATE simulation.

The ^{90}Y source was uniformly distributed throughout the well and between the cells (random locations outside of the cell volumes). Then 10^{10} beta particles with the energy spectrum of ^{90}Y were emitted from the source volume in random directions (figure 1d). Finally, results were scaled to the total number of beta particles which correspond to the range of activities in the well for 8 days' irradiation. Additional simulations were performed for the EBRT case. Cells were irradiated with a 6 MV Flattening Filter Free (FFF) LINAC beam (SSD = 100 cm) to deliver an average 10 Gy dose to the cells. The average number of hits to cell nucleus was calculated as a function of time for each activity. Similarly, the average number of hit to cell nucleus was calculated for EBRT simulation.

Results and Discussion: Figure 2 illustrates the simulation results for average number of beta particle hits to cell nucleus per decay ($\tilde{N}_n$/A(t)). The $\tilde{N}_n$/A(t) decreases exponentially as the activity decays in time. It is evident for ^{90}Y-LDR, $\tilde{N}_n$/A(t) is < 2 for doses ≈ 1-4 Gy during 8 days' irradiation. However, for ^{90}Y-HDR dose range ≈ 31-61 Gy, $\tilde{N}_n$/A(t) > 2 during the 8 days' irradiation. Also since EBRT has a constant dose rate, the average number of hit to cell nucleus was ≈ 295. The Lea–Catcheside factor (equation 1) in extended LQ (ELQ), $\ln(SF) = \alpha D + \beta G D^2$, incorporates the dose-rate effect, the kinetics of DSB

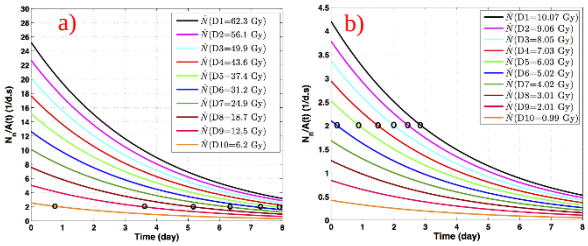

Figure 2. $\tilde{N}_n$/A(t) for HDR(a) and LDR(b) as a function of irradiation time for range of ^{90}Y activities.

creation and DNA repair constant (μ) to estimate the true fraction of surviving cells in an irradiated cell population.

$$G = \frac{2}{D^2}\int_{-\infty}^{\infty}\frac{dD(t)}{dt}\,dt\int_{-\infty}^{t}\frac{dD(t')}{dt'}e^{-\mu(t-t')}\,dt \quad \text{as } T\to\infty,$$
$$G_\infty = \frac{\lambda}{\lambda+\mu} \quad (1)$$

The G factor reaches unity for HDR EBRT because of high dose rate and short irradiation time and therefore greater damage from the quadratic part of LQ. However, G factor for both HDR, LDR ^{90}Y is smaller than 1 (*e.g.*,0.023). ^{90}Y dose rate decreases exponentially, therefore the repair in single strand-break (SSB) leading to DSB decreases exponentially due to decreasing of dose rate. This means insignificant damage from quadratic in the LQ model. Our simulation results also illustrate a similar effect of dose-rate on cell nucleus hit rate for exponentially decreasing beta emission from the ^{90}Y source.

Conclusion: Our simulation results demonstrate that the efficacy of RNT is dependent on the initial dose-rate at which dose is delivered. The RNT dose rate is inversely proportional to the radionuclide half-life for a given total dose. Therefore, a longer half-life radionuclide such as ^{90}Y delivers dose at a relatively lower rate. Therefore, higher initial activity (to obtain higher initial dose-rate), and a larger total dose delivered is required, to achieve an effective outcome.

References:

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2. Jan S, Santin et al (2004). GATE: a simulation toolkit for PET and SPECT *Phys. Med. Biol* 49(19):4543.