

“Parametric modeling study of intracellular radionuclide distribution impact in Targeted Alpha Therapy”

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In the context of predicting biological effects in Targeted Alpha Therapy (TAT), nano/micro-dosimetry are essential to consider the very heterogeneous dose deposition at cell level. The objective of this study is to evaluate theoretically the importance of radionuclide cell internalization in microtumors treated with TAT on physical and biological endpoints. We used Monte Carlo simulations to track alpha particles in complex *in silico* 3D cell populations using the CPOP/Geant4 code [1], which allows deformable cell membrane to mimic tissue compaction. The code was adapted to generate radionuclide source distributions in various internalization cases that may be encountered in targeted therapy [2] and collect specific energies, alpha kinetic energies and cross-fire contribution in each cell nucleus. The biophysical model NanOx (Nanodosimetry and Oxidative stress) [3] was used to calculate therapeutic indexes from the simulation such as Tumor Control Probability (TCP). We also studied the influence of the cell packing, tumor size, cell line, alpha’s energy and ²¹¹At radionuclide daughter diffusion after fixation. When regarding the specific energies, a low impact of radionuclide internalization was found, of less than 5% and 30% in cytoplasm and nucleus source distribution, respectively, compared to membrane adsorption only. The maximum was obtained for small tumors (30 μm radius) because of lower cross-fire contribution. The TCP calculations highlighted larger impact of radionuclide distribution for activity per cell below 30 mBq. For example, a factor up to 18 on TCP was obtained from membrane-to-nucleus distribution in a microtumor of 95μm radius treated with ²¹¹At. An RBEμ of 6.9 was calculated in the membrane distribution case. This study highlights the need for considering biological endpoints in the evaluation of intracellular radionuclide distribution impact in TAT response.

[1] Maigne, L., et al. *Physica Medica* 89 (2021): 41-50

[2] Bavelaar, B. M, et al., *Frontiers in pharmacology* 9 (2018): 996

[3] Cunha, M., et al. *Physics in Medicine & Biology* 62.4 (2017): 1248

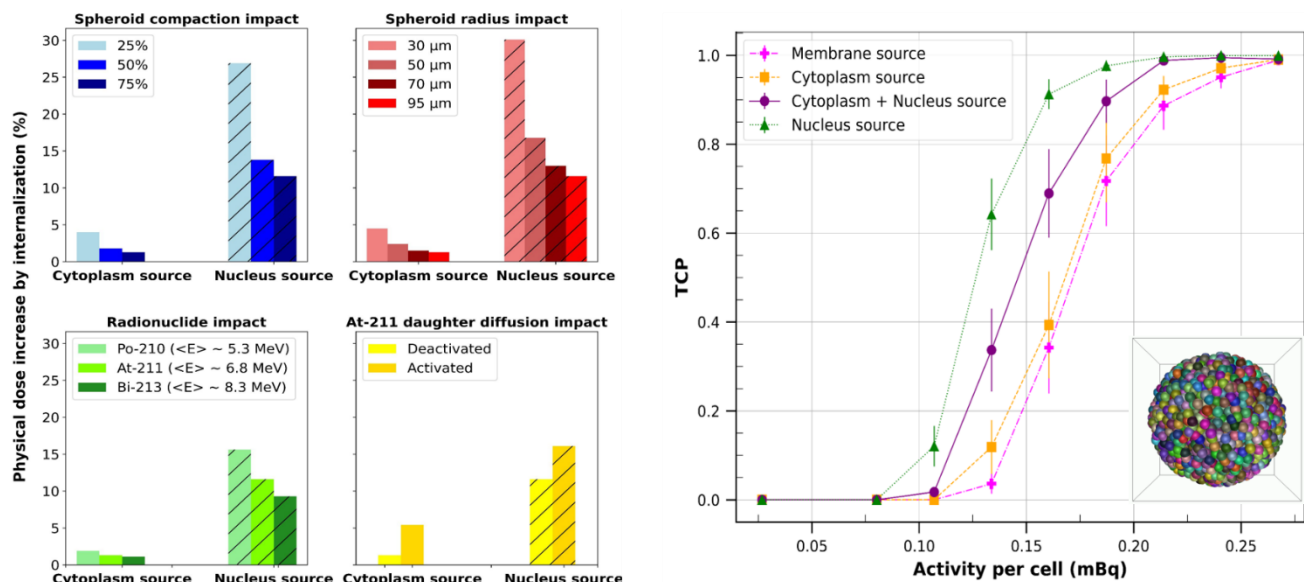


Figure 1: Example of physical and biological endpoints calculated in various cases of TAT treatments in microtumors to evaluate the impact of intracellular radionuclide distribution. Left: physical cell nucleus dose increase for cytoplasm or nucleus internalization compared to membrane source distribution in various treatment cases. Right: TCP calculated as a function of the mean activity per cell and intracellular source distribution, calculated in a 95μm radius spheroid composed of HSG cells and irradiated with ²¹¹At.