" Improvement of the prediction of biological effects for targeted innovative radiotherapies involving short-range ions, using a biophysical approach "

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Background: To understand and predict the therapeutic efficiency of targeted alpha therapy (TAT), nano/micro-dosimetry are needed by considering the very heterogeneous dose deposition at cell level. The objective of this PhD thesis is to develop models in order to improve the biological effects of TAT considering different scales.

Material and Methods: A combined approach is used. On one hand, Monte-Carlo simulations are performed using realistic deformable 3D multi-cellular geometries, with the code CPOP [1] code, based on Geant4. On the other hand, the biophysical model NanOx [2] can predict cell survivals induced by irradiation for specific cell lines. It has only been validated for high energies of hadrontherapy. Part of the work was to adapt this model for low energies of MeV in TAT.

This combined model was used to study the impact of intracellular radionuclide distribution in TAT on relevant dosimetric, biological and clinical endpoints. Radionuclides were generated in various cell compartments: nucleus, cytoplasm or membrane only. Physical absorbed doses in cell nuclei (Dn) of ovarian cancer cell line OVCAR-3, have been calculated, in addition to therapeutic indexes like Tumor Control Probability (TCP), using the biophysical model NanOx [2], which considers in the current version that the cell nucleus is the unique sensitive volume.

Results: For a given number of alpha particles emitted per cell (APC), the radionuclide distribution had a critical influence on Dn in small micro-metastases, while its impact is relatively low in larger spheroids, with a maximum of 30% increase. TCP of 1 were always obtained with a number of APC larger than 10. However, when the number of APC were below 10, TCP could strongly depend on the radionuclide distributions.

Conclusion: A precise modeling of radionuclide intracellular distributions is required for small micro-metastases or tumors presenting regions with relatively low radionuclide concentration.

[1] Maigne, L., et al. Phys. Med. 89 (2021) 41-50
[2] Cunha, M. et al. Phys. Med. Biol. 62 (2017) 12-48