Modelling the effect of daughter migration on dosimetry estimates for Actinium-225 in Targeted Alpha Therapy

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Introduction: Targeted Alpha Therapy (TAT) is a form of targeted systemic cancer therapy. *Why alpha particles?* Alpha particles have a short path-length in tissue, only a few cell diameters, and a high linear energy transfer (LET) of 50-230 keV μm^{-1}. This means alpha particles produce dense ionisations within a cell, causing irreparable double-stranded DNA breaks, resulting in cell death. The short path-length and high-LET of alpha particles allows TAT to deliver a highly localized cytotoxic dose to tumour cells while reducing radiation exposure to the surrounding healthy tissue.

Problems with TAT? In TAT, an alpha-emitting radionuclide is bound to a targeting vehicle which carries the radionuclide to cancer cells expressing the target protein (this can be a primary cancer site, individual circulating cells, or even micrometastases). However, the decay energy of the alpha-emissions is sufficient to break the bond to the targeting vehicle, resulting in free daughter radionuclides released in the body. This is especially concerning for parents that produce multiple unstable daughters, such as actinium-225. In nuclear medicine dosimetry, daughter migration is generally ignored and this can produce inaccurate dose estimates.

Method: A complex multilevel compartment model for actinium-225 and its daughters was developed in Python, where we account for unique biokinetics by assigning each daughter unique transfer rates between compartments (rates from ICRP). Using this model, we obtained the activity of each isotope in the different compartments as a function of time. We determined organ doses for two scenarios: 1) assuming the daughters decay at the site of actinium, and 2) assigning the daughters unique biokinetics. Simulations were performed for 1MBq of free actinium-225 placed in the plasma. The kidney dose was determined. We also performed a sensitivity study, changing the transfer rates by factors from 0.1 to 10 to see the impact on kidney dose.

Results: When the daughters of actinium-225 have their own unique biokinetics, there is a 7.5% increase in dose to the kidneys compared to assuming the daughters decay at the site of actinium-225. The sensitivity study showed a 40% increase in kidney dose when the kidney clearance rate is reduced by a factor of 4.

Conclusion: These results highlight that accurate absorbed dose estimates require accurate modelling of daughter biokinetics. Next, we plan to study doses to other organs and include tumour uptake/retention.