Diffusing Alpha-Emitters Radiation Therapy: Theoretical Modeling

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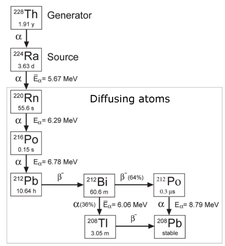
AlphaTAU

BACKGROUND AND PURPOSE

- Diffusing Alpha-Emitters Radiation Therapy ("DaRT") is a new modality which enables, for the first time, treating solid tumors with alpha particles.
- It relies on interstitial sources ("seeds") which carry a few μCi of ^{224}Ra below their surface. As ^{224}Ra decays, it releases into the tumor a chain of short lived alpha-emitting isotopes which spread over several mm by diffusion.
- Preliminary clinical results on recurrent/non-resectable SCC of the skin and head and neck are highly promising: 100% of the tumors shrink by 30-100%, with >75% showing complete response. Local side effects were low grade and transient, resolving within 5 weeks, and there no was evidence for systemic toxicity.
- DaRT dosimetry is governed by the spread of alpha emitters around the seeds. Here we outline an approximate zero-order model to provide quantitative guidelines for determining the starting point for treatment planning in clinical trials.



THE DIFFUSION-LEAKAGE MODEL

Simplifying assumptions:

- The tumor tissue is homogeneous, isotropic and does not change with time.
- The chaotic tumor vasculature allows describing convective spread as effective diffusion.
- Only ^{220}Rn, ^{212}Pb and ^{212}Bi diffusion should be modeled, their short-lived daughters being in local secular equilibrium.
- ^{220}Rn decays inside the tumor, ^{212}Pb and ^{212}Bi removal by the blood modeled as a uniform "sink" term

Model equations:

- ^{220}Rn: $\frac{\partial n_{\mathrm{Rn}}}{\partial t} = D_{\mathrm{Rn}}\nabla^2 n_{\mathrm{Rn}} + s_{\mathrm{Rn}} - \lambda_{\mathrm{Rn}} n_{\mathrm{Rn}}$
- ^{212}Pb: $\frac{\partial n_{\mathrm{Pb}}}{\partial t} = D_{\mathrm{Pb}}\nabla^2 n_{\mathrm{Pb}} + s_{\mathrm{Pb}} - \lambda_{\mathrm{Pb}} n_{\mathrm{Pb}} - \alpha_{\mathrm{Pb}} n_{\mathrm{Pb}}$
- ^{212}Bi: $\frac{\partial n_{\mathrm{Bi}}}{\partial t} = D_{\mathrm{Bi}}\nabla^2 n_{\mathrm{Bi}} + \lambda_{\mathrm{Pb}} n_{\mathrm{Pb}} - \lambda_{\mathrm{Bi}} n_{\mathrm{Bi}} - \alpha_{\mathrm{Bi}} n_{\mathrm{Bi}}$

n_k = number density of the k-th species, D_k = effective diffusion coefficient, λ_k, α_k = decay and leakage rate constants, s_k = volumetric source terms (replaceable by flux boundary conditions).

RESULTS: TUMOR DOSIMETRY

Approximate ("asymptotic") solutions for an ideal point source:

- ^{220}Rn ($t \gg \tau_{Rn}$): $n_{\mathrm{Rn}}^{asy}(\mathrm{r},t) = A_{Rn}\frac{e^{-r/L_{\mathrm{Rn}}}}{r}e^{-\lambda_{\mathrm{Ra}}t}$
- ^{212}Pb ($t \gg \tau_{Pb}$): $n_{\mathrm{Pb}}^{asy}(\mathrm{r},t) = \left(A_{\mathrm{Pb}}\frac{e^{-r/L_{\mathrm{Rn}}}}{r} + B_{\mathrm{Pb}}\frac{e^{-r/L_{\mathrm{Pb}}}}{r}\right)e^{-\lambda_{\mathrm{Ra}}t}$
- ^{212}Bi ($t \gg \tau_{Pb}$): $n_{\mathrm{Bi}}^{asy}(\mathrm{r},t) = \left(A_{\mathrm{Bi}}\frac{e^{-r/L_{\mathrm{Rn}}}}{r} + B_{\mathrm{Bi}}\frac{e^{-r/L_{\mathrm{Pb}}}}{r} + C_{\mathrm{Bi}}\frac{e^{-r/L_{\mathrm{Bi}}}}{r}\right)e^{-\lambda_{\mathrm{Ra}}t}$

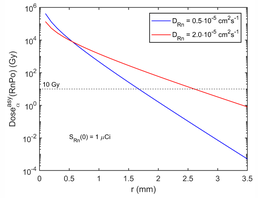
The spatial dependence is governed by the diffusion lengths (found from preclinical data):

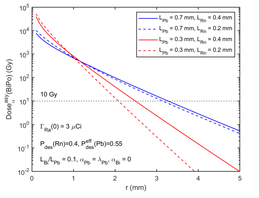
- ^{220}Rn: $L_{\mathrm{Rn}} = \sqrt{\frac{D_{\mathrm{Rn}}}{\lambda_{\mathrm{Rn}}-\lambda_{\mathrm{Ra}}}} \approx 0.2-0.4$ mm
- ^{212}Pb: $L_{\mathrm{Pb}} = \sqrt{\frac{D_{\mathrm{Pb}}}{\lambda_{\mathrm{Pb}}+\alpha_{\mathrm{Pb}}-\lambda_{\mathrm{Ra}}}} \approx 0.3-0.7$ mm
- ^{212}Bi: $L_{\mathrm{Bi}} = \sqrt{\frac{D_{\mathrm{Bi}}}{\lambda_{\mathrm{Bi}}+\alpha_{\mathrm{Bi}}-\lambda_{\mathrm{Ra}}}} \lesssim (0.1-0.2)L_{\mathrm{Pb}}$

The coefficients A_k, B_k, C_k are determined by the seed parameters, the diffusion lengths and rate constants.

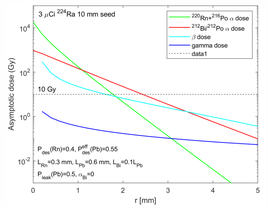
The macroscopic alpha dose comprises contributions from ^{220}Rn + ^{216}Po and ^{212}Bi / ^{212}Po:

- ^{220}Rn + ^{216}Po: $Dose_\alpha\left(^{220}\mathrm{Rn}+{}^{216}\mathrm{Po};\mathbf{r}\right) = \frac{E_\alpha(^{220}\mathrm{Rn})+E_\alpha(^{216}\mathrm{Po})}{\rho}\int_0^\infty \lambda_{\mathrm{Rn}} n_{\mathrm{Rn}}(\mathbf{r},t)dt$
- ^{212}Bi / ^{212}Po: $Dose_\alpha\left(^{212}\mathrm{Bi}/^{212}\mathrm{Po};\mathbf{r}\right) = \frac{E_\alpha(^{212}\mathrm{Bi}/^{212}\mathrm{Po})}{\rho}\int_0^\infty \lambda_{\mathrm{Bi}} n_{\mathrm{Bi}}(\mathbf{r},t)dt$



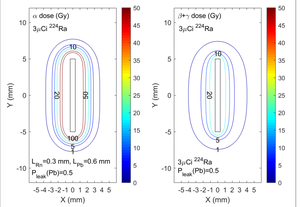


All dose components:

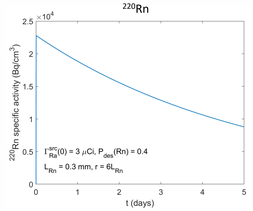


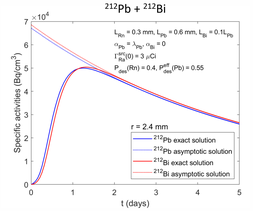
Beta and gamma doses calculated using EGSnrc, insensitive to diffusion

Single-seed dose maps:



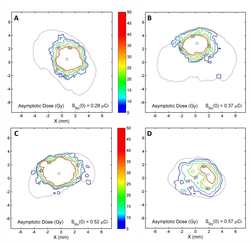
The number densities at a fixed distance from the source:

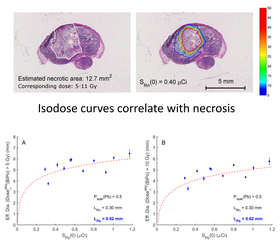




$\Gamma_{Ra}^{src}(0)$ = initial ^{224}Ra source activity, $P_{des}^{eff}(\mathrm{Rn})$, $P_{des}^{eff}(\mathrm{Pb})$ = desorption probabilities of ^{220}Rn and ^{212}Pb from the source.

Autoradiography of mice tumors:

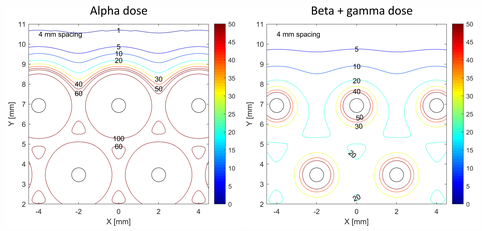




Murine SCC: dose maps based on activity patterns

Diffusion length estimates from global fits

DaRT lattices: alpha and beta/gamma dose (SCC model parameters)



3 μCi seeds, L_{Rn} = 0.3 mm, L_{Pb} = 0.6 mm, P_{leak}(Pb) = 0.5

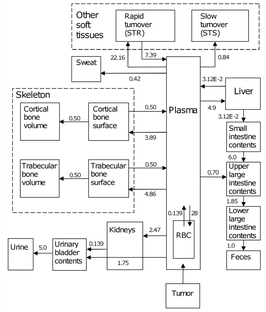
LOCAL AND SYSTEMIC SAFETY

Local safety

- The rapid fall-off of the alpha particle dose completely confines it to the tumor.
- The low-LET dose falls below a few Gy ~3 mm away from the treated region.

Systemic safety

- ^{212}Pb leaving tumor through the blood spreads throughout the body.
- Biokinetic + internal dosimetry calculations (based on the ICRP model for lead and the MIRD formalism) show that organ doses in typical treatments are 1-2 orders of magnitude below tolerance levels.
- Blood and urine measurements in patients are largely consistent with the model prediction, with an average leakage probability of ~40%. The calculated organ doses are a few cGy.



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Preclinical publications: https://www.alphatau.com/publications

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