PBPK-based *in silico* tumor microenvironment model for PSMA-directed radioligand therapy

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Objectives: Despite the early success of radioligand therapy (RLT) targeting prostate specific-membrane antigen (PSMA) for the treatment of metastatic castration-resistant prostate cancer (mCRPC), the β-emitter Lu-177 fails to deliver sufficient dose to bone metastasis. The α-emitter Ac-225 presents a more potent alternative radionuclide for RLT radiopharmaceuticals. The complimentary advantages of α and β-emitting RLTs lead to the concept of "cocktail treatment" to maximize cancer killing, while minimizing irradiation of normal tissues. However, it remains unclear how such a dual radionuclide treatment should be formulated and the potential treatment outcome. In silico modeling based on physiologically-based pharmaco-kinetic (PBPK) models can assist the optimization of PSMA-directed radioligand therapy. We propose a hybrid approach to combine PBPK model with the model of tumor microenvironment to optimize the in silico modeling.

Method: The dynamic distribution of PSMA-617 ligand was modeled by establishing an in silico PBPK-based convection-diffusion-reaction (CDR) model. The tumor microenvironment was simulated by establishing a histology-driven in silico model highlighting microvascular networks applying anti-CD31 immunohistochemistry. The microvessels were segmented and the domain was triangulated. The arterial input function (AIF) has been calculated with the validated PBPK model. The impact of the interstitial fluid pressure and velocity, the presence of hypoxic and necrotic regions, and the spatial variation of physiological parameters have been investigated. A finite-element solution of time-dependent CDR equation was implemented to calculate the distribution of the PSMA-617 at different time points post-injection. The parameters of the model were extracted from literature and optimized accordingly to the reference PBPK model. Once the activity distribution was recovered, the equivalent absorbed dose was calculated to investigate the dose in tumor microenvironment and normal organs.

Results: The established model can extend the PBPK model to the spatio-temporal distribution of PSMA ligand in the tumor microenvironment at different time points. With a proper AIF, the generated time-activity curves are consistent with the PBPK predictions in a ROI where the physiological characteristics are comparable, as shown in Figure 2. Indeed, the mean difference between the PBPK prediction and the CDR model is about the 5%. However, the distribution of the PSMA ligand inside the ROI can vary up to the 20% with respect to the mean value. With this model we can catch the heterogeneities in the PSMA distribution and calculate the absorbed dose in different regions of the tumor.

Conclusion: The proposed hybrid model can give deep insight into the microdosimetry. Further optimization and validation of this model on experimental data is ongoing. The established in silico model provides a potential tool to better understand the microdosimetry and optimize the PMSA-directed RLT.