Matching the reaction-diffusion simulation to dynamic [(18)F]FMISO PET measurements in tumors: extension to a flow-limited oxygen-dependent model.

Abstract:
Positron-emission tomography (PET) with hypoxia specific tracers provides a noninvasive method to assess the tumor oxygenation status. Reaction-diffusion models have advantages in revealing the quantitative relation between in vivo imaging and the tumor microenvironment. However, there is no quantitative comparison of the simulation results with the real PET measurements yet. The lack of experimental support hampers further applications of computational simulation models. This study aims to compare the simulation results with a preclinical [(18)F]FMISO PET study and to optimize the reaction-diffusion model accordingly. Nude mice with xenografted human squamous cell carcinomas (CAL33) were investigated with a 2 h dynamic [(18)F]FMISO PET followed by immunofluorescence staining using the hypoxia marker pimonidazole and the endothelium marker CD 31. A large data pool of tumor time-activity curves (TAC) was simulated for each mouse by feeding the arterial input function (AIF) extracted from experiments into the model with different configurations of the tumor microenvironment. A measured TAC was considered to match a simulated TAC when the difference metric was below a certain, noise-dependent threshold. As an extension to the
well-established Kelly model, a flow-limited oxygen-dependent (FLOD) model was developed to improve the matching between measurements and simulations. The matching rate between the simulated TACs of the Kelly model and the mouse PET data ranged from 0 to 28.1% (on average 9.8%). By modifying the Kelly model to an FLOD model, the matching rate between the simulation and the PET measurements could be improved to 41.2-84.8% (on average 64.4%). Using a simulation data pool and a matching strategy, we were able to compare the simulated temporal course of dynamic PET with in vivo measurements. By modifying the Kelly model to a FLOD model, the computational simulation was able to approach the dynamic [(18)F]FMISO measurements in the investigated tumors.