AbstractID: 8538 Title: Modeling the effect of different oxygenation levels on radiation therapy response using kinetic parameters derived from PET/CT imaging

**Purpose:** Although tumor hypoxia is frequently related to increased radioresistance, the interplay between hypoxia and the time course of tumor response is not well understood. This study investigates effects of different oxygenation levels on therapeutic response using an imaging-based tumor simulation model.

**Method and Materials:** A multiscale tumor model was developed employing cell-line-specific input variables and kinetic parameters derived from pre-therapy $^{18}$F-FLT and $^{61}$Cu-ATSM PET/CT scans, which provided information on cellular proliferation and tumor hypoxia. For each tumor voxel, stochastic simulations were performed by modeling cellular growth and therapeutic response based on the linear quadratic formalism including the oxygen enhancement ratio. Model parameters were fitted to published in-vitro and animal models of head and neck squamous cell carcinoma (HNSCC) cells. Using the obtained parameters, the model was applied to a human HNSCC case to investigate effects of different uniform and non-uniform oxygenation levels. Resulting virtual images were compared for treatment efficacy under various hypoxic conditions.

**Results:** Simulating cell cycle redistribution of cultured cells among the phases of the cell cycle after a single irradiation event yielded excellent agreement (within 3.8 %) with in-vitro data, showing complete redistribution after 50 hours. In comparison to growth and response curves obtained in experiments with murine HNSCC xenografts, the model quantitatively and qualitatively reproduced macroscopic tumor behavior within experimental uncertainties.

Simulations of the clinical case showed increased radioresistance with decreasing oxygen levels. Consideration of the $^{61}$Cu-ATSM uptake resulted in heterogeneous tumor response, featuring pronounced radioresistance below 2.5 mmHg $pO_2$.

**Conclusion:** Our results suggest that hypoxia adversely affects tumor response, especially when applying uniform dose prescriptions to heterogeneous tumors. The developed model is a valuable prospective tool for transforming voxel-based information into patient-specific parameters for outcome modeling and investigating biologically based non-uniform dose prescriptions, thus helping to identify a biologically optimized treatment regimen.