Purpose: Patient-specific differences in tumor radiosensitivity are generally disregarded in radiation therapy (RT), an approach that overlooks subgroups with different therapeutic responses. In this study, we extracted voxel-based radiosensitivity coefficients from multiparametric molecular imaging data using a computational tumor growth and response model.

Methods: Thirteen canine patients with sinonasal tumors underwent pre-therapy PET/CT imaging of metabolic activity ([18F]FDG), proliferation ([18F]FLT), and hypoxia ([61Cu]Cu-ATSM) using bite-block immobilization. Following two RT fractions and two off-treatment days, proliferative response was assessed via [18F]FLT-PET/CT. Using a previously developed tumor simulation model, voxel-based 'effective' linear radiosensitivity coefficients (alpha) were determined by simulating treatment response based upon pre-therapy PET data and iteratively minimizing differences between simulated and imaged proliferative response. Resulting alpha values were investigated for inter- and intra-patient heterogeneity, histology dependence, and spatial correlations with pre-therapy PET data.

Results: Alpha values in carcinomas (mean=0.061/Gy, SD=0.051/Gy) were higher than those found in sarcomas (mean=0.042/Gy, SD=0.024/Gy). Carcinomas were more heterogeneous in response (range=0.554/Gy) than sarcomas (range=0.110/Gy), which correlated with a more heterogeneous pre-therapy uptake of all three PET imaging surrogate markers. Increased [61Cu]Cu-ATSM uptake (SUV>4) alone indicated radioresistance, while simultaneous [18F]FLT uptake lowered effective alpha values. Using Akaike's information criterion, five carcinomas were identified to exhibit bimodal or trimodal alpha distributions, while all sarcomas were found to be unimodal.

Conclusion: Within this patient population, carcinomas were more radiosensitive and heterogeneous in alpha and PET tracer uptake. Extracted alpha values and their correlations with pre-therapy PET data differed between tumor histologies. Results suggest that imaged hypoxia might not necessarily indicate increased levels of radioresistance as high proliferation potentially offsets this effect. After correlating early treatment response to late outcome, this model could be used to identify potential biological targets within tumors, stratify candidate dose painting patients, and to transform voxel-based information into biological treatment planning objectives.