Abstract

Radiopharmaceutical therapy (RPT) is a rapidly expanding cancer treatment modality that delivers targeted cytotoxic radiation systemically to disseminated disease. Unlike external beam radiation therapy, RPT produces inherently heterogeneous absorbed dose distributions, both temporally and spatially. While the varying path lengths of emitted particles dictate localized patterns of energy deposition, this microscale complexity constitutes a primary obstacle to establishing accurate dose-response relationships for therapeutic optimization. To address this challenge, this work developed and applied a multi-scale RPT dosimetry framework to evaluate the biological impact of dose heterogeneity in a preclinical setting.

The ionizing-radiation Quantum Imaging Detector (iQID), a digital autoradiography system, was characterized and calibrated to acquire quantitative microscale activity distributions in thin tissue specimens. Reliable calibration curves ($R^2 \geq 0.9965$) were established at a 20 μm resolution. In cross-modality phantom benchmarking with ^{177}Lu, the iQID demonstrated superior spatial resolution and small-scale activity recovery compared to preclinical μSPECT/CT, yielding differences of 1.4% and 28.7% from the reference activity, respectively.

The calibrated high-resolution iQID imaging was then integrated into RAPID, an in-house dosimetry platform, to develop the multi-scale dosimetry framework using B78 melanoma-bearing murine models treated with [^{177}Lu]Lu-NM600 (alkylphosphocholine analog radiopharmaceutical). Registration and alignment of microscopic tumor sections to macroscopic tumor volumes achieved a Dice similarity coefficient of (0.92 ± 0.02) and a gamma-index passing rate (5%/1 mm) of (0.58 ± 0.06). Subsequently, subject-specific cumulative microscale absorbed dose distributions in the tumor were estimated using Geant4 simulation by applying longitudinal μSPECT/CT-derived pharmacokinetic parameters. The results exhibited a mean absorbed dose difference of (11 ± 6)% relative to partial volume corrected μSPECT/CT and revealed greater dose heterogeneity, with D_{98}/D_2 values of (0.10 ± 0.02) for iQID and (0.23 ± 0.09) for μSPECT/CT.

Radiobiological modeling was then applied to the estimated absorbed dose distributions and paired directly with immunofluorescence biomarkers through voxel-level registration of γH2AX and DAPI images. A mean absorbed dose of (6.27 ± 1.09) Gy and a biologically effective dose (BED) of (6.28 ± 1.10) Gy were estimated for the central tumor sections of the six murine

subjects. Five tumor sections showed low median γH2AX intensities (normalized between 0 and 1) ranging from 0.03 to 0.08 across the 0 to >30 Gy BED range, associated with radionuclide localization primarily in the peripheral regions, whereas one tumor section showed a linear dose-response with a 20-fold increase in γH2AX intensity from 0.02 to 0.40, associated with radionuclide accumulation within the tumor lobules.