Abstract

Radiotherapy delivering immunomodulatory dose to localized disease has been shown to enhance tumor response to systemic and local immunotherapies. In metastatic disease, where conventional radiotherapy is limited, radiopharmaceutical therapy (RPT) with an alkylphosphocholine analog, ^{90}Y-NM600, can deliver immunomodulatory dose to all sites of disease. In preclinical models, cooperative therapeutic effect between immunotherapy and ^{90}Y-NM600 RPT delivering as little as 2 Gy to tumors has been observed. Work presented here describes the development and clinical translation of prospective theranostic dosimetry using pre-therapy imaging of ^{86}Y-NM600 for delivery of low-dose ^{90}Y-NM600 RPT.

Novel methodology for voxel and region level partial volume correction (PVC) of ^{86}Y-based ^{90}Y dosimetry was developed for this framework. Voxel-level PVC improved the recovery of ^{86}Y by up to 17.8% in small 0.5 ml lesions but demonstrated less utility in larger and more heterogeneous cases, necessitating region-based PVC. Region-level PVC increased dosimetry estimates by 45.6% ± 9.8% in preclinical tumors and 23-56% for 16-0.5 ml hot-spheres (10:1) in clinical phantom studies. In application to lung met dosimetry for canine patients, uncorrected dosimetry estimates were 38% ± 8.3% low compared to those with PVC.

Locoregional temporal coregistration approaches for multi-timepoint dosimetry were developed, automated, and validated in a deformable anthropomorphic phantom study. Target volume registration improved by 19.8-38.7% as measured by the dice similarity coefficient. With improved registration, the dosimetric impact of target volume definition was reduced by 30.6% to a difference of 4.4% ± 1.9% in D_{90} across all validation cases.

The developed framework was successfully implemented within a clinically reasonable timeframe (7.5 ± 2.3 days) for five canine patients. Low-dose ^{90}Y-NM600 at the ≥2 Gy level was administered as prescribed, with dosimetry indicating the potential for ≥4 Gy to all tumors. Notably, the constitution of canine patient immune function remained intact with little to no adverse events observed.