Dissertation Abstract

Lung functional avoidance radiation therapy is a technique that has potential to mitigate radiation-induced lung injuries. In functional avoidance, treatment plans are optimized to reduce dose delivered to lung regions labelled as high functioning with the goal of preserving post-treatment function. Successfully avoiding high functioning lung regions requires adequate biomarkers to identify high and low functioning lung tissue. Image-based pulmonary biomarkers have been developed to quantify regional variation in lung function, including ventilation. Specifically, four-dimensional CT (4DCT) based ventilation biomarkers have been used to represent lung function and its radiation-response in a phase II prospective clinical trial (NCT02843568). However, further investigation of such biomarkers is needed to move toward widespread clinical implementation. The purpose of this work was to quantitatively evaluate CT-ventilation repeatability, robustness, accuracy, and role in predicting post-treatment radiation-induced pulmonary toxicity.

CT-ventilation repeatability was assessed by acquiring consecutive scans of mechanically ventilated nonhuman (swine) subjects and free-breathing human subjects. The swine subjects demonstrated significantly better breathing parameter control and biomarker repeatability than humans. Repeatability was significantly increased in human subjects when image data from multiple 4DCT breathing phases was incorporated into the CT-ventilation calculation compared to using a single inhale/exhale image pair. In terms of image quality, biomarkers were not significantly impacted by image noise and playing in-scan audio guidance during 4DCT acquisition significantly reduced presence of image artifacts.

CT-ventilation biomarkers were validated using ex-vivo histopathology, widely accepted as the gold standard for lung function. Biomarkers showed strong agreement with histopathology findings in regions of high and low ventilation. Biomarkers and histopathology also validated radiation-response, showing ventilation decline and histopathological evidence of tissue damage in high dose regions but not in unirradiated regions. CT-ventilation and histopathology both also showed a subject dependent ``indirect'' radiation damage effect, in which regions receiving low dose but fed by a highly irradiated airway demonstrated increased radiation-induced effects compared to regions not fed by unirradiated structures.

Finally, a model predicting radiation-induced pneumonitis was developed using radiation dose to highly ventilated lung region. Quantitative metrics of dose to functional lung were identified as potential treatment plan objectives and evaluation metrics. Dose to functional lung was significantly different for those with and without symptomatic pneumonitis. Even though patients' plans met all conventional total lung dose constraints, failure to meet the identified functional dose metrics was associated with a significantly increased risk of developing radiation pneumonitis.