Quantifying Radiation-Induced Changes in Perfusion for Improved Functional Avoidance Lung Cancer Therapy

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Abstract

Functional avoidance radiation therapy is a promising technique that shows potential to reduce radiation-induced lung injury by selectively avoiding regions identified as high functioning during treatment planning. All current phase 2 prospective clinical trials using this technique are exclusively ventilation based due to the ease of extracting ventilation metrics from 4DCT which is routinely used in treatment planning. However, ventilation is not a comprehensive metric for lung function. In addition to ventilation, perfusion is a crucial component to gas exchange, the ultimate function of the lung. Therefore, the current methods of assessing high vs. low functioning lung need improvement to include metrics for perfusion and more comprehensively model lung function. The purpose of this work was to quantify the dose-response of perfusion, and develop a workflow for measuring these changes that is executable in a standard clinical environment.

Using a dynamic contrast enhanced scan acquired pre and 3-months post-RT, perfusion changes were studied in two swine studies. In the first swine study, imaging measurements and histopathological confirmation studies on the swine lungs post-necropsy showed that above a dose threshold between 15-25 Gy, radiation induces atrophy of the vascular wall leading to blood leakage from the vessel to the non-vessel lung parenchyma and this effect increases in severity with increasing dose. In the second swine study, irradiation was targeted such that separate analysis of the distal regions to the point of max dose could be performed. This analysis showed that an “indirect effect” of perfusion damage is present where regions that are supplied by directly irradiated regions, regardless of the dose they receive, experience declines in function.

While the contrast CT results showed a clear dose-response relationship, in order for these models to become integrated into clinical practice, they must be executable in current clinical workflow. Contrast-CT is not routinely acquired as part of clinical workflow and additionally cannot be tolerated by some patients due to renal function concerns. For this reason, a 4DCT-derived metric is ideal due to CT's high spatial resolution and routine use in treatment planning. To do this, analysis of the changes in vascular anatomy were analyzed as a surrogate for perfusion and a novel vascular segmentation algorithm was developed to accurately segment vasculature in the presence of radiographic change. This was accomplished by combining a conventional vessel segmentation algorithm with texture analysis to remove false positives. The dose-binned changes in vasculature volume were then calculated in the same swine subject cohorts and correlated to the changes in perfusion measured previously. A good correlation ($R^2 > 0.7$) was observed.

Finally, a polynomial predictive model was developed to prospectively predict the changes in vasculature and perfusion. Performance in True Positive Rate, Accuracy, True Negative Rate, and Dice similarity were comparable or better than the performance of the currently used ventilation predictive models suggesting the model has clinical utility. Models accurately predicted direct radiation-induced changes but struggled to predict the indirect effect which is an area for future work.