Pulmonary vascular pruning in response to radiation

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I. Introduction

The lungs are highly sensitive to radiation. Following irradiation, acute endothelial cell damage and inflammatory response is associated with increased production of IL-6 and TNFa and leads to blockage of the lumen of small arterioles. We believe that the long-term vascular response to radiation is similar to that to seen with chronic pulmonary arterial hypertension (PAH) where permanent occlusion leads to resorption (pruning) of microvessels and an unfavorable cycle of increased vascular resistance, leading to increased arterial pressure, leading to escalated damage to vascular endothelium and progressive pruning. Accurate quantification of vascular tree structure may enhance our ability to understand the biological and biomechanical underpinnings of tissue radiation response and the sequelae of events that lead to progressive vascular degeneration and radiation late effects.

II. Hypothesis

Our hypothesis is that radiation damage to pulmonary vascular tissue can be quantified over time as pruning of the vascular tree that scales with regional radiation dose.

III. Methods

1. We collected radiation therapy (RT) treatment plans and repeat follow-up X-ray computed-tomography (CT) scans of the lung of patients receiving stereotactic radiation therapy for targets in the lung. All CT scans were acquired as per standard of care and gathered as per federal and institutional guidelines for use of human subjects in research.

2. Our lab has developed methods to extract the pulmonary vascular structure from 3D CT scans that we have applied successfully to human and animal models[1]. By quantifying the morphological features of the vascular tree, including the number of branches and generations, length and average radius of each branch, bifurcation angles, and vessel tortuosity, one can compute changes over time in the total vascular volume, histograms of branch radii and lengths, and distribution of blood volume among branch radii and generations.

Automatic segmentation of lung volume from chest wall. → Semi-automatic, snake-based segmentation of hilar region. → Manual selection of seed point at vessel tree root.

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Application of initial pixel intensity threshold for vessels. → Fast-marching region growing to extract the connected tree. → Vessel centerline extraction (3D skeletonization).

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Calculation of distance transform (for vessel radius). → Correcting erroneous tree interconnections. → Tree traversal and labeling.

Figure 1. Method for extracting, identifying, traversing, and labeling vascular tree structures. Extraction refers to separating the vessel pixels from the background lung parenchyma. Identification entails the distinction of vessel components from other bright objects in the lung. We rely on standard means to achieve these tasks using adaptive thresholding and manual selection of a seed point within the root of a vessel tree of interest (Fig. 2B). After skeletonization (Fig. 2C), the tree is searched for erroneous branch connections to separate individual trees (Fig. 2D). Finally, fibrotic regions are removed.

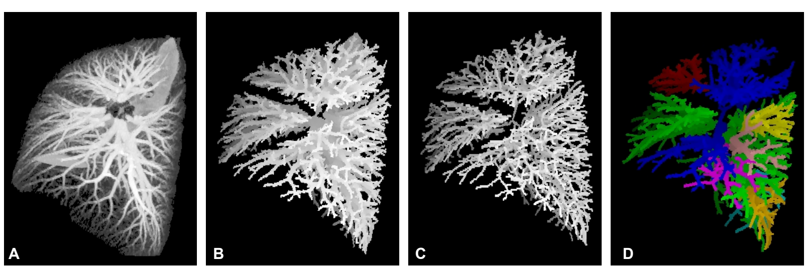

Figure 2. Application of the procedure to a contrast-enhanced CT sca of a healthy adult volunteer. [A] is a maximum intensity projection (MIP) of the right hemi-lung after extraction of lung volume. [B] is a depth-enhanced MIP of the extracted vessel tree after the seeded region growing step. [C] is the skeleton of the structures in [B]. [D] is a colorized MIP of the simulated Image of the eight (8) largest vessel trees after correction of erroneous branch connections. The final extracted tree structure was found to have 1960 branches on 32 independent trees.

III. Results

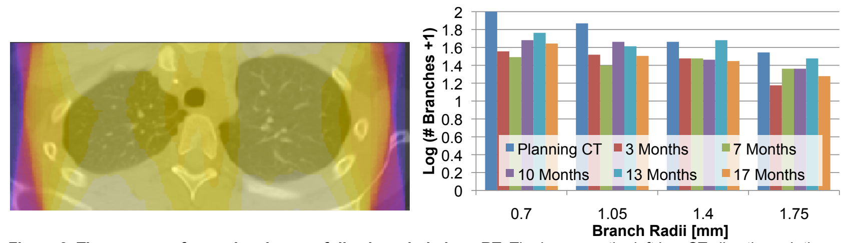

Figure 3. Time course of vascular changes following whole-lung RT. The image on the left is a CT slice through the patient's chest with the treatment radiation dose overlaid in color, with white representing the highest dose. The plot on the right illustrates the number of branches (on a Log_{10} scale) for each of 4 branch radius size ranges. Plotted for each range are data from 6 time points, from pre-treatment to 17 months post-RT. An initial decrease in the number of small vessels is apparent at 3 months and progresses through 7 months post-RT. A partial recovery after 10 months is then seen. All CT images were acquired without contrast and with similar imaging parameters (slice thickness; in-plane pixel size).

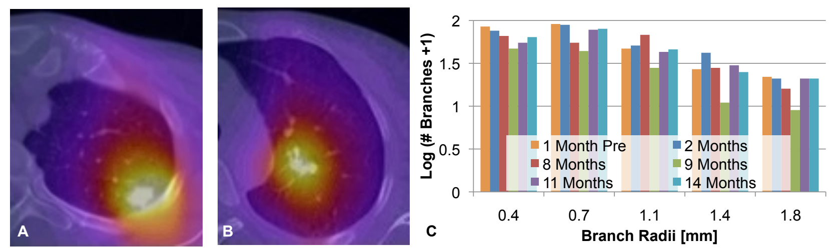

Figure 4. The time course of the branch radii histogram of the left hemi-lung in an RT patient with 2 left-lung tumors and 5 follow-up CT scans. **[A]** shows an RT-planning CT slice through the center of one of the targeted tumors. The color-overlay represents the prescribed dose, where white is the highest doss (~60Gy). **[B]** shows an analogous slice through the 2nd target in this patient. **[C]** shows the radii histogram. A decrease in the number of small vessels through 9 months is followed by a partial recovery. All CT images were acquired without contrast and with similar imaging parameters.

IV. Conclusions/Future work

We have developed and begun to implement image anlaysis tools to quantify progressive pruning of small branches in patients receiving high-dose radiation to the lung. Our analysis tools are written in Java, based on the NIH ImageJ platform. For this work the only manual user interaction is the selection of a seed point near the root of the vessel tree of interest. Our initial observations in patients are consistent with the expectation of radiation-induced vascular pruning and with partial recovery. In patients receiving SRT, the decrease in the in number of small vessels occurs before the appearance of radiation fibrosis. Future work will investigate the relationship between vascular changes and radiation dose, and the association between early-stage pruning and the development of radiation fibrosis at later time points.

V. References

1. O'Dell WG, Govindarajan ST, Salgia A, Hegde S, Prabhakaran S, Finol EA, et al. Traversing and labeling interconnected vascular tree structures from 3D medical images. Proc SPIE 9034, Medical Imaging 2014: Image Processing. San Diego, CA, USA; 2014. p. 90343C–15.
2. O'Dell W, Wang P, Liu H, Fuller D, Schell MC, Okunieff P. In vivo quantification of human lung dose response relationship. In: Manduca A, Hu XP, editors. Proc SPIE 6511, Medical Imaging: Physiology, Function, and Structure from Medical Images, 65110X. 2007.

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