Non-invasive Quantification of the Time Course of Lung Radiation Dose Response in Humans

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Abstract:
We have developed a method to quantify in-vivo the radiation dose response relationship of normal lung tissue based on readily available and non-invasive volumetric CT imaging. We have pioneered the use of high-dose stereotactic radiation therapy to treat small metastatic tumors of the lung; making it possible to deliver a very high radiation dose field (in excess of 50Gy) to the target and immediately adjacent tissue, and a fall-off in the dose field away from the target site. A 94% local control rate for metastases to the lung has been achieved, with a concommittant increase in patient survival. Volumetric CT scans acquired in these patients six months post-treatment reveal a focal region of fibrosis corresponding to the high-dose region during therapy, and no observable long-term damage in distant sites. We are then able to apply knowledge of the 3D dose field around each target to quantify, on a pixel-by-pixel basis, the complete radiation dose response relationship of normal lung tissue. We used this method to validate clinically a correlation between temporal patterns of circulating levels of IL-1a in the blood and the time course of observable lung tissue response, a correlation predicted by prior work in animal models. Our contention is that this method can be used to quantify changes in the radiobiologic response due to the moderating effects of specific agents or interventions and as such will help to develop agents to reduce harmful radiation side effects currently associated with pulmonary stereotactic radiation therapy.

Keywords:
extracranial stereotactic radiation therapy, lung metastases, radiation late effects, radiation dose response, cancer treatment

Purpose:
We have pioneered the use of high-dose stereotactic radiation therapy (SRT) to treat small metastatic tumors of the lung (pulmonary SRT or simply PSRT); making it possible to deliver a very high radiation dose field (in excess of 50Gy) to the target and immediately adjacent tissue, and a fall-off in the dose field away from the target site. Our initial 5-year follow-up study concluded that PST achieves a 94% local control rate for metastases to the lung, with an accompanying increase is patient survival. However because of concern for radaition damage to healthy lung tissue and loss of pulmonary function, treatment is limited to lesions <3cm in diameter and a maximum of 5 lesions are treated in a patient. The overall goal of this work is to better understand the radiobiology of the lung and to develop agents and irradiation protocols that will minimize radiation damage to surrounding lung tissue during PSRT. Toward this end we have developed a method to quantify in-vivo the radiation dose response relationship of normal lung tissue that is based on readily available and non-invasive volumetric CT imaging.

Methods:
Pre-treatment and follow-up volumetric CT scans were obtained in patients treated for one or more metastases to the lung. following automatic segmentation of the lung volumes, the follow-up scans were registered in 3D to the CT image set used to treatment planning. The 3D treatment dose in the neighborhood of each lesion was computed and exported from the SRT planning system software. Note that the 3D dose field is inherently registered with the planning CT image set (see Figure 1). Full dose-response curves for each target were constructed from pixel-by-pixel measurements of changes in CT Hounsfield number (a marker of tissue reaction) and corresponding radiation dose. The pixel-based dose data was aggregated into 5Gy bins and fit by least-squared-error to a model {NTCP = $\exp[(d-d_{50})/s] / (1+\exp[(d-d_{50})/s])$} to generate sigmoidal curves of tissue damage (ΔCT#) versus dose for each target site and for each follow-up time. Blood plasma samples were acquired at corresponding

time points post-exposure and assayed for concentrations of key cytokines involved in the body's inflammatory response: IL-1α, IL-8, TGFβ and monocyte-chemoattractant-protein-1 (MCP-1).

Results:
A representative dose-response dataset is shown in Figure 2 indicating 6 and 12-month time points. A second patient dose response dataset is summarized in Figure 3. The data shows an initial shift to the right over time during the first 16 months post-radiation exposure, corresponding to a decrease in apparent tissue response. However, at 23 months post-exposure we observe an increase in baseline tissue response and left-ward shift of the d_{50} value. This effect is interpreted as an indication of long-term perfusion injury that manifests as delayed downstream tissue damage. The circulating levels of the IL-1α, IL-8, TGFβ and MCP-1at these same time points are presented in Table 1. The normalized cross-correlation coefficient (*r-value*) between the time sequence of fitted d_{50} values and each cytokine is also given in Table 1. As seen in prior animal studies, a strong inverse correlation exists between the time pattern of tissue response and the temporal variation in circulating IL-1α and TGFβ levels, while MCP-1 shows a strong positive correlation.

New or breakthrough work:
This work represents the first time that full dose response data of lung toxicity were collected from independent human subjects. It also demonstrates for the first time a correlation between the time course of blood plasma cytokine levels and the time course of radiation response in normal lung tissue in humans.

Conclusions:
We have validated clinically a correlation between temporal patterns of circulating levels key inflammatory cytokine in the blood and the time course of observable lung tissue response, a correlation predicted by prior work in animal models. This analysis shows that even in the non-optimized state, the assay is sufficiently sensitive and robust to quantify changes in the radiobiologic response due to the moderating effects of specific agents or interventions. It is hoped that this work will provide the basis for accurately predicting toxicity in patients exposed to radiation and help bring to market agents that will ameliorate radiation damage in lung tissue.

References:
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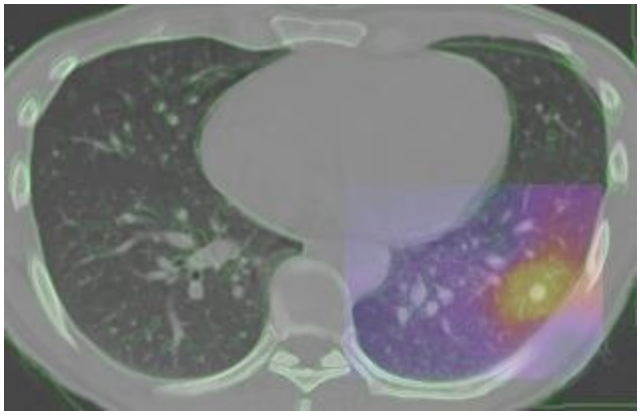
Figure 1: Composite image consisting of the pre-treatment CT image slice (gray-scale image) through a representative lesion; the 6-month follow-up CT image after application of an edge detection filter (green overlay) and following rigid-body registration in 3D; and the spatially registered, colorized 3D dose field computed from the treatment planning system for this representative lung lesion. The close alignment of the initial tumor, the focal region of radiation damage and the high-dose plateau can be readily appreciated.



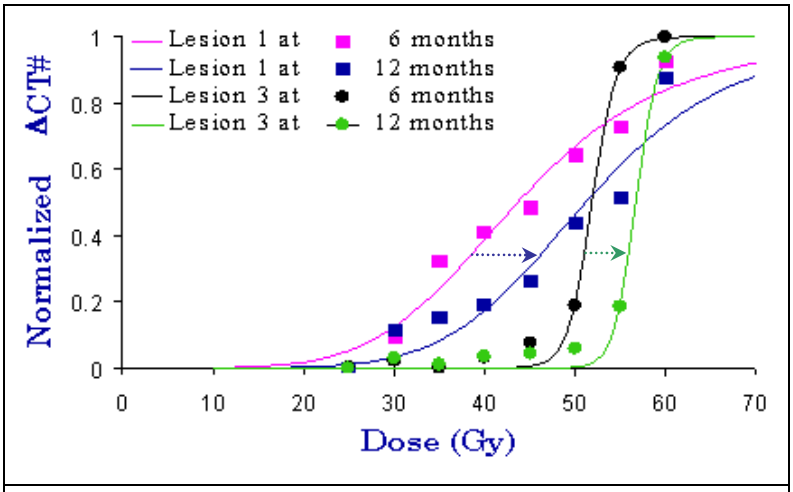


Figure 2. Shift in NTCP curves from 6 to 12 months post-treatment for the two largest treatment volumes in Patient A. The 6-month data (T6) shows a lower d_{50} than the 12-month data (T12) for this patient, indicated by a right-ward shift of the plots, suggesting partial recovery during the interval.

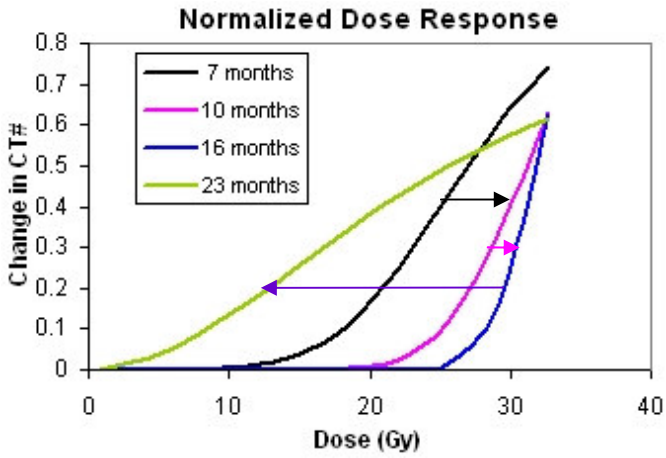


Figure 3. Fitted dose response curves for a patient who was treated for a single 18 mm diameter lung lesion. Shown are the data corresponding to follow-up images that were acquired at 7, 10, 16 and 23 months post treatment. These follow-up times are those associated with blood plasma cytokine measurements acquired in the same subject; presented in Table 1. At the 23-month time point, the slope of the tissue response curve exhibited approximately a 1%/Gy increase.

Table 1. Comparison between the fitted d_{50} dose-response values and blood cytokine measurements at the same time points. As predicted by previous animal studies, the temporal variations in circulating IL-1α and TGFβ show a strong inverse correlation with patterns of tissue response over time, while MCP-1 shows a strong positive correlation.

Date →	7 mo	10 mo	16 mo	23 mo	
Fitted d_{50}	26.98	31.04	31.79	25.70	r-value
IL-1α	3.57	0.00	2.04	5.33	-0.87
TGFβ	22.5	19.7	12.5	24.7	-0.89
IL-8	24.3	10.8	12.6	11.4	-0.39
MCP-1	198.9	538.6	682.1	367.5	+0.85