Intensity Modulated Radiation Therapy Re-Planning coupled with Radiation-Induced Immune Suppression Models Predict Improved Clinical Outcomes in Locally Advanced Non-Small Cell Lung Cancer Patients

Devon Overson, PhD; Cam Nguyen, PhD; Grant Williams; Xin He, MD; Wendy Stuart, MD; JT Morgan, MD; Ryan Gentzler, MD; Constance Hodge, CMD; James Larner, MD; and Krishni Wijesooriya, PhD
University of Virginia, Department of Radiation Oncology, Charlottesville, VA

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ABSTRACT

Introduction: This study investigates a comparative analysis of radiation therapy (RT) plans for advanced-stage non-small cell lung cancer (NSCLC) with the goal of minimizing radiation-induced lymphocyte Depletion (RILD). Previously delivered treatment plans are re-optimized to reduce radiation exposure to immune-rich structures while maintaining the original treatment objectives.

Methods: Using data from 74 patients, we generate alternative RT plans that reduce low-dose radiation (V5) to lymph nodes, heart and great vessels, thoracic spine, liver, and spleen without compromising target or involved LN coverage and maintaining the original treatment objectives. A python-based RILD prediction model was used to evaluate the immune sparing effect. Cox proportional hazards model was utilized to compare overall survival improvements up to 60 months after treatment.

Results: Predictive modeling shows that these RILD-avoidance plans on average decreased LN-CTV, Heart and GV, and T-spine V5 volumes by -30.2±21.3%, -19.0±23.0%, and -22.5±24.7%, respectively (n=52). Range of predicted post Tx ALC improvement ratio at day 60 was 0 to 27 %. Additionally, replanned treatments resulted in 17% of patients spared from becoming G3 lymphopenia (ALC ≥0.5). The reported increase in lymphocyte count is subsequently associated with an estimated hazard model analysis reported range of 3- and 5-year survival likelihood improvements by 0 to 25% and 0 to 27%, respectively. Average overall survival 3- and 5-year benefit for original plans was 45.2 and 28.0%, respectively. Conversely, replanned treatments had an average overall 3- and 5-year survival likelihood of 52.3 and 35.5%, respectively.

Conclusion: This work shows replanning to reduce immune rich organ doses could lead to better OS in advanced stage lung cancer patients.

CONTACT

Devon Overson, PhD
Medical Physics Resident
e: devon.overson@virginia.edu

Cam Nguyen, PhD
Medical Physics Resident
e: cmn5kz@virginia.edu

Krishni Wijesooriya, PhD
Professor
e: kw5wx@virginia.edu
Department of Radiation Oncology
University of Virginia

INTRODUCTION

Evidence suggests a competing dynamic for radiation therapy (RT) and immunological response to tumors. While radiation-induced-lymphocyte-depletion (RILD) inhibits immune processes, which may result in lower tumor control and survival and increase infections and hospitalizations, RT also enhances T-cell infiltration into tumors.[1]

Recently, RILD models[2] for advanced stage non-small cell lung cancer (NSCLC) have accurately predicted both actual lymphocyte count (ALC) and the effects of decreased ALC on patient overall survival (OS) rate. We present here RT re-planning that satisfies original plan requirements, and additionally reduces RT dose to immune-rich structures to mitigate RILD. Predicted change in ALC and OS between original (i.e., administered) and RILD-avoidance RT plans is reported in support of this hypothesis.

METHODS AND MATERIALS

Data from an initial 74 advanced-stage NSCLC patients is presented within this study. Re-planned treatments met original constraints and avoided immune-rich organs, including lymph nodes (LN), heart and great vessels (GV), thoracic spine, liver, and spleen.

ALC was estimated with a novel RILD model[3] via Spearman's correlation for quantitative parameters and point-biserial correlation for categorical parameters (Figure 1) for patients with post treatment ALC values (n=64). Predictive ALC was compared between each set of plans.

Furthermore, the Cox proportional hazards model was utilized to predict OS up to 60 months after treatment for each plan for patient with post treatment ALC values and completed treatment regimen (n=52).

RESULTS & DISCUSSION

From re-planning treatments, average LN-CTV, Heart and GV, and T-spine V5 volumes decreased by -30.2±21.3%, -19.0±23.0%, and -22.5±24.7%, respectively (n=52). Figures 1 and 2 present an example original and replanned treatment. Figure 3 presents all replans comparative to PTV D95 deviation.

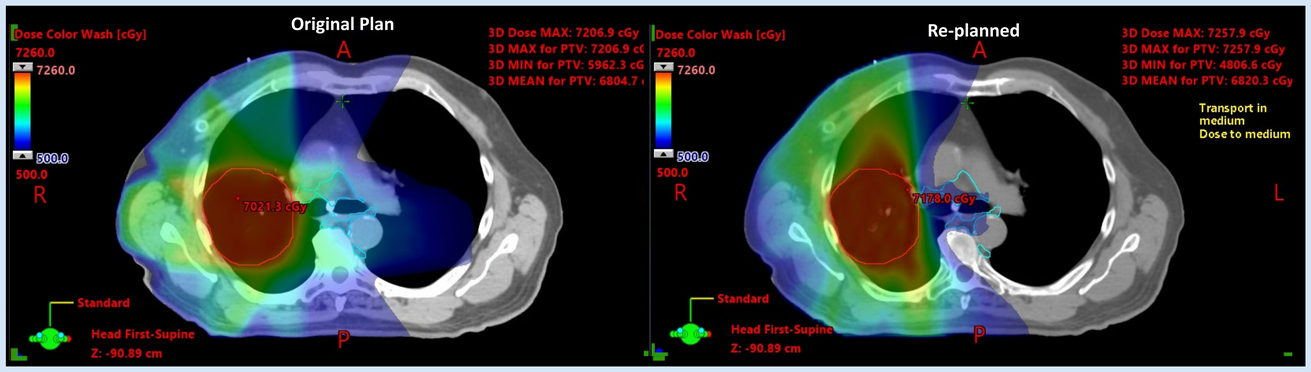

Figure 2. Original (left) and replanned (right) treatment plan achieve similar target goals, while the replanned treatment avoids lymphocyte-rich organs.

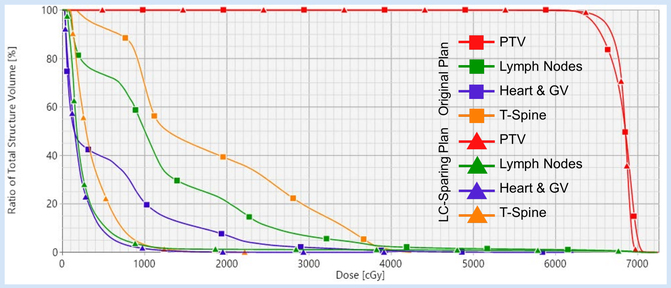

Figure 3. DVHs for original (squares)and replanned (triangles) treatment.

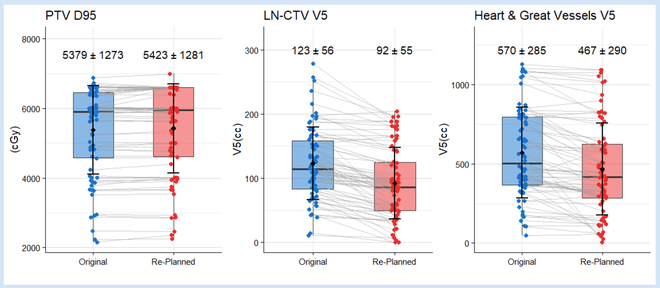

Figure 4. Comparison of PTV D95 (cGy) and V5 for LN-CTV and Heart+GV (cc) .

The improvement in predicted post Tx ALC improvement ratio at day 60 in the replan versus the original treatment plan ranged from 0-27%, presented in Figure 5. Correlations between ALC improvement and change in V5 volumes in non-involved LN and Heart+GV are presented in Figure 6. Additionally, replanned treatments resulted in 17% of patients spared from becoming G3 lymphopenia (ALC ≥0.5) and two patients transitioning out of Grade 4 lymphopenia (ALC ≥0.2) per predictive model. Based on these improvements in ALC (Figure 7), the hazard model analysis reported an absolute improvement in 3- and 5-year survival likelihood ranging from 0-25% and 0-27%, respectively (Figure 8).

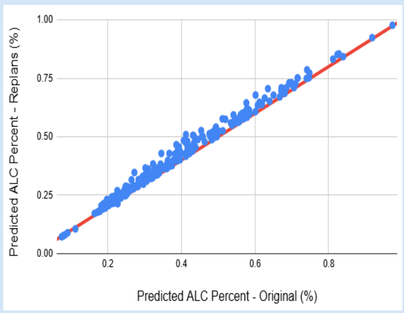

Figure 5. Ratio of ALC improvement

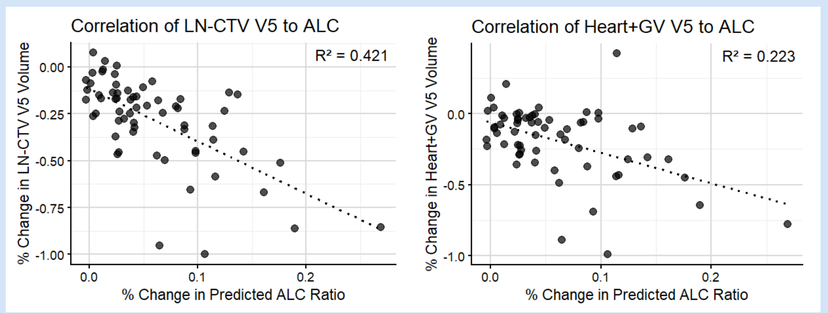

Figure 6. Correlation between % change in predicted ALC ratio and V5 structures

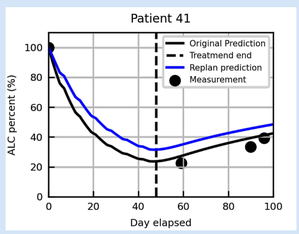

Figure 7. Example predicted ALC Response

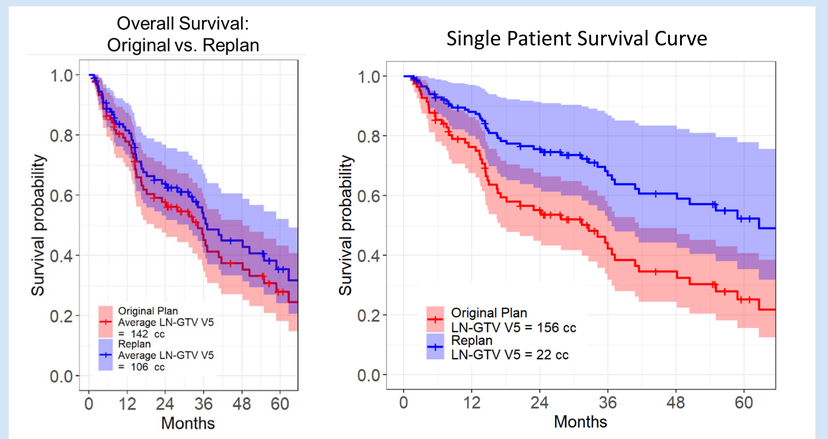

Figure 8. Correlations at 3- and 5-year survival rate and reduction in V5 to LN

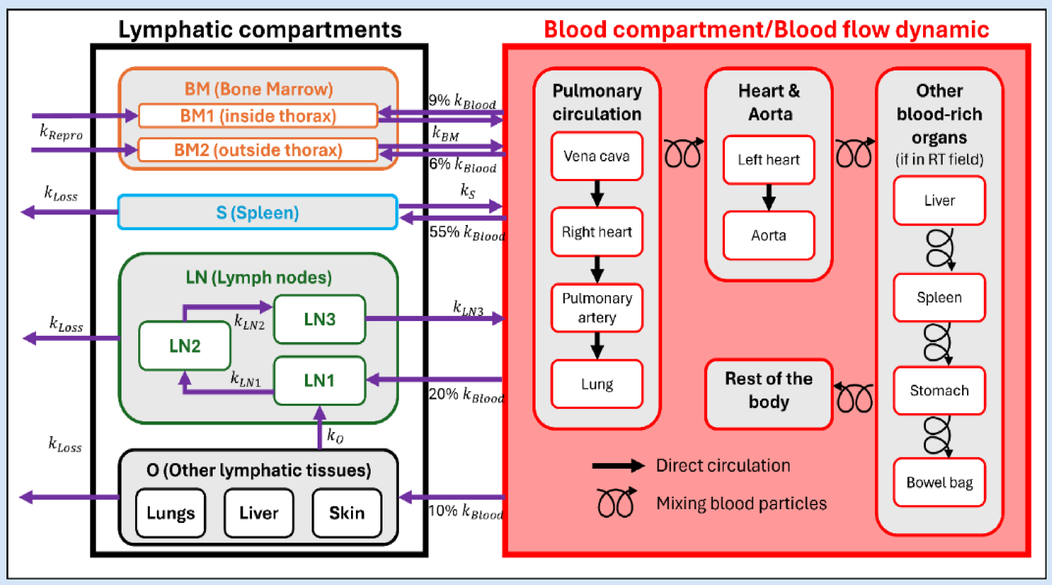

Figure 1. Novel RILD modeling for original and re-planned treatment plans.

CONCLUSION

Leveraging the RILD modeling, avoidance treatment plans can reduce toxicity effects, improve ALC, and enhance OS within NSCLC patients.

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