Background Radiation Therapy (RT) is known to modulate the immune system and generate anti-tumor T cells stimulating T cell infiltration into tumors. However, this anti-tumor activity is offset by radiation-induced immunosuppression (RIIS). Lymphocytes, (80% T cells) are highly radiosensitive and RIIS means destroying existing as well as newly created T lymphocytes. Optimizing RT treatment planning by considering circulating blood and lymphatics as a critical organ at risk may mitigate RIIS and lead to the creation and preservation of cytotoxic T lymphocytes converting the tumor from an immunologically cold to a hot environment increasing the efficacy of immunotherapy (figure 1).

Methods We conducted a NCI funded clinical trial for 50 early stage lung cancer patients treated with SBRT alone, from 2020 to 2023, to investigate the ability to reduce RIIS by reducing dose to circulating blood and lymphatics with the aid of a predictive algorithm. All plans adhered to treatment parameters from national protocols. Patients were randomized to two arms: experimental optimization for RIIS (reduce dose to blood and lymphatic rich organs) versus standard SBRT planning (figure 2). Peripheral blood samples were collected at baseline, end of Tx, 4 weeks and 6 months post Tx. Data acquired for all blood cell types and lymphocyte sub populations CD3+, CD4+, CD8+, CD19+, CD56+. Two sample t-test was used to determine the statistical significance.

Results Standard arm had an ALC reduction of 30% at one week post Tx and a nadir at 4 weeks with a 34% reduction. Absolute percentage reductions in ALC from baseline in the optimized arm compared to the standard arm: end of treatment point (15%, \( p = 0.01 \)), 4 weeks (12%, \( p = 0.05 \)), 6 months (15%, \( p = 0.1 \)), and all three time points together 13% (\( p = 0.001 \)) (figure 3). ALC recovery is faster in the optimized arm. Radiation induced suppression of all blood cell types are also reduced in the optimized arm with respect to standard arm (relative percentages): ALC (38%), WBC (44%), RBC (51%), platelets (44%), monocytes (94%), and neutrophils (50%) at 4 week mark. 32% patients had a net immune increase post SBRT in the optimized arm compared to 6% in the standard arm (figure 4).

Conclusions For the first time, we show that it is possible to significantly reduce RIIS compared to standard of care, via optimized RT planning using a predictive model. This has implications in increasing the efficacy of immunotherapy by preserving the existing tumor reactive T cells in the immune system to enhance anti-tumor activity.
Abstract 629-E Figure 3  Preliminary results showing the reduction of immune suppression in the optimized arm at all three time points for all tumors (top) and centrally located tumors (bottom).

Abstract 629-E Figure 4  (left): measured and simulation predicted absolute lymphocyte counts for all 3 time points of clinical trial data, (middle): time dependence of simulation predicted and measured post Tx lymphocyte count for three sample patients, (right): rate of prediction accuracy for the three time points. 85% of the patients, the prediction is within 0.5 x10^9 cells/L of the measurement.

http://dx.doi.org/10.1136/jitc-2023-SITC2023.0629-E