

Optimizing Clinical Outcome and Toxicity in Lung Cancer Using a Genomic Marker of Radiosensitivity

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ABSTRACT

While radiation therapy serves as the backbone for nearly 40% of all cancer cures, and is received by nearly 70% of all cancer patients at some point in their cancer journey, it has yet to enter the modern era of personalized medicine. While field shape and size is personalized anatomically for all patients, the dose of radiation is still prescribed in a one-size-fits-all manner. Given the reality of inter-tumoral heterogeneity demonstrated by cancer sequencing efforts, we propose that we are working under an outdated null hypothesis in our field: that all patients should respond the same to the same dose of radiation. We have previously developed a method by which to predict optimal dosing for a given patient, which we term the Genomically Adjusted Radiation Dose, given the *a priori* knowledge of a patient's tumor genomics. Knowing how much dose a patient's tumor requires for biological optimization provides the first opportunity to characterize the inefficiencies of one-size-fits-all dosing schemes, that result in both over- and under-dosing for the majority of patients. To elucidate this inefficiency, and therefore the opportunity to improvement using a personalized dosing scheme, we develop a competing hazards-style mathematical model combining the canonical equations for tumor control and normal tissue complication probabilities. Using data from two prospectively collected cohorts of patients with non-small-cell lung cancer, we show how the results of a recent uniform dose escalation study can be explained by the biological inefficiency of empiric uniform dose escalation, and highlight the opportunities for improvement in radiation outcomes available today, without need for new technology or equipment.

Introduction

The empiric basis of radiation therapy (RT), the most commonly utilized therapeutic agent in clinical oncology, has gone unmodified for over 70 years. RT is prescribed based on a uniform, one-size fits all approach, delivering small daily doses of RT over several weeks (i.e. fractionation). This fractionation approach is based on studies performed in rams and rabbits by Regaud, Schinz and Slotopolsky over 100 years ago¹⁻⁵ – and the standard total doses for control of sub-clinical, microscopic and macroscopic disease (50, 60 and 70 Gy) were established in the 1960s based on tumor control probability models for head and neck cancer patients^{6,7}. Although there has been a recent interest in hypofractionation, all of these schedules have also been empirically derived.

Although RT remains a critical curative agent for cancer, it has yet to adapt a biological basis in the clinic. We previously proposed that the gene expression-based radiosensitivity index (RSI), a surrogate for intrinsic cellular radiosensitivity, and the genomic-adjusted radiation dose (GARD), an individualized quantitative metric of the biologic effect of RT, could serve as the first approach to biology-based RT. Both RSI and GARD have been validated in multiple clinical cohorts and disease sites as a predictor of clinical outcome in patients treated with RT^{8-12, 12-16}. Importantly, the Lancet Oncology commission identified GARD as a research priority in the field of radiation oncology¹⁷. In addition, two recent independent studies from Lund University and Milan provide corroborative evidence that RSI is predictive of RT benefit in breast and head and neck cancer; a predictive biomarker¹⁸.

We hypothesize that given the known heterogeneity of cancer, there is an optimal RT dose for each patient that maximizes tumor control and limits toxicity; an ideal personalized therapeutic ratio. Further, we hypothesize that this optimal dose is at least partly defined by tumor biology. In this manuscript, we utilize RSI/GARD to calculate the optimal RT dose for each patient in a cohort of 1,747 NSCLC patients. We identify three distinct radiobiological cohorts in NSCLC: (i) Sensitive patients who are biologically optimized at current standard of care RT dose, (ii) Intermediate patients who may benefit from moderate genomically-directed RT dose escalation and (iii) Resistant patients who require RT dose beyond standard of care. To further understand the consequences for outcome in each of these groups, we develop a novel mathematical model for outcome. This model combines our genomic approach to calculate optimal dose and canonical models of tumor control and normal tissue complications to calculate a patient specific predicted outcome which includes morbidity and mortality from specified causes. To make this combined model simpler to use clinically, we further present decision-support software that provides the first approach to biologically optimize clinical outcome and toxicity for each individual patient. Our data reveals a tapestry of radiosensitivity heterogeneity, provides a biological framework that explains the failure of empiric RT dose escalation, and quantifies the opportunity to improve clinical outcomes in lung cancer by incorporating genomics into RT.

1 Materials and Methods

1.1 Patients

We utilized patients from Total Cancer Care (TCC), a prospective IRB-approved data and tissue collection protocol active at Moffitt and 18 other institutions since 2006¹⁹. Tumors from patients enrolled in TCC protocol were arrayed on Affymetrix Hu-RSTA-2a520709 (Affymetrix, Santa Clara, CA), which contains approximately 60,000 probesets representing 25,000 genes. Chips were normalized using iterative rank-

order normalization (IRON)²⁰. Batch-effects were reduced using partial-least squares (PLS). The normalized, de-batched expression values for 1,747 NSCNC (NSCLC) samples and the ten RSI-genes were extracted from the TCC database. To quantify the impact of the optimal dose on tumor control and toxicity, we utilized a subset of 60 patients with Stage 3 NSCLC treated at Moffitt with post-operative RT, which has also been previously described. The clinical endpoint was local control. The median follow up (based on the reverse Kaplan-Meier method) in censored patients free from local failure was 59.5 months (95 % CI:38.0-68.5 months)²¹.

1.2 Radiosensitivity Index (RSI)

RSI scores were previously generated¹⁴. RSI was previously trained in 48 cancer cell lines to predict cellular radiosensitivity as determined by survival fraction at 2 Gy (SF2)¹³. Each of ten genes in the algorithm is ranked based on gene expression (highest expressed gene is ranked at 10 and lowest at 1) and RSI is calculated using the pre-determined equation:

$$\begin{aligned} \text{RSI} = & -0.0098009 \times \text{AR} + 0.0128283 \times \text{cJun} + 0.0254552 \times \text{STAT1} - 0.0017589 \times \text{PKC} - \\ & 0.0038171 \times \text{RelA} + 0.1070213 \times \text{cABL} - 0.0002509 \times \text{SUMO1} - \\ & 0.0092431 \times \text{PAK2} - 0.0204469 \times \text{HDAC1} - 0.0441683 \times \text{IRF1}, \end{aligned}$$

which has been presented previously¹³.

1.3 Genomic Adjusted Radiation Dose (GARD)

GARD has been previously described¹⁴. Briefly, it is derived using the LQ model ($S = e^{-nd(\alpha+\beta d)}$), and the individual RSI and the radiation dose/fractionation schedule for each patient. First, a patient-specific (genomic) α_g is derived by substituting RSI for Survival (S) in LQ equation, yielding:

$$\alpha_g = -\frac{\ln \text{RSI}}{nd} - \beta d, \quad (1)$$

where dose (d) is 2Gy, n is the number of fractions (here $n = 1$), and β is a constant 0.05/Gy². GARD is then calculated using the classic equation for biologic effect, $\text{GARD} = nd(\alpha + \beta d)$, the patient-specific α_g calculated as per equation 1, and the number of fractions (n) and dose per fraction (d) and received by each patient. It is worth noting that in the case when a patient receives 2Gy fractions, the βd terms drop out, and GARD reduces to $-\ln(\text{RSI})$. A GARD cut-point of 33 was previously identified and published for the lung clinical cohort¹⁴, and will be utilized going forward in this manuscript. It is worth noting, however, that this cutpoint will differ for each cohort.

1.4 Biologically-Optimized Personalized RT dose (RxRSI)

We define RxRSI as the physical dose required to achieve a previously identified GARD threshold (in this paper, $\text{GARD} \geq 33$) in a cohort of lung cancer patients treated with post-operative RT¹⁴. RxRSI is calculated

using the following formula:

$$\text{RxRSI} = \text{GARD} / (\alpha_g + \beta d). \quad (2)$$

Where α_g is calculated based on the patient's RSI as described above and β is a constant ($0.05/\text{Gy}^2$). When comparing RxRSI to the empiric dose received by patients in the lung cancer clinical cohort, we defined that the RxRSI and empiric dose matched if they were within 10% of each other. As GARD was developed based on standard fractionation, we further assume that RxRSI is delivered in a similar manner (i.e. dose per fraction is $\sim 2\text{Gy}$). Methods for calculating optimal doses for altered fractionation schedules can be calculated using the same method, but β needs to be estimated in a different manner.

1.5 Genomic Radiation Treatment Planning

To quantify the impact of the biological optimal RT dose on outcome and toxicity we integrated the algorithms and equations that define RSI, GARD and RxRSI into radiation treatment planning software. We generated 30 RT plans to match the anatomical and biological diversity in the 60 patient cohort. Plans were created for the following biological conditions (RxRSI=48 Gy, RxRSI=54 Gy, RxRSI=62 Gy, RxRSI=74 Gy, RxRSI=88 Gy and RxRSI=95 Gy)(Supplementary Figure 1). Dosimetric parameters for normal tissue including mean heart dose, mean esophagus dose, and mean right and left lung dose, were calculated for all genomic plans. We utilized the resulting data to generate a linear model to estimate the impact of dose personalization on normal tissue (see Supplemental Figure 2).

1.6 Linear Model for Normal Tissue Estimates

The mean dose to each normal tissue target (heart, left lung, right lung and esophagus) were calculated across the 30 genomic plans developed. Mean normal tissue dose was plotted against PTV prescription dose to obtain a Pearson's correlation coefficient for mean heart, left lung, right lung, and esophageal dose (R^2 : 0.98, 0.99, 0.97, 0.99, respectively). These linear relationships were then used to calculate an approximate mean dose to normal tissue on a Gy^{-1} basis.

1.7 Normal Tissue Toxicity

To create a combined model of tumor control and NTCP, we required a model of excess toxicity probability for each organ at risk (OAR) per Gy delivered. Calculations for relative risk for a given dose received or dose adjustment was accomplished using different methods for each tissue site, depending on the available data and recommendations in the literature. When possible, data on rate of complication per dose received was used, or a quantitative NTCP model which has the benefit of flexibility in choosing dosing parameters. For generalizability, specific dose-toxicity endpoints were not referenced. This method can be extended to any OARs, but for this manuscript we focus on the three main drivers of complications in NSCLC radiation therapy that have quantifiable models: pneumonitis, esophagitis and radiation induced heart disease.

In the QUANTEC review of lung complications, the primary endpoint is radiation pneumonitis²². The

reviewers conducted a meta-analysis of applicable studies and performed logistic regression on rates of radiation pneumonitis versus mean lung dose (MLD),

$$p = \frac{\exp b_0 + b_1 \times \text{MLD}}{1 + \exp b_0 + b_1 \times \text{MLD}}. \quad (3)$$

Parameters for b_0 and b_1 were calculated for a model in the above form. The QUANTEC reported recommendations for toxicity endpoints for the esophagus were inconclusive due to the volume-dependent effect of the available data²³. Two of the studies, both published in 2005, provided quantitative models in the form of the Lyman-Kutcher-Burman equation, with parameters m and TD_{50} that were within bounds of the confidence intervals^{24,25},

$$\text{NTCP} = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^t e^{-x^2/2} dx, \quad \text{where} \quad t = \frac{EUD - TD_{50}}{m \cdot TD_{50}}. \quad (4)$$

Cardiac complications due to radiation were modeled as a fixed rate of 7.4% increased risk per 1 Gy dose received by the heart. The endpoint included coronary events as defined by myocardial infarction, coronary revascularization, or death from ischemic heart disease²⁶.

1.8 Statistical Methods

A survival regression model was used to quantify the impact of individual GARD on local control. By applying the cut-point of 33 to define two strata, a time-dependent parametric model was developed that could then be adjusted by normal-tissue effects. This initial calculation of parameters for a Weibull distribution was done using the Surv-Reg package in R, of the form $H(t) = \lambda t^p$, as the hazard function, and $S = e^{\lambda t^p}$ as the survival function. The adjusted outcome models were developed in python in the defined form such that

$$H(t) = \int_0^t h(u) du \quad \text{and} \quad S(t) = [S_0(t)]^{\exp(H(t))}, \quad (5)$$

and implemented in the Dash open source library for data visualization.

2 Results

2.1 The biological optimized dose (RxRSI) identifies three distinct radiobiological clinical cohorts in NSCLC

As we have demonstrated before¹⁴, there is wide heterogeneity in the radiation sensitivity in NSCLC. In Figure 1A, we plot the distribution of of RSI in a large (1,747 patients) cohort of NSCLC patients from

the TCC cohort (range: 0.079-0.752). Of note, there is a bimodal distribution of RSI dose across this population, suggesting that a uniform, one-size fits all approach to RT dose is sub-optimal for the majority of patients. Taking into consideration a separate cohort of post-operative NSCLC patients with known clinical history, including post-operative radiation dose, we calculate RxRSI (the physical dose predicted to optimize biological outcome). The distribution of this calculation across this cohort (Figure 1B), reveals three distinct radiobiological cohorts in this subset of patients: 1. Radiosensitive patients which achieve RxRSI at current standard of care RT dose (50 Gy or less in this post-operative setting), 2. Intermediate sensitivity which achieve RxRSI within the standard of care accepted range(50-70Gy) and 3. a radioresistant group which require doses above standard of care (>70 Gy for post-operative RT) to achieve RxRSI.

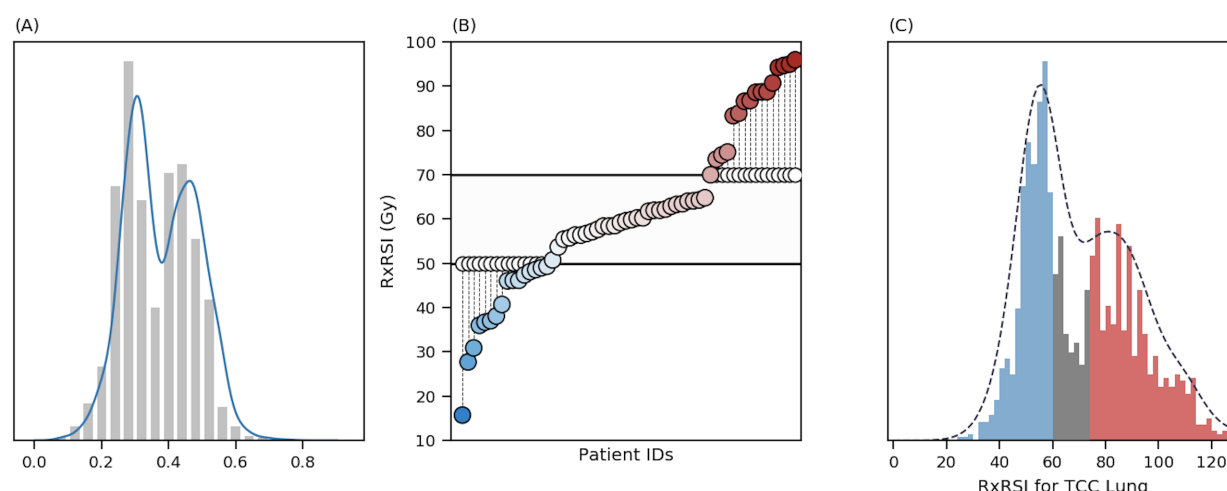


Figure 1. We identify three distinct groups of patients from genomics and standard RT dosing schedules. (A) Distribution of RSI in a cohort of 1,747 patients with NSCLC in the TCC cohort. (B) Calculating RxRSI (the physical dose required to achieve an optimized biological outcome) for each patient in a clinical cohort of 60 patients with known clinical outcome, dose received and RSI reveals three groups: patients who require less than SOC dose (50Gy), patients who require a dose within the SOC range (50-70Gy) and patients who require more than the SOC dose (> 70Gy). (C) Translating to primary radiation doses and a larger (TCC) cohort, we see that there is a subset of patients who are optimized by 60Gy (blue), a small subset of patients would benefit from moderate (up to 74Gy - grey) and a large cohort (red) who would need greater than 74Gy.

Translating this calculation to the larger (TCC) cohort, and into primary radiation dosing, we see a similar split into three groups, but now notice another interesting finding: in the area of recent dose-escalation (60-74Gy) there is a very low number of patients, suggesting that very little is to be gained in this region. Figure 1C shows three regions, (blue) where any patient would be optimized by 60Gy, (grey) where moderate dose escalation to 74Gy is required and (red) a large region where doses above 74Gy would be required (of note, this region contains approximately 42% of the population, which happens to be approximately the percentage who experience local failure with chemoradiation).

2.2 Empiric RT dose is biologically imprecise and results in an inefficient distribution of RT-related toxicity and clinical benefit

Historical models of radiation response have always considered either tumor control or normal tissue complications. This was all that was possible, because no estimate of *required* dose was available. With the advent of our predicted optimal dose, we now have the ability to quantify *excess* dose received by individual patients when receiving empiric dosing. To quantify the untoward effects of empiric RT dose then, we generated 30 radiation treatment plans representing the distribution observed for RxRSI in the lung cancer patients treated with post-operative RT. We calculated the excess normal tissue dose delivered (when the patient was given more than RxRSI) or the additional normal tissue dose required (when patients receive a dose lower than the RxRSI). For 25% of the patients in our cohort, the empiric dose and RxRSI matched while for 75% it did not match (supplementary table 1-4). We then calculated the impact on normal tissue dose and toxicity of actually delivering RxRSI for each patient using RT doses within standard of care guidelines (RT dose 50-70 Gy). In sensitive post-operative patients, adjustment to the RxRSI (set to a minimum dose of 50 Gy) would have resulted in an overall mean dose **decrease** to the esophagus, right and left lung and heart (supplementary table 4). In intermediate post-operative patients, adjustment to the RxRSI would also have resulted in a mean **increase** in dose to normal tissue (supplementary table 2). The mean increase in normal tissue dose for intermediate patients (RxRSI>Dose received) is very similar to mean decreases experienced by sensitive patients (RxRSI<Dose received). Thus, since resistant patients are not adjusted because RxRSI is above standard of care (supplementary table 3), the overall risk profile for normal tissue complications for the whole population is not expected to be affected by the dose adjustments proposed by RxRSI. The predicted impact of personalized dose adjustments on normal tissue toxicity is shown in supplementary table 5. In summary our data demonstrates that it is possible to deliver RxRSI to 75% of the patients without changing the overall toxicity profile for the whole population.

2.3 Development of combined mathematical model to correct tumor control by toxicity from excess dose

To estimate the clinical potential for personalized prescription RT dose beyond simply tumor control, we developed a mathematical model to utilize genomic markers of radiosensitivity to optimize radiation outcomes considering **both tumor control and individual toxicity**. While great efforts have been made to understand the untoward effects of radiation over the decades²⁷, **knowledge of excess dose for an individual patient has not been possible**, and this information has not been able to be incorporated into personalized predictions. Our genomic framework, in particular the estimate of required dose, RxRSI, provides a first estimate of this. To understand the combined contributions of tumor and excess normal tissue effects on outcomes, we have created a competing hazards style risk model. We term the outcome the “penalized local control” (pLC), which includes local recurrence (classic TCP) and events related to RT-related toxicity (styled after NTCP), but does not account for death due to disease progression or other causes. The penalized local control curve for a population is calculated as $S(t) = C_1 S_1(t) + C_2 S_2(t)$ where C_i ($i \in 1, 2$) represents the fraction of patients that receive a tumor dose that is either adequate ($i = 1$, RT dose \geq RxRSI), or inadequate ($i = 2$, RT dose $<$ RxRSI), and $S(t)$ is the survival function derived from the individual cohort’s KM analysis (see Methods 1.8). Finally the convolved survival curves is then adjusted for the predicted toxicity hazard ratios

as per Methods 1.7:

$$pLC(t) = [S_{74Gy}(t)]^{\overline{HR}_C \cdot \overline{HR}_E \cdot \overline{HR}_P}. \quad (6)$$

Here \overline{HR}_C , \overline{HR}_E , \overline{HR}_P are the risks for each adverse outcome including cardiac, esophagitis and pneumonitis, respectively).

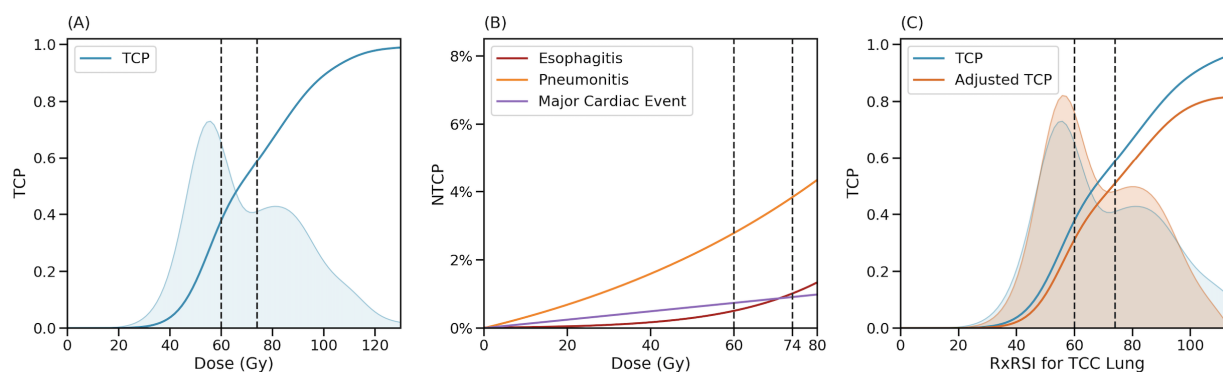


Figure 2. Combined TCP and NTCP model). (A) The cumulative distribution function of the (bi-modal) RxRSI is a TCP curve (and approximates a sigmoid). (B) Probability of grade 3 or greater toxicity with dose for each of esophagus (purple), lung (yellow) and heart (blue). (C) TCP (blue) corrected by NTCP (yellow) as a function of dose.

2.4 Combined tumor control and NTCP model accurately predicts the outcome of RTOG 0617

To validate the combined TCP and NTCP model, we designed an *in silico* clinical trial (a phase *i* trial if you will²⁸), to match the recent trial of uniform dose escalation in NSCLC (RTOG 0617 60Gy vs 74Gy). As in RTOG 0617 we assigned (uniformly at random), 200 patients for a 74Gy arm, and 200 patients for a 60Gy arm. We calculated the expected clinical outcome for each arm based on an estimate of tumor control and toxicity for each patient. We performed 100 iterations of this *in silico* trial, randomly assigning an RSI value to each in silico patient using data from the TCC NSCLC cohort. This trial is schematized in Figure 3A. Of note, this empiric distribution is statistically indistinguishable from the smaller, 60 patient cohort reported above ($p \ll 0.001$ using Anderson-Darling and Kolmogorov-Smirnov tests (Supplementary Figure 3).

As shown in Figure 3B, the combined model predicts that uniform dose escalation to 74 Gy to unselected patients would result in no radiation-associated overall gains when compared to 60 Gy, consistent with the results observed in the actual clinical trial. In addition, as shown in Figure 3C, the model correctly predicts the 1 and 2 year local control observed in RTOG 0617. To further understand the biological underpinnings to explain this result, we determined the proportion of patients that were expected to derive a benefit from dose escalation to 74 Gy. As seen in Figure 4C (blue group), 39.6% of the patients achieved or exceed RxRSI at 60 Gy. Only an additional 18.6% reached RxRSI at 74 Gy (grey group). However, our model predicts that still about 41.7% of the patients may need higher doses (>74Gy, red group). Thus, in an unselected

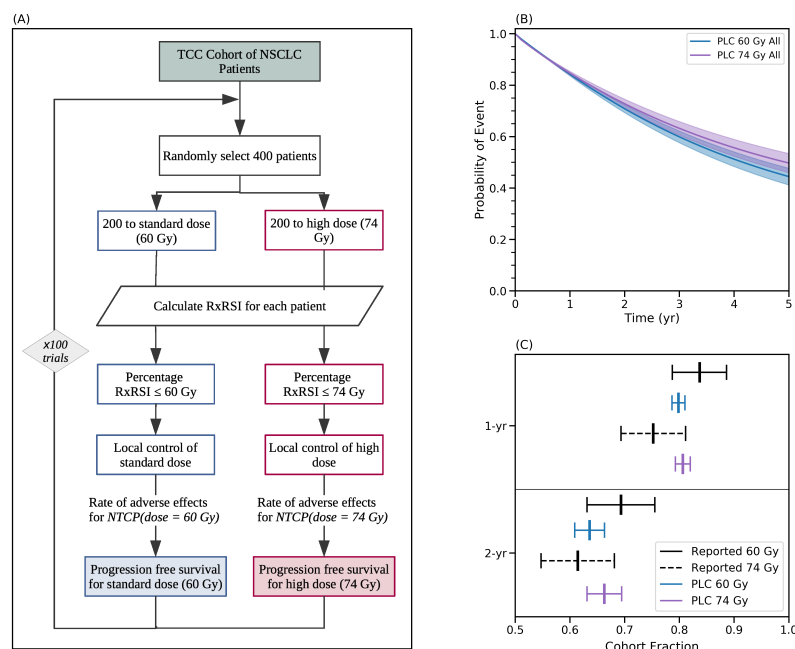


Figure 3. An *in silico* trial of dose escalation using the competing outcomes model in NSCLC matches the outcomes of a recent cooperative group trial. (A) Schematic of our *in silico* trial designed to match RTOG 0617, with patients drawn uniformly at random from the TCC cohort. **(B)** A Kaplan-Meier curve depicting penalised local control (pLC). The 60 and 74Gy arms are predicted to have statistically indistinguishable outcomes (penalised local control) through 5 years. **(C)** Using the combined model accurately predicts the results of RTOG 0617.

population, uniform dose escalation to 74 Gy benefits only a minority (grey only) of patients and exposes the majority (blue and grey) of patients to additional toxicity, obfuscating any radiation-associated clinical gains. However, a targeted dose escalation strategy, where only patients in the cohort of patients with intermediate radiosensitivity (RxRSI, 62-74 Gy) receive 74 Gy would be expected to improve the local control for the whole cohort by an absolute 3.6% at 2 years, and 7.8% at 5 years (Figure 4B). This small, but significant gain, would increase to 3.8% at 2 years and 8.1% at 5 years if patients were given the exact dose that was predicted to optimize their outcome, rather than the full 74Gy, as they would be spared the additional toxicity. Taken to the logical limit, where each patient is given only the dose they need, to an upper limit of 80Gy (lower bound of 45Gy), would further increase the outcomes by another 2.3% and 4.8% at 2 and 5 years, respectively, highlighting the opportunity when radiation therapy is truly personalized.

3 Discussion

In this paper, we present a clinically-feasible system to personalize RT prescription based on biological parameters, and quantify the clinical opportunity for improved clinical outcomes inherent in personalized RT for patients with NSCLC. Our proposal for personalized RT prescription is based on three parameters: (i) RSI which defines the patient's individual tumor radiosensitivity; (ii) GARD, which defines the individualized

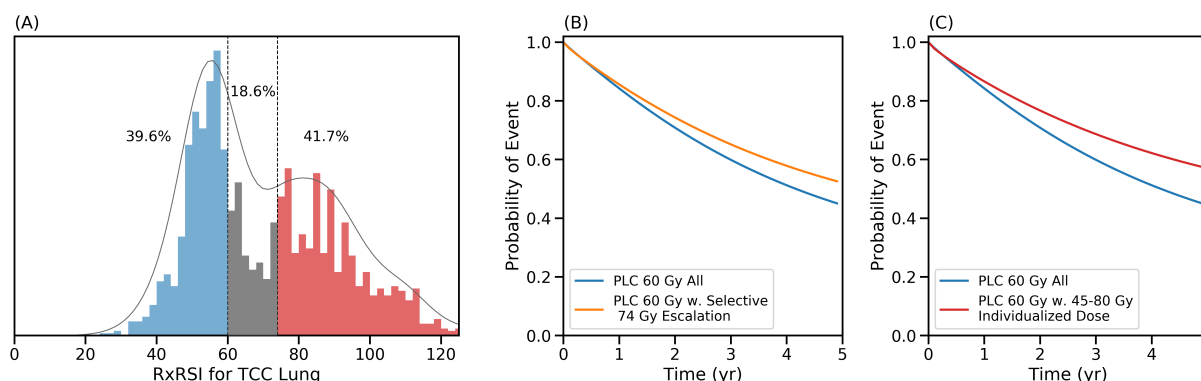


Figure 4. Empiric dose escalation reached a local optima at 60Gy, but personalized dosing offers significant benefits with current technology. (A) A radiation dose of 60Gy will provide optimal tumor control for approximately 40% of the population, and escalation to 74Gy will only optimize a further 18.6%, while exposing all to additional toxicity. (B) A Kaplan-Meier curve depicting an *in silico* trial of 60Gy vs. 74Gy, with escalation only for those the RSI based model predicts who would benefit. (C) A Kaplan-Meier curve depicting an *in silico* trial of predicted optimal dose in the range 45-80Gy.

clinical effect of a given dose of RT in a given patient with a distinct RSI; and, (iii) RxRSI, the biologically-optimal RT prescription dose, which we define as the prescription dose required to achieve a GARD target value associated with improved clinical outcome. Personalized RT prescription provides an alternative to the empiric-based one-size fits all approach that is currently standard in the field.

In two cohorts of patients with NSCLC, we showed that prescribing uniform, empiric-based RT dose is biologically imprecise, with 75% of patients we analyzed receiving non-optimal doses of RT. Conversely, we showed that the personalized, RxRSI-based prescription approach can deliver optimal doses to up to 75% of the patients in the clinical cohort even when we restrict ourselves to a dose range within the standard of care. This optimal dose can be achieved without an overall increase in expected normal tissue toxicity for the whole cohort. To quantify the clinical potential of personalized RT prescription to improve outcomes in lung cancer, we developed a first-in-class mathematical model combining tumor control and normal tissue toxicity. The model assumes an ideal biological dose to maximize tumor control and estimates outcome based on whether the RxRSI is achieved, then incorporates a penalization scheme based on the added toxicity to which patients are potentially exposed when their RxRSI is exceeded.

To validate the model, we tested it using published data from RTOG-0617, a Phase 3 randomized trial in lung cancer that assessed whether a uniform 14 Gy dose escalation would result in clinical gains in lung cancer. The model correctly predicted both qualitatively and quantitatively the (counter-intuitive) trial outcome: that uniform, empiric dose escalation to 74 Gy does not result in any radiation-associated clinical gains, which it explains is secondary to the potential gains in tumor control being outweighed by the number of patients exposed to additional toxicity. However, the model predicts that a personalized strategy to deliver 74 Gy only to the patient subset most likely to benefit (RxRSI 62-74 Gy) would have improved the radiation-associated outcome for the whole cohort by 7.8% in local control at 5 years. Thus, we propose that the delivery of biologically-inaccurate RT doses results in a significant detriment of clinical outcome for lung cancer patients treated with RT.

While the classic LQ model predicts that every individual in a population has the same opportunity to benefit from uniform dose escalation, the RxRSI model predicts that only a minority of patients (16.2% in this analysis) have the opportunity to benefit from dose escalation to 74 Gy. This opportunity to benefit is outweighed by potential increase toxicity to the rest of the patients. Inspecting the distribution of RSI in the two cohorts for lung cancer also illustrates an interesting point. Dose escalation from 45-60Gy results in capturing the lion's share of the patients in the first peak of the distribution. However, escalation from 60-74Gy only captures the tail of the first mode, and does not affect the second peak. This may explain how uniform dose escalation to 60Gy shows benefit to the entire population, as the benefit outweighs the harm. In addition, our model postulates that 42% of the patients are still undertreated at 74 Gy, which is consistent with the local failure rate reported in 0617²⁹. We postulate that the distributions we measured here are conserved, and further analysis of them in different disease sites could provide insight into opportunities for personalized dose escalation and de-escalation. On the strength of this analysis, we submit that our lack of understanding of biological heterogeneity, and how to treat it, explains the failure of biologically naïve uniform RT dose escalation.

The framework to personalize RT prescription presented in this paper has a number of advantages over the current empiric approach. First, it accounts for biological heterogeneity that is specific to RT, updating the naïve assumption of homogeneous biology across our patients, which is inherent in the empiric approach. Second, since it uses biological information to formulate an optimized and personalized RT prescription dose, it requires that genomic data be collected for every patient. This provides the framework to identify novel biology that impacts RT benefit. Thus the precision RxRSI model is only the first step towards a more efficient and optimal approach to RT prescription. In contrast, multiple Phase 3 clinical trials have demonstrated that additional clinical benefit from the empiric approach is unlikely²⁹⁻³³. Critically, as we have demonstrated, this novel personalized system can be utilized within the standard of care framework for RT dose, and can be done so without the need for additional equipment or medicines.

While significant interest has been focused on the development of better therapeutic agents including targeted agents and immunotherapy, RT remains a fundamental curative treatment for the majority of patients with cancer. It has been estimated that 40% of all cancer cures are due to RT³⁴. In contrast, to date, no targeted agent or immunotherapy has shown similar curative potential in solid tumors. Shifting to a biology-based system will provide a new direction for radiation oncology with multiple opportunities to improve clinical outcome. And that opportunity is not small. Approximately, 50% of all cancer patients receive RT which translates to about 850,000 patients in the US³⁵. A moderate improvement in RT-based cures of 5% would represent an additional 42,500 patients potentially achieving cure. According to the American Cancer Society, this is approximately the same number of patients that die from breast cancer every year in the US.

In conclusion, radiation oncology has employed an empiric uniform approach to prescribe RT that is based on models developed and published over 70 years ago. We demonstrate that this one-size fits all approach is biologically inaccurate for the majority of patients, and results in significant detriment of clinical outcome for patients treated with RT. We propose a new paradigm, where the field updates its assumptions by acknowledging the biological heterogeneity of tumors and moves towards the delivery of biological optimal doses of RT.

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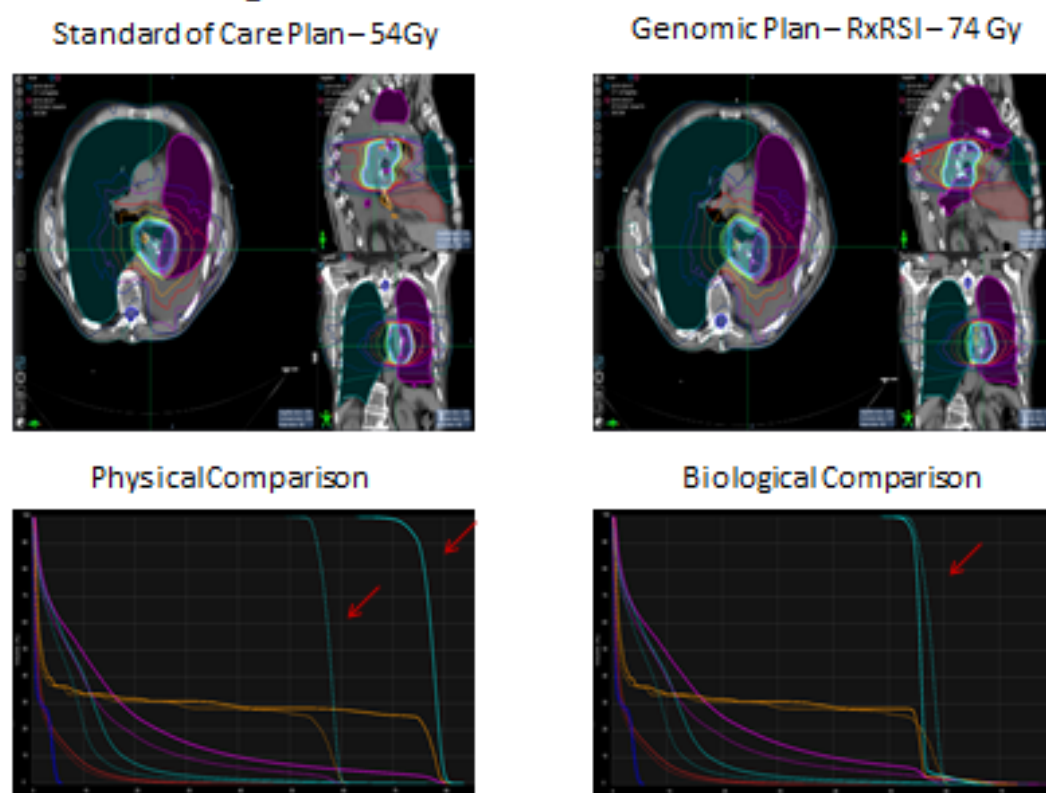
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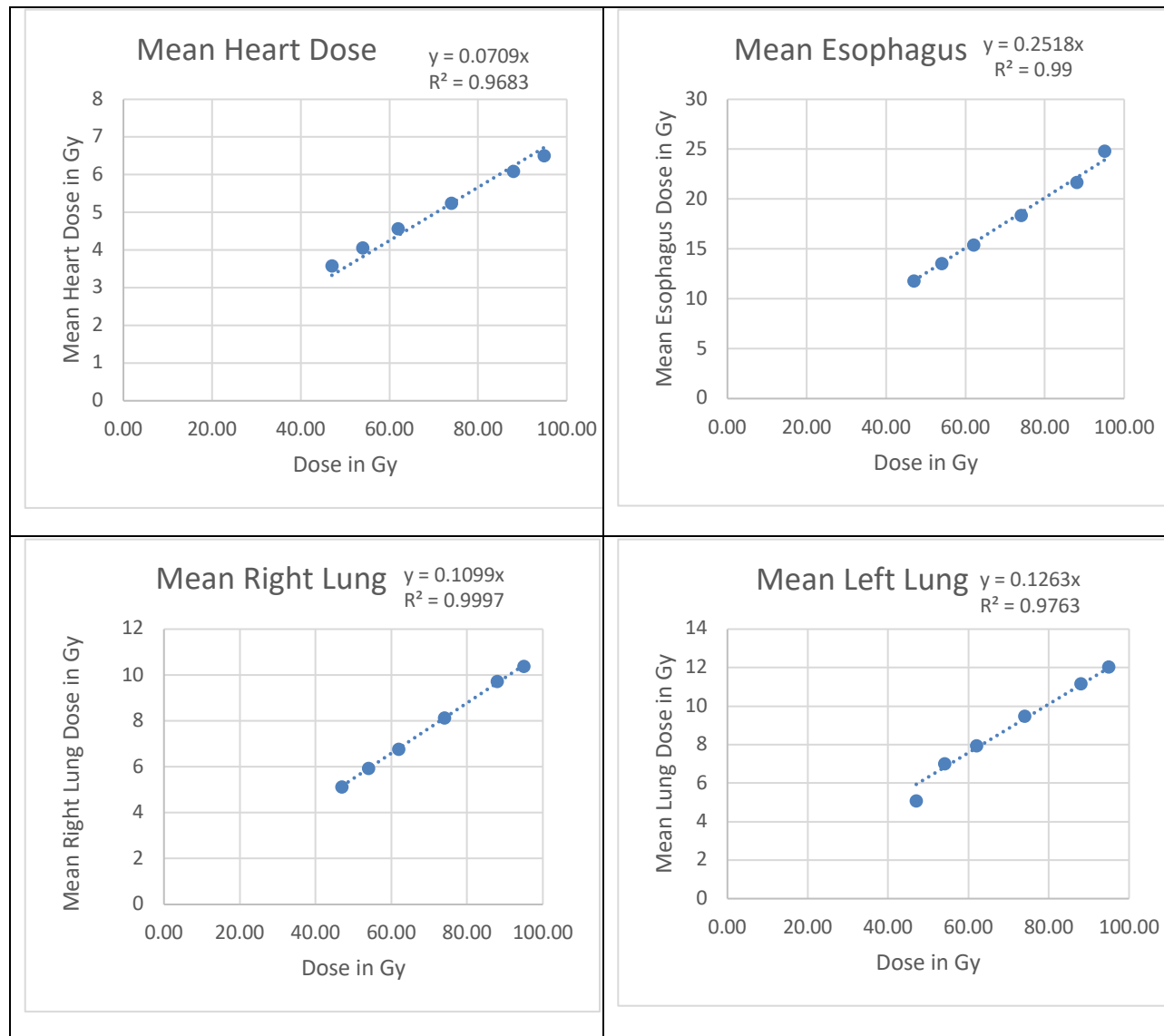
Supplementary Data: Personalizing Radiotherapy Prescription Dose Using Genomic Markers of Radiosensitivity

Precision Genomic Radiation Therapy: Optimizing RT dose with RSI/GARD : Figure 3

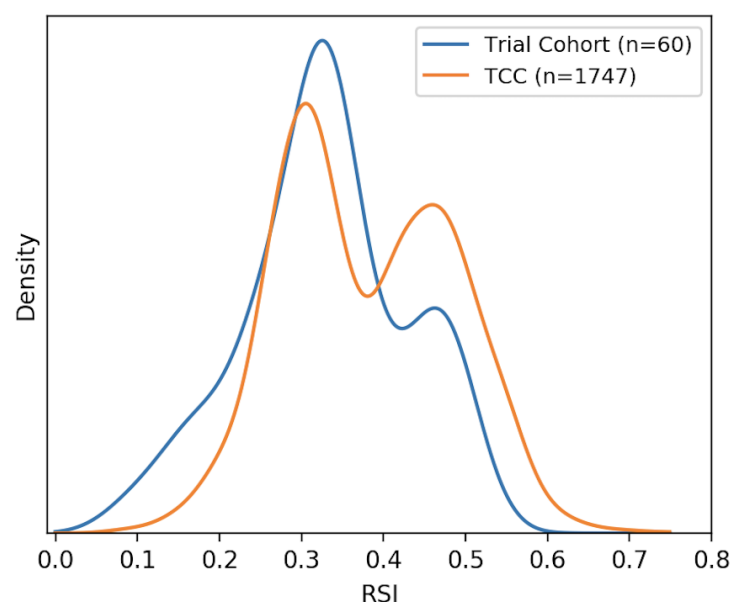


Supplementary Figure 1 Genomic Radiation Therapy Planning: Optimizing and Personalizing RT dose with RSI/GARD. We developed a novel capacity for genomic radiation treatment planning by integrating the algorithms for RSI, GARD and RxRSI into a commercially-available RT treatment planning system. The system integrates imaging, biological and prescription information and generates a standard plan based on empiric dosing and an alternative genomic radiation plan based on the patient's RSI, GARD and RxRSI. The actual treatment plans used to treat the Moffitt lung cancer clinical cohort were not retrievable. However the clinical prescription utilized, the genomic data and clinical outcome were retrievable via our TCC database. We created a set of de-identified radiation treatment plans for post-operative RT in lung cancer. We selected five base plans that represented common treatment areas in post-operative lung, including central lesions, right and left-sided lesions as well as large and smaller fields. We then created 6 different plans for each of the five base plans to represent different biological conditions requiring RxRSIs within the range observed in our cohort (48 Gy, 54 Gy, 62 Gy, 74 Gy, 88 Gy, 95 Gy). (A,B) Standard of care and genomic plan for a patient receiving post-operative RT. (C, D) The standard dose plan was prescribed to 54 Gy. Genomic planning calculates the RxRSI in this example as 74 Gy.

Normal Tissue Linear Model From Composite NSCLC Plans



Supplementary figure 2. A linear model to estimate impact of RT dose adjustment and normal tissue dose. Using the plans generated we calculated the mean dose to each normal tissue target across all 30 genomic plans. A linear model was generated by blotting dose to PTV vs. mean dose to each of the normal tissues. The resulting linear equation was utilized to calculate an approximate mean dose to normal tissue on a per gray basis.



Supplementary Figure 3. RSI distribution for both the Moffitt clinical cohort ($n = 60$) and the TCC modeling cohort ($n = 1,747$). Both distributions are statistically similar using Anderson-Darling and Kolmogorov-Smirnov tests, $p < 0.001$.

Supplementary Tables

Pt ID	Actual dose	RSI	GARD	RxRSI	Actual vs RxRSI Dose Δ	Mean Esophageal Δ @ RxRSI	Mean Left Lung Δ @ RxRSI	Mean Right Lung Δ @ RxRSI	Mean Heart Δ @ RxRSI	Δ number treatment weeks (rounded up to whole fraction)
46	54	0.26	36.378	48.986	-5.014	-1.263	-0.633	-0.551	-0.355	-1
47	60	0.31	35.126	56.369	-3.631	-0.914	-0.459	-0.399	-0.257	-0.8
48	60	0.31	35.126	56.369	-3.631	-0.914	-0.459	-0.399	-0.257	-0.2
49	63	0.33	34.885	59.596	-3.404	-0.857	-0.43	-0.374	-0.241	-1
50	61.2	0.334	33.522	60.246	-0.954	-0.24	-0.12	-0.105	-0.068	-0.6
51	50	0.262	33.453	49.323	-0.677	-0.171	-0.086	-0.074	-0.048	0
52	54	0.292	33.192	53.688	-0.312	-0.079	-0.039	-0.034	-0.022	-0.6
53	60	0.332	33.088	59.841	-0.159	-0.04	-0.02	-0.018	-0.011	0
54	61.2	0.343	32.711	61.74	0.54	0.136	0.068	0.059	0.038	-0.6
55	55.8	0.312	32.464	56.721	0.921	0.232	0.116	0.101	0.065	-0.4
56	61.2	0.357	31.538	64.038	2.838	0.715	0.358	0.312	0.201	-0.2
57	60	0.35	31.493	62.87	2.87	0.723	0.363	0.315	0.204	0.4
58	61.2	0.358	31.406	64.306	3.106	0.782	0.392	0.341	0.22	-0.2
59	60	0.357	30.884	64.111	4.111	1.035	0.519	0.452	0.291	0.6
60	54	0.328	30.107	59.189	5.189	1.307	0.655	0.57	0.368	0
Mean	58.4	0.3	33	58.5	0.1	0	0	0	0	-0.307

Supplementary Table 1. Group 1 sub-cohort. In these patients, the dose delivered and the calculated RxRSI matched.

Pt ID	Actual dose	RSI	GARD	RxRSI	Actual vs RxRSI Dose Δ	Mean Esophageal Increase @ RxRSI	Mean Left Lung Increase @ RxRSI	Mean Right Lung Increase @ RxRSI	Mean Heart Increase @ RxRSI	Increase number treatment weeks (rounded up)
16	45	0.272	29.265	50.744	5.744	1.446	0.725	0.631	0.407	1
17	50	0.306	29.597	55.749	5.749	1.448	0.726	0.632	0.408	1.2
18	50.4	0.315	29.112	57.131	6.731	1.695	0.85	0.74	0.477	0.2
19	46	0.318	26.33	57.654	11.654	2.934	1.472	1.281	0.826	1.2
20	50	0.323	28.26	58.387	8.387	2.112	1.059	0.922	0.595	2
21	43.2	0.324	24.371	58.496	15.296	3.852	1.932	1.681	1.084	1.2
22	54	0.328	30.107	59.189	5.189	1.307	0.655	0.57	0.368	0
23	54	0.334	29.577	60.249	6.249	1.573	0.789	0.687	0.443	0.2
24	45	0.345	23.965	61.965	16.965	4.272	2.143	1.864	1.203	1.2
25	54	0.345	28.757	61.967	7.967	2.006	1.006	0.876	0.565	0.2
26	54	0.346	28.638	62.225	8.225	2.071	1.039	0.904	0.583	1.4
27	54	0.353	28.152	63.3	9.3	2.342	1.175	1.022	0.659	0.4
28	50	0.353	26.014	63.428	13.428	3.381	1.696	1.476	0.952	1.4
29	50.4	0.361	25.669	64.794	14.394	3.624	1.818	1.582	1.021	1
30	60	0.389	28.293	69.983	9.983	2.514	1.261	1.097	0.708	1
Mean	50.667	0.334	27.74	60.351	9.684	2.438	1.223	1.064	0.687	0.907

Supplementary Table 2. Group 2a patients. In this group, patients received lower dose by more than 10% than the calculated RxRSI. Adjustment of these patients dose could be done within standard of care range (50-70 Gy).

Pt ID	Actual dose	RSI	GARD	RxRSI	Actual vs RxRSI Dose Δ	Mean Esophageal Increase @ RxRSI	Mean Left Lung Increase @ RxRSI	Mean Right Lung Increase @ RxRSI	Mean Heart Increase @ RxRSI	Increase number Rx weeks (rounded up)
31	61.2	0.407	27.475	73.507	12.307	3.099	1.554	1.353	0.873	0.6
32	55.8	0.412	24.731	74.458	18.658	4.698	2.357	2.051	1.323	1.4
33	60	0.415	26.36	75.115	15.115	3.806	1.909	1.661	1.072	1.6
34	60	0.453	23.765	83.315	23.315	5.871	2.945	2.562	1.653	2.4
35	45	0.455	17.702	83.891	38.891	9.793	4.912	4.274	2.757	3.4
36	64.8	0.467	24.697	86.587	21.787	5.486	2.752	2.394	1.545	1.6
37	54	0.467	20.546	86.732	32.732	8.242	4.134	3.597	2.321	2.8
38	50.4	0.475	18.77	88.61	38.21	9.621	4.826	4.199	2.709	3.4
39	50	0.475	18.601	88.704	38.704	9.746	4.888	4.254	2.744	4
40	55.8	0.475	20.747	88.753	32.953	8.298	4.162	3.622	2.336	2.8
41	50	0.483	18.189	90.714	40.714	10.252	5.142	4.475	2.887	4.2
42	50.4	0.496	17.648	94.242	43.842	11.039	5.537	4.818	3.108	4
43	45	0.498	15.685	94.677	49.677	12.509	6.274	5.46	3.522	4
44	54	0.499	18.764	94.971	40.971	10.316	5.175	4.503	2.905	3.6
45	60	0.503	20.638	95.939	35.939	9.049	4.539	3.95	2.548	3.6
Mean	54.427	0.465	20.954	86.681	32.254	8.122	4.074	3.545	2.287	2.893

Supplementary Table 3. Group 2b patients. Similar to group 2a patients, these patients received lower doses than the RxRSI. However dose adjustments for these patients are outside the standard of care and in many cases result in plans that do not meet DVH guideline criteria at our institution

Pt ID	Actual dose	RSI	GARD	RxRSI min set to 50Gy	RxRSI	Actual vs RxRSI min 50 Gy Dose Δ	Actual vs RxRSI Dose Δ	Mean Esophageal Decrease @ RxRSI	Mean Left Lung Decrease @ RxRSI	Mean Right Lung Decrease @ RxRSI	Mean Heart Decrease @ RxRSI	Decrease number Rx weeks (rounded up)
1	59.4	0.015	124.78	50	15.71	9.4	43.69	2.367	1.187	1.033	0.666	1.6
2	59.4	0.092	70.758	50	27.703	9.4	31.697	2.367	1.187	1.033	0.666	1.6
3	60	0.118	64.117	50	30.881	10	29.119	2.518	1.263	1.099	0.709	1
4	70	0.166	62.947	50	36.698	20	33.302	5.036	2.526	2.198	1.418	2
5	66	0.177	57.198	50	38.078	16	27.922	4.029	2.021	1.758	1.134	1.6
6	50	0.16	45.875	50	35.967	0	14.033	0	0	0	0	1.6
7	50	0.168	44.588	50	37.006	0	12.994	0	0	0	0	1
8	54	0.198	43.788	50	40.696	4	13.304	1.007	0.505	0.44	0.284	1
9	60	0.238	43.028	50	46.016	10	13.984	2.518	1.263	1.099	0.709	1
10	60	0.239	42.907	50	46.146	10	13.854	2.518	1.263	1.099	0.709	1
11	60	0.248	41.802	50	47.366	10	12.634	2.518	1.263	1.099	0.709	2
12	70	0.304	41.671	55.435	55.435	14.565	14.565	3.668	1.84	1.601	1.033	1
13	60	0.254	41.159	50	48.106	10	11.894	2.518	1.263	1.099	0.709	2

14	70	0.323	39.564	58.38 7	58.38 7	11.613	11.61 3	2.924	1.467	1.276	0.823	1
15	54	0.239	38.621	50	46.14 1	4	7.859	1.007	0.505	0.44	0.284	1
Mean	60.18 7	0.196	53.52	50.92 1	40.68 9	9.265	19.49 8	2.333	1.17	1.018	0.657	1.36

Supplementary Table 4. Group 3 patients. In this group, patients receive a higher dose by more than 10% than the calculated RxRSI. Adjustments to dose on these patients sometimes were set to a minimum dose of 50 Gy.

	esophagus Δ dose	esophagitis	left lung Δ dose	Radiation pneumonitis	right lung Δ dose	Radiation pneumonitis	heart Δ dose	Risk of major coronary event
Group 2a	-2.438	-0.2%	-1.223	-0.7%	-1.064	-0.6%	-0.687	-5.1%
Group 2b	-8.122	-1.5%	-4.074	-2.9%	-3.545	-2.2%	-2.287	-16.9%
Group 3	2.333	0.2%	1.17	0.7%	1.018	0.5%	0.657	4.9%

Supplementary Table 5. Estimating the impact of personalized dose adjustments (RxRSI) on normal tissue risk. Difference calculated as *dose given* – dose received if adjusted to RxRSI. Positive values indicate increased risk when comparing empiric dose and proposed RxRSI dose. Negative values correspond to risk taken on if given RxRSI dose.