ORIGINAL ARTICLE

Personalizing Radiotherapy Prescription Dose Using Genomic Markers of Radiosensitivity and Normal Tissue Toxicity in NSCLC

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Received 3 August 2020; revised 10 November 2020; accepted 15 November 2020
Available online - 8 December 2020

ABSTRACT

Introduction: Cancer sequencing efforts have revealed that cancer is the most complex and heterogeneous disease that affects humans. However, radiation therapy (RT), one of the most common cancer treatments, is prescribed on the basis of an empirical one-size-fits-all approach. We propose that the field of radiation oncology is operating under an outdated null hypothesis: that all patients are biologically similar and should uniformly respond to the same dose of radiation.

Methods: We have previously developed the genomic-adjusted radiation dose, a method that accounts for biological heterogeneity and can be used to predict optimal RT dose for an individual patient. In this article, we use genomic-adjusted radiation dose to characterize the biological imprecision of one-size-fits-all RT dosing schemes that result in both over- and under-dosing for most patients treated with RT. To elucidate this inefficiency, and therefore the opportunity for improvement using a personalized dosing scheme, we develop a patient-specific competing hazards style mathematical model combining the canonical equations for tumor control probability and normal tissue complication probability. This model simultaneously optimizes tumor control and toxicity by personalizing RT dose using patient-specific genomics.

Results: Using data from two prospectively collected cohorts of patients with NSCLC, we validate the competing hazards model by revealing that it predicts the results of RTOG 0617. We report how the failure of RTOG 0617 can be explained by the biological imprecision of empirical uniform dose escalation which results in 80% of patients being overexposed to normal tissue toxicity without potential tumor control benefit.

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Drs. Scott and Sedor contributed equally to this work.

Disclosure: Drs. Scott, Eschrich, and Torres-Roca are shareholders in Cvergenx, a genomics company that holds the commercial license for the radiosensitivity index and GARD. The remaining authors declare no conflict of interest.

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ISSN: 1556-0864

https://doi.org/10.1016/j.jtho.2020.11.008

Conclusions: Our data reveal a tapestry of radiosensitivity heterogeneity, provide a biological framework that explains the failure of empirical RT dose escalation, and quantify the opportunity to improve clinical outcomes in lung cancer by incorporating genomics into RT.

Keywords: Radiation oncology; Personalized medicine; Non–small cell lung cancer; Mathematical modeling

Introduction

The empirical basis of radiation therapy (RT), the most often used therapeutic agent in clinical oncology, has gone unmodified for more than 70 years. RT is prescribed on the basis of a uniform, one-size-fits-all approach, delivering small daily doses of RT in several weeks (i.e., fractionation). This fractionation approach is based on studies performed in rams and rabbits by Regaud, Schinz, and Slotopolsky more than 100 years ago[1-5]—and the standard total doses for control of subclinical, microscopic and macroscopic disease (50, 60, and 70 Gy) were established in the 1960s on the basis of tumor control probability (TCP) models for patients with head and neck cancer.[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. That radiation response is heterogeneous, even within disease groups, is well known. Furthermore, that this heterogeneity is driven and influenced by changes in the tumor genome is now accepted—indeed, large-scale classification efforts have been performed to understand these differences.[8-10] In addition, there have been several efforts to understand surrogate genomic metrics for individual patient's resistance to radiation,[9] imaging-based studies,[11] and theoretical studies of the tumor microenvironment.[12] 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 biological 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.[13-21] Importantly, the Lancet Oncology commission identified GARD as a candidate biomarker for personalized radiation oncology[22] and the European Organisation for Research and Treatment of Cancer identified the totality of the evidence surrounding RSI/GARD as a priority for phase 3 trials.[23] Furthermore, 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 biomarker.[24]

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. Furthermore, we hypothesize that this optimal dose is at least partly defined by tumor biology, as has been posited before.[25] In this manuscript, we used RSI/GARD to calculate the optimal RT dose for each patient in a cohort of 1747 patients with NSCLC. We identify the following three distinct radiobiological cohorts in NSCLC: (1) sensitive patients who are biologically optimized at current standard-of-care RT dose; (2) intermediate patients who may benefit from moderate genomically directed RT dose escalation; and (3) 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 that 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 reveal a tapestry of radiosensitivity heterogeneity, provide a biological framework that explains the failure of empirical RT dose escalation, and quantify the opportunity to improve clinical outcomes in lung cancer by incorporating genomics into RT.

Materials and Methods

Patients

We used patients from the Total Cancer Care (TCC), a prospective institutional review board–approved data, and tissue collection protocol active at Moffitt and 18 other institutions since 2006.[26] Tumors from patients enrolled in the TCC protocol were arrayed on Affymetrix Hu-RSTA-2a520709 (Affymetrix, Santa Clara, CA), which contains approximately 60,000 probe sets representing 25,000 genes. The chips were normalized using iterative rank-order normalization.[27] Batch effects were reduced using partial-least squares. The normalized, debatched expression values for 1747 NSCLC samples and the 10 RSI genes were extracted from the TCC database. To quantify the effect of the optimal dose on tumor control

and toxicity, we used a subset of 60 patients with stage III NSCLC treated at Moffitt with postoperative RT, which has also been previously described. The clinical end point was local control. The median follow-up (on the basis of the reverse Kaplan-Meier method) in censored patients free from local failure was 59.5 months (95% confidence interval: 38.0–68.5 mo).[28]

Radiosensitivity Index

RSI scores were previously generated.[19] RSI was previously trained in 48 cancer cell lines to predict cellular radiosensitivity as determined by survival fraction at 2 Gy.[18] Each of 10 genes in the algorithm is ranked on the basis of gene expression (highest expressed gene is ranked at 10 and lowest at one), and RSI is calculated using the following predetermined equation:

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

which has been presented previously.[18]

Genomic-Adjusted Radiation Dose

GARD, a unitless measure of genomic radiation effect, has been previously described.[19] 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:

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

where dose (d) is 2 Gy, n is the number of fractions (here $n = 1$, recall as we are deriving α_g from RSI which was trained on a survival fraction at 2 Gy assay), and β is a constant at 0.05/Gy^2. GARD is then calculated using the classic equation for biological effect, $\mathrm{GARD} = nd(\alpha + \beta d)$, the patient-specific α_g calculated as per Equation 1, and the number of clinical fractions (n_c) and dose per fraction (d) received by each patient. It is worth noting that in the case when a patient receives a single 2 Gy fraction, the βd terms drop out, and this genomic 2 Gy equivalent (GARD^{2Gy}, similar in spirit to equivalent dose in 2 Gy fractions) is:

$$\mathrm{GARD}_{2Gy} = 2\mathrm{Gy}\left[\frac{-\ln \mathrm{RSI}}{2\mathrm{Gy}} - \beta\, 2\mathrm{Gy} + \beta\, 2\mathrm{Gy}\right] = -\ln \mathrm{RSI}. \quad (2)$$

For a clinical GARD (which we will from here on denote GARD_c), one can simply scale this by the number of fractions given (assuming 2 Gy fraction) yielding $\mathrm{GARD}_c = \frac{n_c}{n_e}(-\ln \mathrm{RSI})$, where n_i in which $i \in \{c, e\}$ is the number of doses given in the $c$linical scenario (individualized per patient) and the experimental (by definition $n_e = 1$) conditions. However, for generality, we define the clinical GARD as:

$$\mathrm{GARD}_c = n_c d(\alpha_g + \beta d). \quad (3)$$

A GARD cut-point of 33 was previously identified and published for the lung clinical cohort[19] and will be used going forward in this manuscript. It is worth noting, however, that this cut-point will differ for each cohort. Briefly, this threshold is found by minimizing the p value for the Kaplan-Meier statistic by iterating through possible cut-points for GARD in a cohort with known outcomes. For the cohort used in this manuscript, for which we identified a $\mathrm{GARD}^{T=33}$, we report this analysis in Supplementary Section 3 (step by step derivation of biologically optimized personalized RT dose [RxRSI]) and include the code in the linked github repository.

Biologically Optimized Personalized RT Dose

Here, we define a new term, RxRSI, as the physical dose (in Gy) required to achieve a previously identified GARD threshold (GARD_T, in this article, $\mathrm{GARD}^{T=33}$) in a cohort of patients with lung cancer treated with postoperative RT.[19] RxRSI is calculated using the following formula:

$$\mathrm{RxRSI} = \frac{\mathrm{GARD}_T}{(\alpha_g + \beta d)}. \quad (4)$$

Where α_g is calculated on the basis of each individual patient's RSI per Equation 1 and β is a constant (0.05/Gy^2). When comparing RxRSI to the empirical dose received by patients in the lung cancer clinical cohort, we defined that the RxRSI and empirical dose matched if they were within 10% of one another. As GARD was developed on the basis of standard fractionation, we further assume that RxRSI is delivered in a similar manner (i.e., dose per fraction is ~2 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.

Genomic Radiation Treatment Planning

To quantify the effect 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 Fig. 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 used the resulting data to generate a linear model to estimate the effect of dose personalization on normal tissue (Supplementary Fig. 2).

Linear Model for Normal Tissue Estimates

The mean dose to each normal tissue target (heart, left lung, right lung, and esophagus) was calculated across the 30 genomic plans developed. Mean normal tissue dose was plotted against planning target volume 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.

Normal Tissue Toxicity

To create a combined model of TCP and normal tissue complication probability (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 were 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 were used, or a quantitative NTCP model which has the benefit of flexibility in choosing dosing parameters. For generalizability, specific dose toxicity end points were not referenced. This method can be extended to any OARs, but for this manuscript, we focus on the following three main drivers of complications in NSCLC RT that have quantifiable models: pneumonitis, esophagitis, and radiation-induced heart disease.

In the Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) review of lung complications, the primary end point is radiation pneumonitis.[29] The reviewers conducted a meta-analysis of applicable studies and performed logistic regression on rates of radiation pneumonitis versus mean lung dose (MLD),

$$p = \frac{\exp b_0 + b_1 \times \mathrm{MLD}}{1 + \exp b_0 + b_1 \times \mathrm{MLD}}. \quad (5)$$

Parameters for b_0 and b_1 were calculated for a model in the above-mentioned form. The QUANTEC-reported recommendations for toxicity end points for the esophagus were inconclusive owing to the volume-dependent effect of the available data.[30] Two of the studies, both published in 2005, provided quantitative models in the form of the Lyman-Kutcher-Burman equation, with parameters m and $TD50$ that were within bounds of the confidence intervals,[31,32]

$$\mathrm{NTCP} = \frac{1}{\sqrt{2\pi}} \int_{\infty}^{t} e^{-x^2/2} dx, \quad \text{where} \quad t = \frac{EUD - TD_{50}}{m \cdot TD_{50}}. \quad (6)$$

Cardiac complications owing to radiation were modeled as a fixed rate of 7.4% increased risk per 1 Gy dose received by the heart. The end point included coronary events as defined by myocardial infarction, coronary revascularization, or death from ischemic heart disease.[33]

Statistical Methods

A survival regression model was used to quantify the effect 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 $H(t) = \lambda t^{\rho}$, as the hazard function, and $S = e^{\lambda t^{\beta}}$ as the survival function. The adjusted outcome models were developed in python in the defined form such that

$$H(t) = \int_{0}^{t} h(u)\, du \quad \text{and} \quad S(t) = [S_0(t)]^{\exp(H(t))}, \quad (7)$$

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

Results

The RxRSI Identifies Three Distinct Radiobiological Clinical Cohorts in NSCLC

As we have revealed previously,[19] there is wide heterogeneity in the radiation sensitivity in NSCLC. In Figure 1*A*, we plot the distribution of RSI in a large

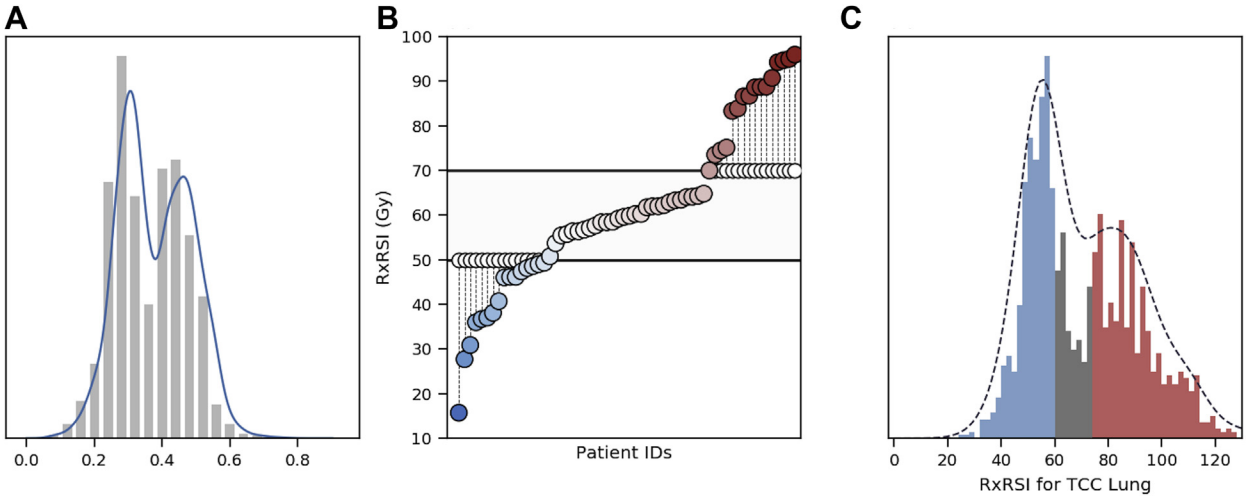

Figure 1. We identify wide heterogeneity in RxRSI which can be simplified into three distinct groups of patients from genomics and RT dosing schedules. (*A*) Distribution of RSI in a cohort of 1747 patients with NSCLC (the TCC cohort). (*B*) Calculating RxRSI (the physical dose required to achieve an optimized biological outcome) for each patient in a clinical cohort of 60 patients with known clinical outcome, dose received, and RSI that reveals the following three groups: patients who require less than SOC dose (50 Gy), patients who require a dose within the SOC range (50–70 Gy), and patients who require more than the SOC dose (>70 Gy). (*C*) Translating to primary radiation doses and a larger (TCC) cohort, we found that there is a subset of patients who are optimized by 60 Gy (blue), a small subset of patients would benefit from moderate (up to 74 Gy—gray), and a large cohort (red) who would need greater than 74 Gy. ID, identification document; RSI, radiosensitivity index; RT, radiation therapy; RxRSI, biologically optimized personalized RT dose; SOC, Standard of Care; TCC, Total Cancer Care.

(1747 patients) cohort of patients with NSCLC 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 suboptimal for most patients. Taking into consideration a separate cohort of postoperative patients with NSCLC with known clinical history, including postoperative radiation dose, we calculate RxRSI (the physical dose predicted to optimize biological outcome). The distribution of this calculation across this cohort (Fig. 1*B* and Supplementary Fig. 5 for the raw RSI $\rightarrow \alpha_g$ transformation for this cohort) reveals a continuous and broad distribution of predicted dose which we can simplify into the following three distinct radiobiological cohorts in this subset of patients: (1) radiosensitive patients who achieve RxRSI at current standard-of-care RT dose ($\leq$50 Gy in this postoperative setting); (2) patients with intermediate sensitivity who achieve RxRSI within the standard-of-care accepted range (50–70 Gy); and (3) a radioresistant group who requires doses above the standard of care (>70 Gy for postoperative RT) to achieve RxRSI.

Translating this calculation to the larger (TCC) cohort, and into primary radiation dosing, we found a similar split into the three groups, but now we notice another interesting finding—in the area of recent dose escalation (60–74 Gy), there is a very low number of patients, suggesting very little is to be gained in this region. Figure 1*C* reveals the following three regions: (blue) where any patient would be optimized by 60 Gy, (gray) where moderate dose escalation to 74 Gy is required, and (red) a large region where doses above 74 Gy 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). Calculating RSI requires only gene expression, though many groups have studied the effects of mutations at the gene level on radiation response. Although this may be so, in our own data, there is no correlation between specific mutations and RSI (see Supplementary Section 3 where we report a cohort of patients with NSCLC, their RSI, and a list of all "usual suspect" genes related to radiation response curated from Yard et al.[34]).

Empirical 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 empirical dosing. To quantify the untoward effects of empirical RT dose then, we generated 30 radiation treatment plans representing the distribution observed for RxRSI in the patients with lung cancer treated with postoperative 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 empirical dose and RxRSI matched whereas for 75% it did not match (Supplementary Tables 1–4). We then calculated the effect on normal tissue dose and toxicity of actually delivering RxRSI for each patient using RT doses within the standard-of-care guidelines (RT dose = 50–70 Gy). In sensitive postoperative 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 postoperative 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 the 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 effect of personalized dose adjustments on normal tissue toxicity is illustrated in Supplementary Table 5. In summary, our data reveal that it is possible to deliver RxRSI to 75% of the patients without changing the overall toxicity profile for the whole population.

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 use genomic markers of radiosensitivity to optimize radiation outcomes considering both tumor control and individual toxicity (Fig. 2*A–C*). Although great efforts have been made to understand the untoward effects of radiation over the decades,[35] 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 (akin to the classic TCP[36,37]) and events related to RT-related toxicity (styled after NTCP) but does not account for death owing to disease progression or other causes. The pLC curve for a population is calculated as $S(t) = C_1S_1(t) + C_2S_2(t)$ where C_i $(i \in 1, 2)$ represents the fraction of patients who 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 the Materials and Methods section). Finally, the convolved survival curves are then adjusted for the predicted toxicity hazard ratios as per the Materials and Methods section:

$$\text{pLC}(t) = \left[S_{74\ Gy}(t)\right]^{\overline{HR_C} \cdot \overline{HR_E} \cdot \overline{HR_P}} \quad (8)$$

Here, $\overline{HR_C}$, $\overline{HR_E}$, and $\overline{HR_P}$ are the risks for each adverse outcome including cardiac, esophagitis, and pneumonitis, respectively.

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 1 trial if you will[38]), to match the recent trial of uniform

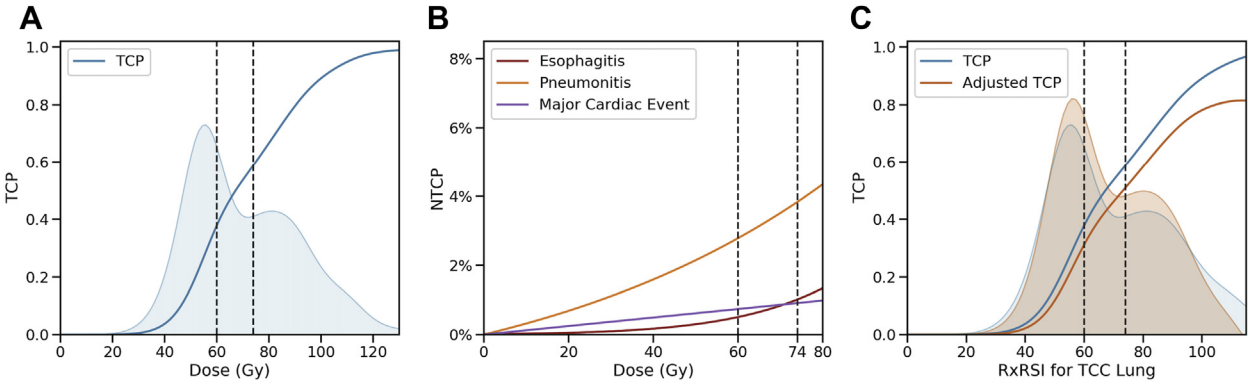

Figure 2. Combined TCP and NTCP model. (*A*) The cumulative distribution function of the (bimodal) RxRSI is a TCP curve (and approximates a sigmoid). (*B*) Probability of grade 3 or greater toxicity with dose for each of esophagus (purple), lung (yellow), and heart (blue). (*C*) TCP (blue) corrected by NTCP (yellow) as a function of dose. NTCP, normal tissue complication probability; RT, radiation therapy; RxRSI, biologically optimized personalized RT dose; TCP, tumor control probability.

dose escalation in NSCLC (RTOG 0617 60 Gy versus 74 Gy). As in RTOG 0617, we assigned (uniformly at random) 200 patients for a 74 Gy arm and 200 patients for a 60 Gy arm. We calculated the expected clinical outcome for each arm on the basis of 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 3*A*. Of note, these two empirical distributions (clinical and TCC) are strikingly similar to one another, sharing two dominant modes with 1% of one another (Supplementary Fig. 4).

As found in Figure 3*B*, the combined model predicts that uniform dose escalation to 74 Gy to unselected patients would result in no radiation-associated overall gains when compared with 60 Gy, consistent with the results observed in the actual clinical trial. Furthermore, as found in Figure 3*C*, 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 who were expected to derive a benefit from dose escalation to 74 Gy. As found in Figure 4*A* (blue group), 39.6% of the patients achieved or exceeded RxRSI at 60 Gy. Only an additional 18.6% reached RxRSI at 74 Gy (gray group). However, our model predicts that still approximately 41.7% of the patients may need higher doses (>74 Gy, red group). Thus, in an unselected population, uniform dose escalation to 74 Gy benefits only a few patients (gray only) and exposes most patients (blue and gray) to additional toxicity, obfuscating any radiation-associated clinical gains. However, a targeted dose-escalation strategy, in which only patients in the cohort of patients with intermediate radiosensitivity (RxRSI = 62–74 Gy) receive 74 Gy

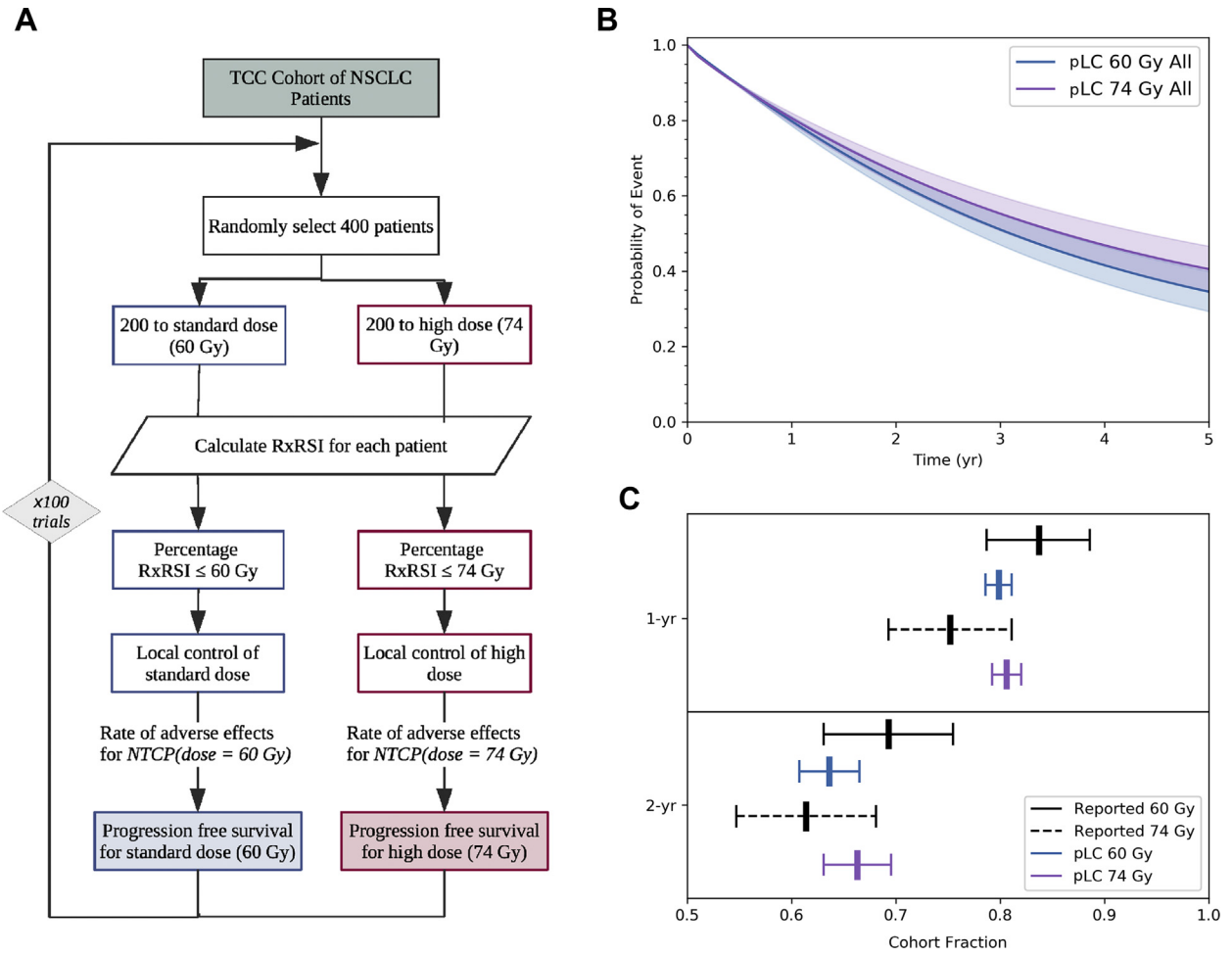

Figure 3. An in silico trial of dose escalation using the competing outcomes model in NSCLC matches the outcomes of a recent cooperative group trial. (*A*) Schematic of our in silico trial designed to match RTOG 0617, with patients drawn uniformly at random from the TCC cohort. (*B*) A Kaplan-Meier curve depicting pLC. The 60 and 74 Gy arms are predicted to have statistically indistinguishable outcomes (pLC) through 5 years. (*C*) Using the combined model accurately predicts the results of RTOG 0617. NTCP, normal tissue complication probability; pLC, penalized local control; RT, radiation therapy; RxRSI, biologically optimized personalized RT dose; TCC, Total Cancer Care; yr, year.

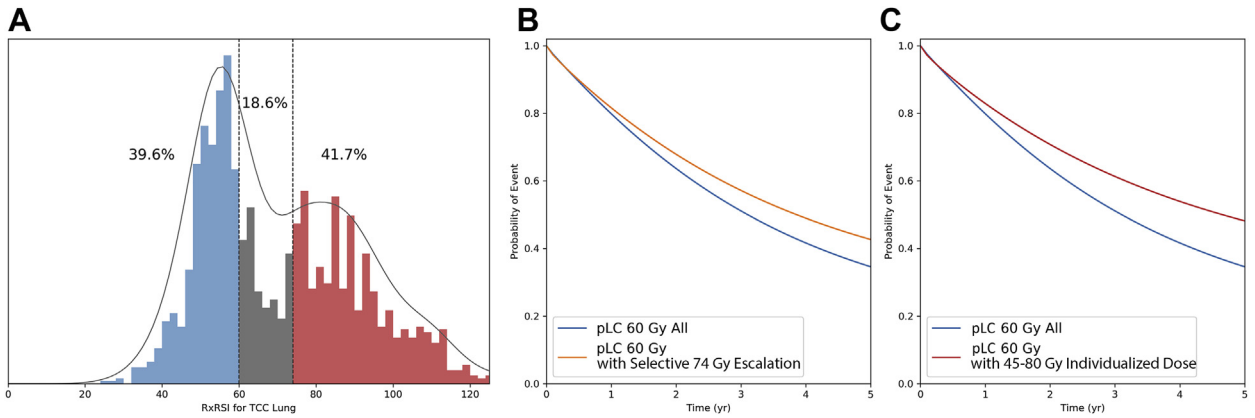

Figure 4. Empirical dose escalation reached local optima at 60 Gy, but personalized dosing offers considerable benefits with current technology. (*A*) A radiation dose of 60 Gy will provide optimal tumor control for approximately 40% of the population, and escalation to 74 Gy will only optimize a further 18.6%, while exposing all to additional toxicity. (*B*) A Kaplan-Meier curve depicting an in silico trial of 60 Gy versus 74 Gy, 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 to 80 Gy. pLC, penalized local control; RSI, radiosensitivity index; RT, radiation therapy; RxRSI, biologically optimized personalized RT dose; TCC, Total Cancer Care; yr, year.

would be expected to improve the local control for the whole cohort by an absolute 4.1% at 2 years and 7.8% at 5 years (Fig. 4*B*). This small, but considerable gain, would increase to 4.3% 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 74 Gy, as they would be spared the additional toxicity. Taken to the logical limit, in which each patient is given only the dose they need, to an upper limit of 80 Gy (lower bound of 45 Gy), would further increase the outcomes by another 2.8% and 5.4% at 2 and 5 years, respectively, highlighting the opportunity when RT is truly personalized (Fig. 4*C*).

Discussion

In this article, we present a clinically feasible model to personalize RT prescription on the basis of biological parameters and estimate the clinical opportunity for improved clinical outcomes inherent in personalized RT for patients with NSCLC. Our proposal for personalized RT prescription is based on the following three parameters: (1) RSI, which defines the patient's individual tumor radiosensitivity; (2) GARD, which defines the individualized clinical effect of a given dose of RT in a given patient with a distinct RSI; and (3) 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 empirical-based one-size-fits-all approach that is currently standard in the field.

Using a retrospective cohort of patients treated with RT for NSCLC which included tumor gene expression, radiotherapy dose, and clinical outcome, we derive a new quantity we term RxRSI—the radiation dose each individual patient our model proposes is needed to optimize outcome. We subsequently find, using two separate cohorts of untreated patients, that empirical dosing would only achieve this RxRSI (within a tolerance of 10%) in one out of every four of cases. Critically, however, small changes (up or down) to individual patient doses could increase this number to three of four without going outside the standard of care.

In the calculations for achieving optimal dose, we realized that not only were some patients predicted to be underdosed, but just as many were predicted to be overdosed—potentially subjecting them to increased toxicity. In other words, the toxicity cost for achieving the RxRSI was different for each individual patient. To address this, we developed a first-in-class mathematical model combining the canonical models for TCP and NTCP. The model assumes an ideal biological dose to maximize tumor control (RxRSI) and estimates outcome on the basis of whether this is achieved and then incorporates a penalization scheme on the basis of the added toxicity to which patients are potentially exposed when their RxRSI is exceeded. At this stage in the model development, we have kept NTCP estimates on the basis of population averages and have attempted to propagate the (large) uncertainty that comes with this abstraction through the data. We have made a first attempt to propagate this error through our mixed modeling framework in the supplements, and although the general findings for Radiotherapy Oncology Group 0617 are strengthened, the findings for our proposed dose escalation are somewhat weakened. This highlights the need

for personalized planning, not just avatar-based OAR calculations. In future, we hope to be able to personalize prediction of NTCP as well, but this lies outside the scope of this work as RSI and GARD are not designed to predict personalized normal tissue toxicity.

To validate the combined RxRSI-toxicity model, we tested it using published data from RTOG-0617, a phase 3 randomized trial in lung cancer that assessed whether unselected patients with NSCLC would benefit from a 14 Gy dose escalation (from 60 to 74 Gy). Although we did not have access to the tumor tissue from the prospective trial, we ran an in silico trial with the same schema and drew randomly from a large cohort of surgical NSCLC samples from an institutional biorepository. We iterated this in silico trial 100 times. The results of this model-driven in silico trial qualitatively and quantitatively agree with the reported trial (counterintuitive) outcome: that uniform, empirical dose escalation to 74 Gy does not result in any radiation-associated clinical gains. This has been previously explained as secondary to the potential gains in tumor control being outweighed by the number of patients exposed to additional toxicity, a conclusion our model supports. In a hypothesis-generating extension, 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.

Although the classic LQ model predicts that every individual in a population has the same opportunity to benefit from a uniform dose escalation, the RxRSI model predicts that only a few patients (16.2% in this analysis) have the opportunity to benefit from dose escalation from 60 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 to 60 Gy results in capturing the lion's share of the patients in the first peak of the distribution. However, escalation from 60 to 74 Gy only captures the tail of the first mode and does not affect the second peak. This may explain how uniform dose escalation to 60 Gy has a benefit to the entire population, as the benefit outweighs the harm. In addition, our model suggests that 42% of the patients are still undertreated at 74 Gy, which is consistent with the local failure rate reported in RTOG 0617.[39] 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 naive uniform RT dose escalation.

The framework to personalize RT prescription presented in this article has a number of advantages over the current empirical approach. First, it accounts for biological heterogeneity that is specific to RT, updating the naive assumption of homogeneous biology across our patients, which is inherent in the empirical 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 affects RT benefit and to update our models as we move forward. Thus, the precision RxRSI model is only the first step toward a more efficient and optimal approach to RT prescription in which toxicity and tumor control can be quantitatively optimized in parallel by maximizing the survival function (Eq. 8) as part of the same inverse problem we are accustomed to solving for physical dose distributions. In contrast, multiple phase 3 clinical trials have revealed that additional clinical benefit from the empirical approach is unlikely.[39-43] Critically, as we have found, this novel personalized system can be used within the standard-of-care framework for RT dose and can be done so without the need for additional equipment or medicines.

To make this approach a reality for day-to-day clinical use, widespread adoption of tumor sequencing/expression profiling will be necessary—similar to the adoption of commercially available clinical decisions tools such as Oncotype and Mammaprint in medical oncology. Using this framework in clinical trials is straightforward as entering the input parameters in our online algorithm will provide a specific prediction about patient survival which can be directly used for power calculations. This could be further used for posthoc analyses for trials in which tissue and specific radiation plans exist. Using the combined RxRSI-toxicity model is limited to lung cancer at present, but we plan to add further toxicity models to our database of other tumor types to allow further generalization.

Although considerable interest has been focused on the development of better therapeutic agents including targeted agents and immunotherapy, RT remains a fundamental curative treatment for most patients with cancer. It has been estimated that 40% of all cancer cures are due to RT.[44] In contrast, to date, no targeted agent or immunotherapy has been found to have 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 70% of all patients with cancer receive RT, which translates to approximately 850,000 patients in the United States.[45] A moderate improvement in RT-based cures of 5% would represent an additional 42,500 patients potentially achieving cure.

In conclusion, radiation oncology has used an empirical uniform approach to prescribe RT that is based on models developed and published more than 70 years ago. We propose that this one-size-fits-all approach is biologically inaccurate for most patients and may result in considerable detriment of clinical outcome for patients treated with RT. We propose a new paradigm, in which the field updates its assumptions by acknowledging the biological heterogeneity of tumors and moves toward the delivery of biological optimal doses of RT.

Acknowledgments

Dr. Scott thanks the National Institutes of Health (NIH) Loan Repayment Program for their generous support and the Paul Calabresi Career Development Award for Clinical Oncology (NIH K12CA076917) and NIH R37CA244613. Dr. Torres-Roca acknowledges support from the DeBartolo Family Personalized Medicine Institute.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2020.11.008.

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