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Extracting the normal lung dose–response curve from clinical DVH data: a possible role for low dose hyper-radiosensitivity, increased radioresistance

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Abstract

In conventionally fractionated radiation therapy for lung cancer, radiation pneumonitis' (RP) dependence on the normal lung dose-volume histogram (DVH) is not well understood. Complication models alternatively make RP a function of a summary statistic, such as mean lung dose (MLD). This work searches over damage profiles, which quantify sub-volume damage as a function of dose. Profiles that achieve best RP predictive accuracy on a clinical dataset are hypothesized to approximate DVH dependence.

Step function damage rate profiles $R(D)$ are generated, having discrete steps at several dose points. A range of profiles is sampled by varying the step heights and dose point locations. Normal lung damage is the integral of $R(D)$ with the cumulative DVH. Each profile is used in conjunction with a damage cutoff to predict grade 2 plus (G2+) RP for DVHs from a University of Michigan clinical trial dataset consisting of 89 CFRT patients, of which 17 were diagnosed with G2+ RP.

Optimal profiles achieve a modest increase in predictive accuracy— erroneous RP predictions are reduced from 11 (using MLD) to 8. A novel result is that optimal profiles have a similar distinctive shape: enhanced damage contribution from low doses (<20 Gy), a flat contribution from doses in the range ~20–40 Gy, then a further enhanced contribution from doses above 40 Gy. These features resemble the hyper-radiosensitivity / increased radioresistance (HRS/IRR) observed in some cell survival curves, which can be modeled using Joiner's induced repair model.

A novel search strategy is employed, which has the potential to estimate RP dependence on the normal lung DVH. When applied to a clinical dataset, identified profiles share a characteristic shape, which resembles HRS/IRR. This suggests that normal lung may have enhanced sensitivity to low doses, and that this sensitivity can affect RP risk.

Keywords

lung cancer; radiation pneumonitis; radiation hypersensitivity

1. Introduction

Radiation pneumonitis (RP) is the principal dose-limiting complication in radiation therapy (RT) for lung cancer, occurring in 5–50% of patients (Marks *et al* 2010). In the case of conventionally fractionated RT (CFRT), the principal strategy for minimizing patients' risk is to observe empirically established constraints, such as $V20 \leq 30\text{--}35\%$ and $MLD \leq 20\text{--}23$ Gy (Tucker *et al* 2010). (VD is the fraction of lung volume receiving dose D or greater. MLD is mean lung dose.) However, relationships between RP risk and dose statistics such as MLD vary between institutions (Marks *et al* 2010, Tucker *et al* 2010). No convincing explanation has yet been provided for that variability. Ideally, one would like a more fundamental understanding of the relationship between RP risk and normal lung's biological response to radiation. This might help explain the variation of RP risk versus MLD plots with patient characteristics and institutional treatment planning practices, leading to better predictive models of RP and radiation-induced lung damage.

The raw data for this work consists of anonymized RP grading plus dose–volume histograms (DVHs) for 89 patients from the University of Michigan (UM) CFRT clinical trial reported in Kong *et al* (2006). RP grading was according to SWOG criteria. We focus on two categories: grade one or lower (G1–) DVHs, versus grade 2 or higher (G2+) DVHs. A local damage / injury model similar to Jackson *et al* (1995) is adopted. We assume that lung is a parallel organ, and that radiation-induced loss of function can be modeled using a biological dose–response profile $P_{\text{bio}}(D)$, which gives the probability of sub-volume damage as a function of local dose D. RP risk is assumed to be a function of integral damage G , obtained as the integral of $P_{\text{bio}}(D)$ with the DVH. The greater the damage, the greater the risk of RP. One can specify a damage cutoff G_{cut} above (below) which patients are predicted to be at high (low) risk of RP. In any clinical dataset, classification of high versus low risk patients will be imperfect, because risk depends on a variety of non-dose factors—e.g. concurrent chemotherapy, comorbidities, etc. However, one can choose G_{cut} to minimize the combined number N_{FNFP} of false negatives (G2+ cases erroneously predicted to be G1–) and false positives (G1 – cases erroneously predicted to be G2+).

In the above framework, the profile $P_{\text{bio}}(D)$ is the sought-after dose–response curve, which is initially unknown. Intuitively, if one were to guess at different forms for $P_{\text{bio}}(D)$, the guesses which come closest to the true function should provide best classification of G1 – versus G2+ DVHs. Specifically, suppose many candidate functions $P(D)$ are used to compute integral damage values G for the 89 patients. For each $P(D)$, the G_{cut} value that minimizes N_{FNFP} is adopted. As one iterates over candidate profiles $P(D)$, one identifies the profiles that produce the overall minimum value of N_{FNFP} . It is intuitively reasonable to use the identified profiles to estimate the true dose–response profile $P_{\text{bio}}(D)$.

This work implements the above search strategy. It searches over a large number of candidate damage profiles $P(D)$, and identifies a relatively small subset of 'optimal' profiles that minimize N_{FNFP} . Optimal profiles exhibit a common shape, featuring an enhanced damage contribution from low doses (<20 Gy), a flat contribution from doses in the range ~20–40 Gy, then a further enhanced contribution from doses above 40 Gy. These features resemble the hyper-radiosensitivity / increased radioresistance (HRS/IRR) observed in some

cell survival curves, including the normal lung cell survival curve obtained by Singh *et al* (1994). In summary, the significance of this work is to propose a heuristic methodology for estimating $P_{\text{bio}}(D)$ from clinical DVHs. The profile $P_{\text{bio}}(D)$ estimated from the UM DVH dataset makes a tentative connection from clinical RT data to the enhanced low-dose sensitivity observed *in vitro* in many cell lines, including normal lung.

2. Methods and materials

2.1. University of Michigan clinical trial data

Clinical data for this study consist of 89 lung DVHs from patients enrolled in the UM Institutional Review Board approved dose escalation study reported in Kong *et al* (2006). That study enrolled 109 patients treated for non-small-cell lung cancer. Treatments were either RT alone or RT with neoadjuvant chemotherapy. RT planning employed 3D conformal RT (3DCRT). Patients received daily fractions of 2.1 Gy, with total dose escalated from 63 Gy based on normal tissue tolerance. Grading of RP was according to SWOG (www.swog.org) rules, with clarifications noted in Kong *et al*. Further details are given in the text and cited publications in Kong *et al* (2006).

Data for the present study were provided in anonymized form for patients who had known RP status at a time point 6 months after the start of treatment. Data for 20 patients who were lost to follow-up prior to that time point were not provided, leaving 89 patients with RP grading as follows (G = grade): G_0 : 42, G_1 : 30, G_2 : 12, G_3 : 5, G_{4+} : 0. Data consisted of DVHs for total lung minus gross tumor volume (GTV), consisting of absolute lung volumes (in cubic centimeters (cc)) in dose bins with centers from 0.5 Gy to 119.5 Gy in steps of 1 Gy. (The dose bin centered at 0.5 Gy included the lung volume receiving [0 Gy, 1 Gy), etc). DVHs were calculated using the UMPlan treatment planning system.

DVH dose values were provided as 2 Gy equivalent (EQD2) using an α/β ratio of 2.5 Gy. The present study converted EQD2 doses to physical doses before integrating with damage profiles. In addition to RP grade and DVH, patient data included prescription dose (63 Gy–102.9 Gy), number of fractions (30–49), elapsed days between RT start and end (40–74), elapsed days between RT start and last follow-up (139–3217), elapsed days between RT start and G_{2+} RP (52–316 for 17 G_{2+} cases), and (by virtue of the DVHs) total lung volume (2042 cc–8042 cc). Data on patient performance status, or on which patients received chemotherapy, were not included. A subset of the DVHs—specifically, all G_{2+} DVHs and a subset of G_1 – DVHs having comparable MLDs—is shown in figure 1.

2.2. Local injury / damage model

In the following $DVH(D)$ and $cDVH(D)$ denote differential and cumulative DVHs:

$DVH(D) = (d/dD) cDVH(D)$, $cDVH(D) = \int_D^\infty DVH(d)$. This work adopts a local damage/injury model similar to Jackson *et al* (1995) (see also Niemierko and Goitein (1993) and Rutkowska *et al* (2012)). It is assumed that lung is a parallel organ, and that radiation-induced loss of function can be modeled using a damage probability profile $P(D)$, which gives the probability of sub-volume damage as a function of local dose D . ($P(D)$ is assumed to be independent of the subvolume location within the lungs.) The exact nature of the

damage is not specified, but could represent, e.g. loss of perfusion (blood flow), diffusion (oxygen transport), or both. The integral damage G to normal lung is calculated by integrating the product of DVH(D) and $P(D)$. Mathematically this is equivalent to integrating the product of cDVH(D) and $R(D)$, where $R(D)$ is the derivative of $P(D)$: $R(D) = (d/dD) P(D) \equiv P'(D)$. For this work, functions $P(D)$ are referred to as damage profiles, and functions $R(D)$ are referred to as rate profiles.

$$G = \int_0^\infty \text{DVH}(D) \cdot P(D) dD = \int_0^\infty \text{cDVH}(D) \cdot R(D) dD \quad (1)$$

Radiation pneumonitis is assumed to occur when G exceeds a threshold. As in Jackson *et al* (1995), normal tissue complication probability (NTCP)—i.e. RP risk—is given by $\text{NTCP} = H(G)$ where $H(G)$ is the cumulative distribution of functional reserves in the patient population. This work effectively assumes $H(G)$ is a step function, increasing from 0 to 1 at $G = G_{\text{cut}}$. Based on whole lung irradiation data—see, e.g. Marks *et al* (2010) figure 3— $H(G)$ increases from 0 to 1 over a narrow damage range. Hence the step function approximation is reasonable.

2.3. DVHs and damage profiles

Figures 2(a)–(f) illustrate damage and rate profiles relevant to this work. Profiles are superimposed on an example differential DVH (blue solid line in figures 2(a), (c) and (e)) or cumulative DVH (blue solid line in figures 2(b), (d) and (f)). Figure 2(a) shows three examples. The first is a linear profile $P_0(D) = \kappa D$, where arbitrarily $\kappa = 1/80 = 0.0125$. Damage G is κ times the mean lung dose, appropriate if RP incidence were perfectly correlated with MLD. Profiles $P_1(D)$ and $P_2(D)$ are linear quadratic (LQ) profiles, having the functional form: $P(D) = 1 - \exp(-D(a + \beta D/N))$. The LQ model has been widely used in radiation biology to model cell survival curves, though estimates of α and β parameters remain open to debate and revision (O'Rourke *et al* 2008). Commonly, $P(D)$ is the probability of cell reproductive death: $P(D) = 1 - S(D)$ where $S(D)$ is the surviving fraction at dose D (Niemierko and Goitein 1993). For $P_1(D)$, $\alpha = 0.2 \text{ Gy}^{-1}$, $\beta = 0.667 \text{ Gy}^{-2}$ and $\alpha/\beta = 3 \text{ Gy}$. The value $\alpha = 0.2 \text{ Gy}^{-1}$ is consistent with many *in vitro* measurements of cell survival (Singh *et al* 1994, Williams *et al* 2008, Guirado *et al* 2012). Similarly, $\alpha/\beta \approx 3 \text{ Gy}$ is a conventional assumption for normal tissues.

It is possible to use the LQ equation, but equate $P(D)$ with functional loss rather than cell reproductive death. For $P_2(D)$, $\alpha = 0.01 \text{ Gy}^{-1}$, $\beta = 0.005 \text{ Gy}^{-2}$ and $\alpha/\beta = 2 \text{ Gy}$. This α value is derived from the *in vivo* SPECT perfusion loss measurements reported by Koontz *et al* (2005). (That work measured ED_{50} , the dose required to produce 50% perfusion loss. Plots of $1/\text{ED}_{50}$ had an intercept of approximately 0.015 Gy^{-1} . Substituting $P(\text{ED}_{50}) = 0.5$ in the LQ equation implies $\alpha \approx 0.01 \text{ Gy}^{-1}$.) Recent measurements (Koontz *et al* 2005, Scheenstra *et al* 2014) suggest that the α/β ratio for normal lung is lower than 3 Gy, motivating the value $\alpha/\beta = 2 \text{ Gy}$ for $P_2(D)$. For both $P_1(D)$ and $P_2(D)$, the number of fractions is assumed to be $N = 33$. Perhaps because it is based on *in vivo* data that measures clinically relevant functional loss, rather than *in vitro* cell survival, the profile $P_2(D)$ appears to give a more realistic model of RP-associated damage. In particular, due to its lower α value, $P_2(D)$ is more closely proportional to MLD, an established RP predictor, than $P_1(D)$. The rate

profiles $R_n(D)$ in figure 2(b) are the derivatives of the damage profiles $P_n(D)$ in figure 2(a), multiplied by a factor of 30 for display purposes.

Figure 2(c) shows a piecewise linear damage profile $P_3(D)$, which varies linearly over 4 segments defined by 4 dose points d_0 , d_1 , d_2 and d_3 . Figure 2(d) shows the corresponding rate profile $R_3(D)$, which is a step function whose step heights are equal to the slopes of the linear segments of $P_3(D)$. As described in section 2.5, this work searches over a large number of piecewise linear profiles to identify those that minimize N_{FNFP} .

Joiner's induced repair model (IRM) (Lambin *et al* 1994) modifies the LQ model by adding an initial low-dose section with steeper slope, followed by a section with shallower slope, before asymptoting to LQ behavior. The IRM equations for the damage profile $P(D)$ are:

$$P(D) = 1 - \exp(-D[\alpha(D) + \beta D]) \quad (2)$$

$$\alpha(D) = \alpha_r - (\alpha_r - \alpha_s) \cdot \exp(-D/D_c) \quad (3)$$

where α_s is the initial slope and α_r is the final slope of the single-fraction cell survival curve, D_c is a critical dose that determines the transition from α_s to α_r , and β is the usual LQ parameter. Figure 2(e) shows an example IRM damage profile $P_4(D)$. Figure 2(f) shows the corresponding rate function $R_4(D)$. For these plots, $\alpha_s = 0.04$, $\alpha_r = 0.0032$, $\beta = 0.000091$, $D_c = 7.7$.

Other damage profiles have been proposed. For example, Jackson *et al* (1995) utilize the log-logistic function. For a more extensive discussion, see the AAPM Task Group 166 report (Li *et al* 2012). This work is restricted to the profiles given above. Functions $P(D)$ and $R(D)$ are employed in this work to rank order DVHs based on calculated damage. Consequently, the shapes of functions $P(D)$ and $R(D)$ are important, but their absolute values are not, and rescaling of $P(D)$ or $R(D)$ on the y-axis (i.e. by a factor of 30) has no effect on the results.

2.4. N_{FNFP} calculation

A rate profile $R(D)$ corresponding to candidate damage profile $P(D)$ is integrated with UM cumulative DVHs to generate 89 damage values G , as in equation (1). The 89 damage values are ordered and normalized so the largest value is 0.98. (Damage values are scaled to the range [0,1].) A damage cutoff G_{cut} is then selected. Damage values below (above) G_{cut} are predicted to experience G1 – (G2+) RP. False positives and negatives are tallied. G_{cut} may be a fixed value (e.g. 0.85), or it may be selected to minimize N_{FNFP} for that candidate profile $P(D)$. In the latter case, G_{cut} is moved from 0 to 1 in small steps until the minimum is found.

2.5. Profile search strategy

The profile search utilizes piecewise linear profiles as in figures 2(c) and (d). A large number of rate profiles is generated by moving points d_0 , d_1 , d_2 and d_3 progressively from $D = 0$ Gy to $D = 100$ Gy on the dose axis, using a variety of spacings (step widths) $d_1 - d_0$,

$d_2 - d_1$ and $d_3 - d_2$. For each set (d_0, d_1, d_2, d_3), step heights are independently varied from 0 to 0.9 in increments of 0.1. This generates approximately 19 million rate profiles $R(D)$ and corresponding damage profiles $P(D)$ —see figures 4(a)–(c) for examples. For each of these profiles N_{FNFP} is calculated. The set of profiles that minimize N_{FNFP} is recorded.

3. Results

Figure 3 is a plot of MLD versus DVH number. Pink solid triangles are grade 3 DVHs. Red solid circles are grade 2 DVHs. Blue hollow diamonds are grade 1 DVHs. Gray hollow squares are grade 0 DVHs. On the UM dataset, with optimal cutoff, MLD achieves 11 erroneous predictions: 9 false negatives (FN) and 2 false positives (FP). The horizontal line is the cutoff that gives $N_{\text{FNFP}} = 11$. For comparison, V20 has $N_{\text{FNFP}} = 13$ (12 FN, 1 FP). V30 also has $N_{\text{FNFP}} = 13$ (10 FN, 3 FP). The LQ $P_1(D)$ model has $N_{\text{FNFP}} = 12$ (9 FN, 3 FP). The LQ $P_2(D)$ model also has $N_{\text{FNFP}} = 12$ (12 FN, 0 FP).

The search over step function rate profiles $R(D)$ identified ~19000 profiles that could achieve $N_{\text{FNFP}} = 8$. No sampled step function profiles were able to achieve $N_{\text{FNFP}} < 8$. Five of the profiles had 0 FP and 8 FN. The remainder had 1 FP and 7 FN. Figures 4(a)–(c) illustrate optimal step function profiles. Figure 4(d) is an intensity plot where the intensity at each point is proportional to the number of the ~19 000 optimal rate profiles $R(D)$ passing above the point. Figure 4(d) indicates that optimal profiles $R(D)$ have common features: a peak at low doses, a valley at mid-range doses around 20 Gy, and a peak or plateau at higher doses.

If one averages all of the optimal rate functions $R(D)$, one obtains the average rate function $\bar{R}(D)$ (blue dotted line) in figure 4(e). The rate function can be integrated to get the corresponding damage profile $\bar{P}(D)$ (red solid line). Note that $\bar{P}(D)$ has been rescaled to attain a value of one at 120 Gy—the profile search can identify the shape of $P(D)$ but not its absolute scale, so renormalization is permissible. Relative to the MLD damage profile (straight line $P_0(D)$ in figure 2(a)), $\bar{P}(D)$ exhibits a steeper slope at low doses, a shallower slope at midrange doses, then reverts to approximately linear behavior at high doses. The red dashed line in figure 4(e) is the induced repair model fit to $\bar{P}(D)$, discussed below. Figure 4(f) plots damage versus DVH number for one of the optimal profiles. Optimal profiles produce a different ordering of points in comparison to figure 3, which in turn produces lower N_{FNFP} . The horizontal line in figure 4(f) is the optimal damage cutoff for the selected profile.

Selection of optimal profiles is driven by the toxicities assigned to the UM DVHs: selected profiles are those that tend to produce large damage values for DVHs labelled G2+, and low damage values for DVHs labelled G1 – . One would like to verify that the profiles selected in figure 4 are selected by all of the G2+ DVHs, not just the subset of 10 near the top of figure 4(f). Similarly, one would like to verify that the optimal profiles in figure 4 are not selected by G1 – DVHs.

The ability of the lower 7 G2+ DVHs (i.e. those below the cutoff in figure 4(f)) to select optimal profile can be tested by omitting from analysis G2+ DVHs having MLD > 20 Gy,

and G1 – DVHs having $MLD > 18.5$ Gy. The achievable minimum in this case is $N_{FNFP} = 3$. If one allows G_{cut} to assume its optimal value for each candidate profile a large number of profile ($\sim 360\,000$) is selected. The corresponding plots of intensity, average profile and damage are shown in figure 5(a)–(c). Note that the optimal cutoff in figure 5(c) is close to 0.56.

In figure 5(b), the average profile $\overline{P}(D)$ approximates a straight line. The profile search iterates over a large number of rate functions $R(D)$. If there is no reason to select functions $R(D)$ that are weighted specifically towards low or high doses, the average function $\overline{R}(D)$ will converge to a horizontal line, and the average profile $\overline{P}(D)$ will correspondingly converge to a straight line. The fact that profile $\overline{P}(D)$ approximates a straight line indicates that no specific shape is favored for $P(D)$.

If, however, one repeats the analysis with G_{cut} fixed at 0.6, a smaller number of optimal profiles (~ 700) is selected. The corresponding plots are shown in figures 5(d)–(f). The profiles $\overline{P}(D)$ and $\overline{R}(D)$ resemble the functions in figure 4(e). It appears that fixing G_{cut} at a higher value (i.e. 0.6 versus 0.56) makes it more difficult to push G2+ DVHs above the cutoff, while keeping G1 – DVHs below, thereby selecting the smaller set of profiles that can successfully ‘separate’ the G2+ DVHs versus G1 – DVHs. This suggests that a heuristic search over profiles will only identify a small set of optimal profiles in cases where G2+ DVHs and G1 – DVHs are difficult to separate. If they are easy to separate, the search becomes non-specific, returning a large number of profiles. In this case, profiles that approximate $P_{bio}(D)$ are among the identified profiles, but the search is too non-specific to be of value in identifying $P_{bio}(D)$.

Finally, to show that the profiles selected in figure 4 are in fact associated with G2+ DVHs, and not an artifact of the analysis, one can artificially label G2+ DVHs as G1 – DVHs, and re-label the 17 bona fide G1 – DVHs having largest MLDs as G2+ DVHs. A search for optimal profiles on the relabeled data set achieves $N_{FNFP} = 11$. Regardless of G_{cut} , optimal profiles in this case resemble figures 5(a)–(c). Specifically, profile $\overline{P}(D)$ approximates a straight line, indicating that no specific shape is selected. This shows that, as one might hope, the profile search fails to identify a small set of optimal profiles when provided bogus data in which G2+ and G1 – labels are reversed.

4. Discussion

This work began as an attempt to improve the accuracy of RP prediction. By searching over candidate profiles $P(D)$, it hoped to find a subset that could better predict DVHs associated with high RP risk. Success in this respect was limited: on the UM dataset, the number of erroneous predictions was marginally reduced from $N_{FNFP} = 11$ (using MLD) to $N_{FNFP} = 8$.

This lack of success is not entirely surprising. Clinical data is acquired from heterogeneous patient populations, ensuring ‘noisy’ data (Onjukka *et al* 2015). RP risk is known to depend on non-dose-related factors, such as concurrent chemotherapy and co-morbidities. Finally, the challenges of diagnosing RP are well-documented (Kong *et al* 2006, Marks *et al* 2010). A significant percentage of patients whose symptoms are caused, either partially or wholly,

by non-dosimetric confounding factors, are diagnosed with RP. These cases manifest as false negatives, since based on radiation dose alone the patient is predicted not to experience RP. For these reasons, accurate quantitative prediction of RP risk based solely on DVHs is a challenging problem.

The novel result to emerge from the analysis is that the optimal profiles that provide best predictive accuracy have a similar distinctive shape: they have a steep rise at low doses (<20 Gy), a flat or shallow rise at mid-doses (~20–40 Gy), then revert to quasi-linear (or LQ) behavior at high doses (>40 Gy). We hypothesize that subsets of G2+ DVHs are capable of identifying optimal profiles, even when accurate prediction of all G2+ cases is not achievable. Our results suggest that a profile search may be able to estimate the underlying dose–response, provided the search results are sufficiently specific. If one searches for profiles that can correctly predict G1 – and G2+ cases whose damage values are already well-separated, the search will return a large number of profiles, and the ‘true’ profiles will be buried like needles in a haystack. If, however, the search is challenged to correctly predict G1 – and G2+ cases that are difficult to discriminate on the basis of other metrics such as MLD, the search results can identify the smaller set of true biological profiles. Our search strategy could potentially be improved, for example by ignoring G_{cut} values that lack specificity.

If one accepts that the optimal profiles identified in figure 4 approximate the underlying biological dose–response curve $P_{\text{bio}}(D)$, the implication is that normal lung has enhanced sensitivity to low doses, in comparison to the prevailing LQ model. This result establishes a tentative connection from clinical DVH data to the low-dose hyper-radiosensitivity, increased radioresistance (HRS/IRR) discovered by Joiner and colleagues, and reviewed by Marples and Collis (2008). To radiation biologists, HRS/IRR is uncontroversial. It has been verified using *in vitro* measurements of cell survival curves for multiple cell types including normal lung (Singh *et al* 1994), though not all cell types exhibit the behavior (Singh *et al* 1994, Joiner *et al* 1986, Joiner and Johns 1988, Marples *et al* 2004). The phenomenon manifests as elevated sensitivity to radiation for single doses below ~0.5 Gy. As the single dose is increased from ~0.5 to 1 Gy, cellular mechanisms trigger increased resistance to radiation, i.e. flattening of the survival curve. Then as single dose is increased beyond ~1 Gy, the survival curve bends down and asymptotes towards linear-quadratic behavior. The shape of the survival curve at low to intermediate doses can be modeled via Joiner’s induced repair model, the equations for which are given above.

In figure 4(e), the profile $\bar{P}(D)$ and its IRM fit represent the damaged fraction of an irradiated tissue volume. Figure 6 subtracts these profiles from one, to get the undamaged fraction, and re-plots them on a semi-log scale. ($\bar{P}(D)$ is the blue solid line, the IRM fit the red dashed line.) Note that the IRM curves in figures 2(e), 4(e) and 6 are all the same IRM model, with parameters given in section 2.3. Figure 4(e) shows this model asymptoting to one for doses beyond 120 Gy. Also plotted on figure 6 is the single-fraction normal lung cell survival curve obtained by Singh *et al*, who were the first to document HRS/IRR for normal lung cells (Singh *et al* 1994). The cell survival curve (green dash-dot line) is reconstructed from figure 3 in Singh. It has been stretched along the dose-axis by a factor of 27.5, to enable direct comparison with the CFRT profiles derived from 30+ fraction treatments. In

the lower dotted section of the curve it has also been extrapolated beyond the range of the Singh figure, to facilitate comparison. The intent of figure 6 is not to achieve quantitative agreement between the Singh curve and IRM fit to $\overline{P}(D)$. Rather it is to show qualitative agreement between these curves—both show qualitatively similar low-dose behavior, suggesting that low-dose sensitivity may affect clinical outcomes in lung cancer RT.

Several works have investigated the potential relevance of HRS/IRR to clinical radiation therapy, either for tumor control probability (TCP) or NTCP modeling. Regarding tumor control, Smith *et al* (1999) and Slonina *et al* (2007) looked for an effect but found little or none. However, the Smith study was critiqued by Short *et al* (2001) who did find an effect. On NTCP modeling, Marples *et al* (2004) cite a study by Hamilton *et al* (Hamilton *et al* 1996, Turesson and Joiner 1996). Honoré and Bentzen (2006) performed a planning study that showed the potential relevance of HRS/IRR to clinical planning. However, in spite of continued interest (Skov 1999, Beauchesne 2013, Prasanna *et al* 2014) research into clinical applications appears to have languished due to absence of compelling evidence for the clinical relevance of HRS/IRR. It would appear surprising if low-dose sensitivity had gone unnoticed in clinical and pre-clinical data. However, historical arguments favoring the LQ model have rested on *in vivo* studies where the focus is usually on high-dose endpoints such as lethality, elevated breathing rate, acute skin reactions, intestinal damage, paralysis, etc (Brown *et al* 2014). It is possible that RHS/IRR has remained undetected due to the difficulty of experimentally exposing low-dose effects.

If normal lung does indeed follow a dose–response curve as in figure 4(e), two clinical applications suggest themselves. First, an ongoing debate has centered on whether its better to use dose distributions that deliver ‘high doses to small volumes’ or ‘low doses to large volumes’ (Wennberg *et al* 2011). The low-dose sensitivity suggested by our results may provide insight. In particular, if validated, an IRM-type dose–response curve may provide a quantitative model for assessing the relative contributions of low versus high doses. Second, no good explanation has yet been given for the variability of RP risk versus MLD plots between different institutions (Marks *et al* 2010, Tucker *et al* 2010). The non-linear form of $P(D)$ in figure 4(f) means that two DVHs having the same MLD, but different weighting between low and high doses, can produce different RP risks. This property could potentially explain the variability observed in clinical RP risk versus MLD plots.

5. Conclusions

Using a University of Michigan DVH dataset obtained in a dose-escalation trial, this work searched for piecewise-linear normal lung damage profiles that could achieve more accurate radiation pneumonitis prediction than mean lung dose. A family of optimal profiles was identified that were able to reduce erroneous predictions from 11 to 8 (out of 89). The optimal profiles all exhibited the same qualitative features: a steep low-dose response, followed by a flatter response at intermediate doses, then a steeper response at high doses. The shape of the profiles resembles Joiner’s induced repair model (IRM), raising the possibility that *in vivo* normal lung response to fractionated therapy follows an IRM-like profile. These results are derived from a single institution’s data, and so need to be confirmed through analysis of larger multi-institutional datasets.

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Figure 1.

A subset of cumulative dose volume histograms (DVHs) from the University of Michigan dataset. This subset includes all 17 G2+ DVHs (red dotted lines), plus 9 G1 – DVHs (blue solid lines) having comparable mean lung dose.

Figure 2.

(a) Lung differential dose volume histogram (DVH) with simple linear damage probability profile $P_0(D)$ and two linear-quadratic (LQ) damage probability profiles $P_1(D)$ and $P_2(D)$. (b) The corresponding cumulative DVH and damage rate profiles $R_0(D)$, $R_1(D)$ and $R_2(D)$, scaled by a factor of 30 for display purposes. (c) A piecewise linear damage profile $P_3(D)$ with 4 dose points (circles) and segments. (d) The corresponding step function rate profile $R_3(D)$. (e) An induced repair model (IRM) damage profile $P_4(D)$. (f) The corresponding rate profile $R_4(D)$.

Figure 3.

Plot of mean lung dose versus DVH number. Pink solid triangles are grade 3 DVHs. Red solid circles are grade 2 DVHs. Blue hollow diamonds are grade 1 DVHs. Gray hollow squares are grade 0 DVHs. The horizontal line is the cutoff above (below) which DVHs are predicted to experience (not experience) G2+ RP. The cutoff is set at the value which produces the minimum number of erroneous predictions: $N_{\text{FNP}} = 11$.

Figure 4.

Optimal step function profiles giving lowest number of erroneous predictions ($N_{\text{FNFP}} = 8$) on the UM dataset. All profiles are rescaled to have a maximum of one. (a–c) Examples of optimal profiles, which all give $N_{\text{FNFP}} = 8$ in spite of variations in shape. (d) Intensity plot of rate profiles $R(D)$. Intensity is proportional to the number of profiles $R(D)$ passing above each point. (e) The average rate profile $R(D)$ (blue dotted line), corresponding damage profile $P(D)$ (red solid line), and induced repair model (IRM) fit to the damage profile (red dashed line). (f) Plot of damage versus DVH number for a single optimal profile. The horizontal line is the optimal cutoff G_{cut} .

Figure 5.

Plots of intensity, $\bar{R}(D)$ (blue dotted line), $\bar{P}(D)$ (red solid line), and damage values, similar to figure 4(d) and (e), for the case where G2+ DVHs having MLD > 20 Gy and G1 – DVHs having MLD > 18.5 Gy are excluded from the analysis. (a–c) G_{cut} assumes its optimal value. The profile search returns ~360 000 profiles. $\bar{P}(D)$ approximates a straight line, indicating that no specific shape for $\bar{P}(D)$ is selected. (d and e) $G_{\text{cut}} = 0.6$. The profile search returns ~700 profile resembles figure 4(e).

Figure 6.

The blue solid line is $\overline{P}(D)$ from figure 4(e), subtracted from one to give undamaged fraction instead of damaged fraction, and plotted on semi-log axes. The red dotted line is the IRM fit to $\overline{P}(D)$ from figure 4(e), similarly replotted. The green dashdot line is the single-fraction cell survival curve for normal lung cells, reconstructed from figure 3 in Singh *et al* (1994). This curve is stretched by a factor of 27.5 on the dose axis to permit direct comparison of the cell survival curve with $\overline{P}(D)$ obtained from UM conventionally fractionated data. The Singh curve has additionally been extrapolated beyond the range in Singh *et al* (lower dotted section). The IRM fit to $\overline{P}(D)$ and the Singh cell survival curve show qualitatively similar low-dose behavior—they both exhibit enhanced sensitivity to low doses.