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BIOLOGY CONTRIBUTION

THE IMPACT OF HEART IRRADIATION ON DOSE–VOLUME EFFECTS IN THE RAT LUNG

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Purpose: To test the hypothesis that heart irradiation increases the risk of a symptomatic radiation-induced loss of lung function (SRILF) and that this can be well-described as a modulation of the functional reserve of the lung.
Methods and Materials: Rats were irradiated with 150-MeV protons. Dose–response curves were obtained for a significant increase in breathing frequency after irradiation of 100%, 75%, 50%, or 25% of the total lung volume, either including or excluding the heart from the irradiation field. A significant increase in the mean respiratory rate after 6–12 weeks compared with 0–4 weeks was defined as SRILF, based on biweekly measurements of the respiratory rate. The critical volume (CV) model was used to describe the risk of SRILF. Fits were done using a maximum likelihood method. Consistency between model and data was tested using a previously developed goodness-of-fit test.
Results: The CV model could be fitted consistently to the data for lung irradiation only. However, this fitted model failed to predict the data that also included heart irradiation. Even refitting the model to all data resulted in a significant difference between model and data. These results imply that, although the CV model describes the risk of SRILF when the heart is spared, the model needs to be modified to account for the impact of dose to the heart on the risk of SRILF. Finally, a modified CV model is described that is consistent to all data.
Conclusions: The detrimental effect of dose to the heart on the incidence of SRILF can be described by a dose dependent decrease in functional reserve of the lung.

Normal tissue damage, Lung, Heart, Radiotherapy.

INTRODUCTION

In non–small-cell lung cancer, escalation of the radiation dose to the tumor is expected to result in increased local control (1–3). The dose that can be administered without inducing life-threatening complications is, however, limited by the tolerance of the lung to radiation.

Improved treatment techniques, including three-dimensional conformal radiotherapy and intensity-modulated radiotherapy either using photons or charged particles, result in better accuracy in the delivery of radiation dose to the tumor and consequently in a smaller volume of coirradiated normal tissues (4, 5). For the optimal use of these advanced techniques, which all spare the normal tissue in considerably different ways, more insight into the relation between the dose distribution and the risk of radiation-induced lung damage is needed.

Radiation-induced decreases in lung capacity result from locally occurring processes that damage a defined area (local loss of function) (6). In addition, the tolerance dose of the lung for symptomatic radiation-induced morbidity is also influenced by pretreatment pulmonary function (7), and patient pretreatment performance status (8). Furthermore, the lung is able to tolerate a very high dose to a small volume (8–17). Together, these observations suggest the presence of a reserve capacity (functional reserve) in the lung. From these observations it can be hypothesized that the risk of symptomatic loss of function is given by the probability that the total amount of local loss of function exceeds the functional reserve capacity of the lung (18). This hypothesis (#1) can be translated in a mathematical model for symptomatic radiation-induced loss of lung function (SRILF), which

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would, if the hypothesis is correct, describe the dependence of the risk of SRILF on dose and irradiated volume. This has resulted in the critical-volume (CV) model (18–20) (Appendix). To test hypothesis #1, the measured risk of SRILF for various irradiated lung volumes and doses were compared with the estimates obtained from the use of the CV model.

Another factor that codetermines the probability of SRILF is the location of the irradiated volume (16, 17, 21–25). This position-dependent response of the lung to radiation is caused by nonuniform distribution of function over the lung (17, 22, 23) and coirradiation of the heart (23, 24).

The main aim of the current study is to test whether the CV model can be modified to describe the effect of heart irradiation on the risk of SRILF by assuming that dose to the heart modulates the functional reserve of the lung (hypothesis #2). To determine the dependence of loss of lung function on heart and lung dose, the increase in breathing frequency was measured after various combinations of heart and partial-lung irradiations. Based on these data, the previously mentioned model was modified to include the effect of heart dose. Subsequently, we fitted it to data obtained after partial-lung irradiations, with and without coirradiation of the heart, and tested if the fitted model was consistent to these data.

MATERIALS AND METHODS

Study design

To determine the importance of irradiated volume on the loss of lung function, dose–response curves were obtained for irradiated lung volumes of 25% (28–36 Gy), 50% (15–20 Gy), 75% (12–22 Gy), and 100% (6–13 Gy). The irradiated volume either excluded (Fig. 1A–C) or included the heart (Fig. 1D–F). The doses used were determined by inter- and extrapolation of dose response curves obtained from previously described experiments (9, 22, 23). Where possible, the irradiated volumes were taken at the lateral parts of the lung, because these parts of the lung have a more uniform distribution of alveolar tissue when compared with the mediastinal part of the lung (22).

To establish the dependence of the impact of dose to the heart on loss of lung function on both heart dose and lung dose, three dose–response curves were determined. In these experiments, the dose to the heart and to (parts of) the lung were varied. For the first series (Fig. 1G), the lateral parts of the lung (25% lung volume) were irradiated to 16 Gy, which is just below the dose expected to give rise to SRILF (18 Gy) (23). In addition, various doses (16–21 Gy) were given to the heart. Because the heart field includes 25% of the total lung volume, there was a need to measure the effect of an increase in dose in this 25% lung volume separately. To this end, in a second series of studies the heart dose was fixed at 19 Gy, whereas the dose to the lateral lung fields was varied from 16–21 Gy (Fig. 1H). In a third series of studies, a 25% subvolume of the lung, caudal to the heart, was irradiated with 19 Gy while the dose to the lateral lung fields was varied from 16 to 21 Gy (Fig. 1I). From these three series of experiments, the threshold dose to the heart, which significantly influences lung function could be established.

Irradiation technique

Wistar rats were irradiated (single fraction) with 150 MeV protons from the cyclotron at the Kernfysisch Versneller Instituut, Groningen, using the shoot-through technique as previously published (26). In short, the shoot-through technique only employs high-energy protons and no lower energy (Bragg peak) protons. This results in a very uniform dose distribution in the longitudinal direction (±1%) and sharp lateral field edges (20–80% isodose distance: 1 mm) (27).

The irradiation ports were designed using computed tomography scans of animals of the same age and weight by a previously described procedure (22). For both the heart and the lung, separate contours were designed based on five individually positioned animals.

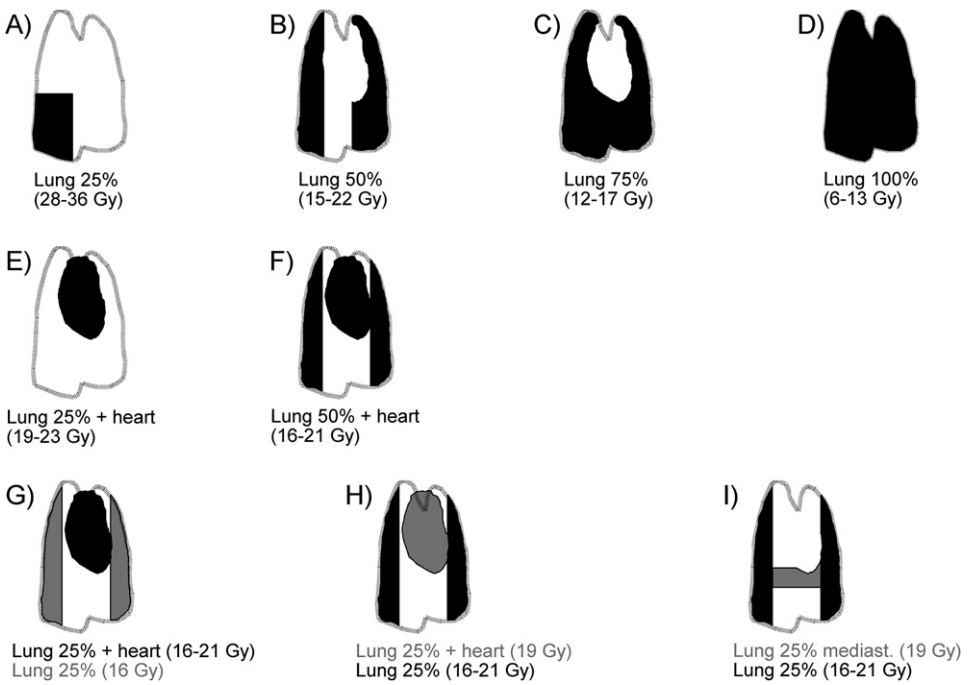

Fig. 1. Overview of irradiation ports used. A gray area indicates a fixed dose, whereas a black area indicates a region in which the dose was varied. Percentage values indicate the percentage of the total lung volume.

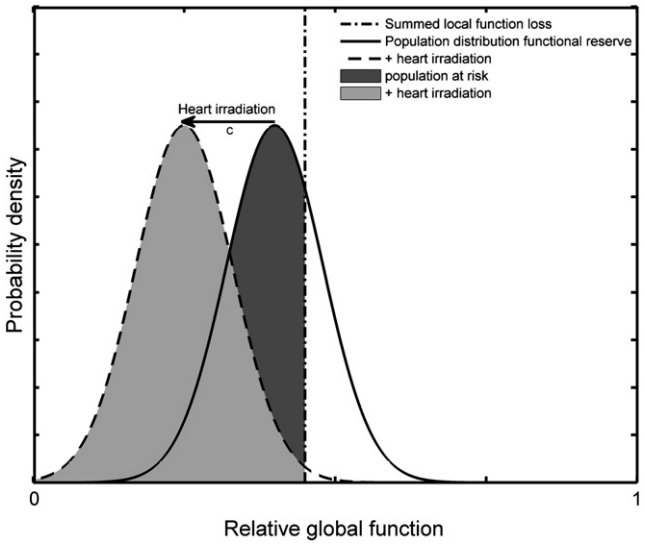

Fig. 2. Including the effect of heart irradiation in the critical-volume (CV) model. The CV model assumes that local dose deposition leads to local function loss (dash-dotted line). Second, the CV model assumes that the probability of symptomatic function loss equals the probability that the sum of all local loss of function exceeds the functional reserve. The effect of heart irradiation will be incorporated by assuming that it leads to a reduction of the functional reserve (thus shifting the distribution to the left), leading to an increased normal tissue complication probability (NTCP) at the same amount of summed local function loss.

In the resulting heart contour, the heart of each individual animal was contained. This ensures that for animals irradiated on the heart, the heart is always entirely included in the irradiated volume. For the lung, the variation in position resulted on average in spread in the irradiated lung volume of 3% of the total lung volume. Shape and uniformity of the dose distribution were verified using a scintillating screen and CCD camera (28).

Follow-up

Just before and after the irradiations, breathing rate measurements were performed biweekly up to Week 12, as described previously (22). In a previous study, it was found that the increase in breathing rate at 6–12 weeks after irradiation is mainly characterized by inflammation (22). Therefore, the increase of the mean breathing rate in this period, relative to the mean breathing frequency in Weeks 0–4 after irradiation, was used as an indicator of the functional status of the lung (23). The use of mean values in a time span instead of single actual values increases the statistical stability of the analysis. To distinguish between animals showing symptomatic radiation-induced function loss and healthy animals, a threshold on this increase was defined based on measurements of nonirradiated controls. From these control measurements, the mean increase and its standard deviation was calculated. The mean value plus twice the standard deviation was used (19 beats/min) (23). An increase of breathing rate above this threshold, indicating a significant increase at $p < 0.05$, was defined to represent symptomatic loss of lung function. For each dose group the fraction of symptomatic animals was determined. This fraction equals the normal tissue complication probability (NTCP).

The CV model

To test the hypothesis that the risk of symptomatic loss of function is given by the probability that the total amount of local loss of function exceeds the functional reserve of the lung, the measured risk of SRILF for different irradiated lung volumes and doses was compared with the estimates obtained from the CV model. The CV model consists of calculations of *(1)* the total amount of local loss of function and *(2)* calculation of the probability that the total amount of loss of local function exceeds the functional reserve (18–20) (Appendix; Eq. 1, 2, and 4 with $c_h = 0$).

To calculate the total amount of local loss of function we first calculated the amount of function loss for each subvolume in the lung using one single sigmoid curve, parameterized by Eq. 2 (Appendix). Next, all local contributions were summed to determine the global loss of function (Eq. 1). Finally, the fraction of the population whose functional reserve is lower than this global loss of function is calculated (Eq. 4, Fig. 2). To this end, we assume that the functional reserve among different rats is distributed according to the normal distribution. The mathematical formulation of the CV model used in the current study is given in the Appendix.

Statistics

The statistical methods used in this study have been described previously (29). Briefly, the model parameters were determined using the maximum likelihood method. Differences between model predictions and data were tested using a Monte Carlo goodness of fit test, specifically designed to test the consistency of this type of models and data (29). In this test 10,000 simulated datasets were used. The outcome of the test is the probability that the deviance between data and model would be equal to or larger than the observed deviance, if the experimental outcomes were explained fully by the model. As such, an outcome below 0.05 was defined to be a significant difference between model and data, leading to rejection of the model.

To reduce the computer time required to perform these fits a parameter transformation (29) from parameters a and b to parameters m (slope) and D_s (ED_{37}) of the curve describing loss of local function, was used (Eq. 2).

To determine the ability of the models to separate responders from nonresponders, the area under the receiver-operator characteristic curve (30, 31) was determined for all fits. This area can take values between 0.5 and 1, with higher values indicating a higher predictive power.

RESULTS

Strategy

Testing the hypothesis that the effect of dose to the heart on the risk of SRILF can be described by a modulation of the functional reserve of the lung (Fig. 2) requires that it is demonstrated that the concept of the functional reserve can be used to describe the dependence of the risk of SRILF on the irradiated lung volume and dose, without coirradiation of the heart. Subsequently, it needs to be demonstrated that this concept cannot predict the risk of SRILF if the heart is coirradiated. Finally, it needs to be shown that the proposed model modification does describe this effect correctly.

Dose–volume effects in the lung

To establish the influence of dose to the heart on pulmonary function loss various differently sized subvolumes of the lung were irradiated, either with or without inclusion of the heart. Figure 3 shows the increase in breathing rate as a function of dose for all dose distributions used. The dashed

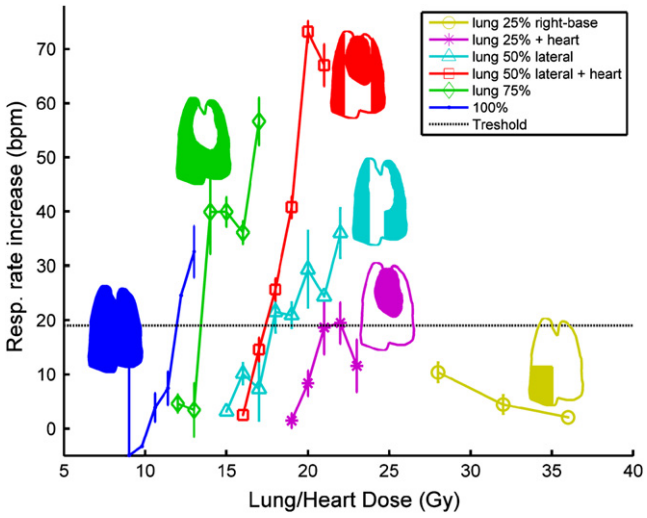

Fig. 3. Variations in the increase in respiration rate (beats/min) as a function of dose for various irradiated volumes including and excluding heart irradiation. The dotted line indicates significant increases ($p < 0.05$) with respect to nonirradiated control animals. Error bars indicate the standard error of the mean.

line in Fig. 3 indicates the threshold of a significant ($p < 0.05$) increase in respiratory rate above the control population (23). Large differences were observed between dose distributions including and excluding the heart. If 50% of the lung is irradiated, including the heart, the increase in breathing rate was more pronounced. When 25% of the lung is irradiated up to a dose of 36 Gy, hardly any increase in breathing rate was observed when the heart is included, whereas irradiation of 25% of the lung and the heart to 21 Gy already did result in function loss.

As a result, the occurrence of SRILF is not only volume dependent, but also depends on the region that was irradiated. The risk of SRILF is especially high when the heart is coirradiated (22).

Dependence of the risk of SRILF on dose and irradiated lung volume

Symptomatic radiation-induced loss of lung function was defined as a significant increase of the respiratory rate with respect to that of the control population. The NTCP thus equals the fraction of animals showing SRILF. In Fig. 4, the fraction of animals showing an increase over the aforementioned threshold is shown as a function of dose for all different dose distributions used.

To test the hypothesis that the risk of symptomatic loss of function is given by the probability that the total amount of local loss of function exceeds the functional reserve of the lung (18) (hypothesis #1), the CV model was fitted to data obtained with different irradiated lung volumes (excluding the heart) and doses, and resulting model NTCP values were compared with this same subset of the data. It was found that the differences between the fitted model and the data were not significant ($p = 0.19$; Table 1, row A; Fig. 4A), indicating that the CV model can describe the risk of SRILF in animals that receive dose to the lungs only.

Predictions of the fitted model for animals whose heart is coirradiated, however, do significantly differ from the observed NTCP values ($p < 0.001$; Table 1, row B; Fig. 4B, solid line). Even if the CV model is refitted to the entire dataset (including animals with heart coirradiation), the difference remains significant ($p < 0.001$; Table 1, row C; Fig. 4B, dashed line). These results demonstrate that, although the CV model can describe the incidence of SRILF as long as only the lung is irradiated, coirradiation of the heart requires a modification of the model.

Effect of dose to the heart on loss of lung function: a threshold dose

To establish how the impact of dose to the heart on the risk for SRILF depends on the dose to heart and lung, the dose to lung and heart were varied independently.

Figure 5A shows the dependency of the breathing rate increase on the dose to the heart region while giving a subtolerance dose of 16 Gy to the 25% lateral lung volumes (Fig. 1G). A distinct increase is visible between 18 and 19 Gy. This increase may be the result of the increased dose to the heart, but may also result from an increase of dose to 25% of the total lung volume, which is included in this field.

To separate the influence of dose to the heart from dose to the lung, a fixed dose of 19 Gy was administered to either the heart (Fig. 1H), or to 25% lung volume caudal of the heart (Fig. 1I), whereas the dose to the lateral 25% of the lung volume was varied. Figure 5B shows that including or excluding the heart leads to an enhanced loss of lung function, irrespective of the dose to lung.

These results demonstrate that heart irradiation enhances pulmonary function loss starting between 18 and 19 Gy. For the remainder of the study, a threshold dose of 18.5 Gy will be used, above which a reduction of the functional reserve is assumed to occur (Fig. 2).

Dependence of the risk of SRILF on lung and heart dose and irradiated lung volume The hypothesis that the impact of heart irradiation on the risk of SRILF can be described by a reduction of the functional reserve of the lung (hypothesis #2, Fig. 2) can be tested by comparing the measured incidence of SRILF after irradiation of various irradiated lung-volumes, including and excluding heart irradiation, to predicted incidences from the improved CV model, fitted to all data. (Appendix with c_h given by Eq. 3.)

Data on the dependence of the effect of dose to the heart on loss of lung function indicate that it is subject to a threshold dose and is independent of the dose to the lung. As such, the model is adjusted by decreasing the functional reserve with a fixed amount for those dose groups in which the heart dose exceeds the observed threshold dose.

Finally, the improved model (Appendix) is consistent to the data (Table 1, row D; Fig. 4C). Interestingly, the parameters describing the dependence of the risk of SRILF on dose to the lung (D_s, m, r, and σ) have the same values as in fit A, suggesting that the additional variability introduced by the addition of data including heart irradiations can be completely described by this single added parameter. The value

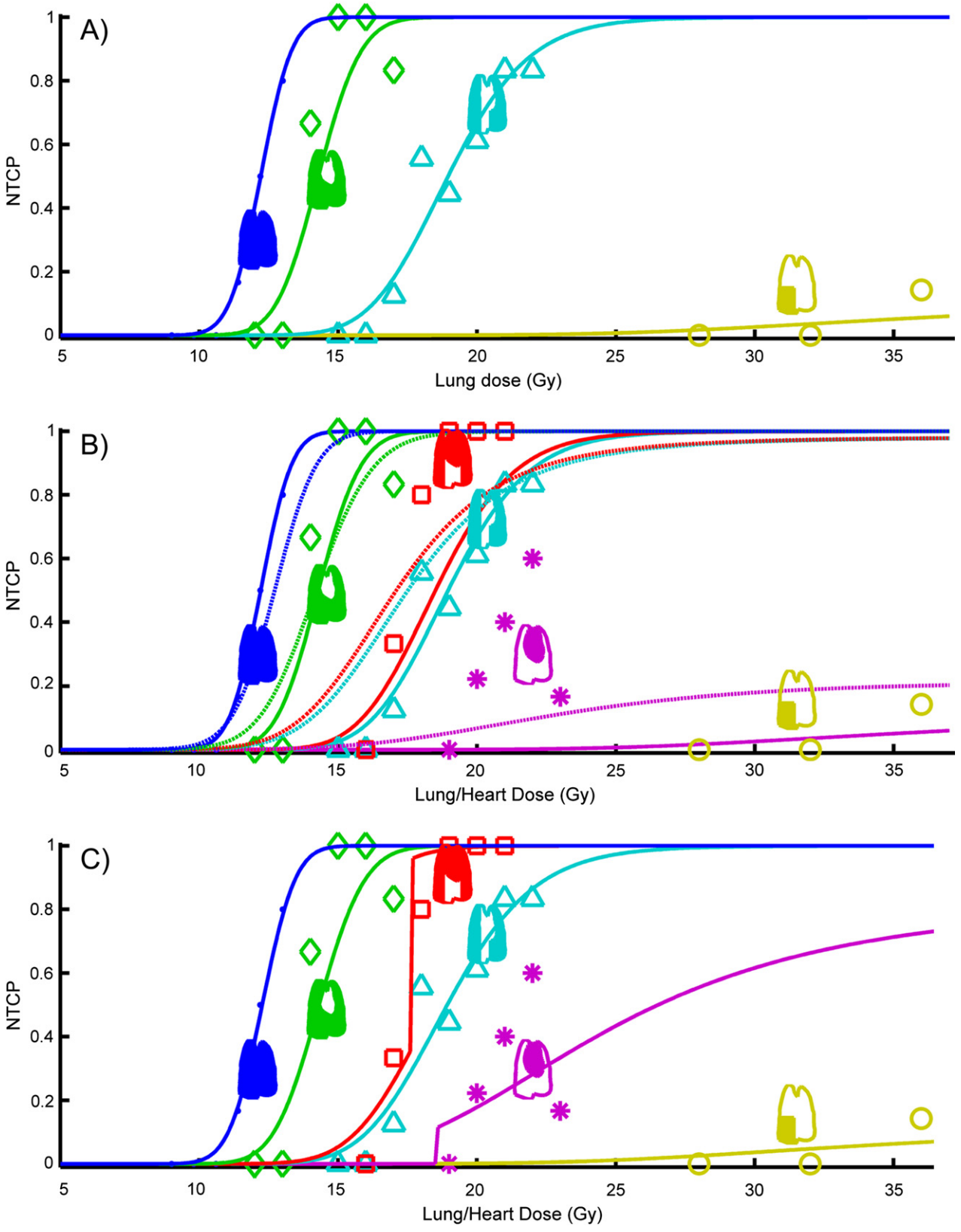

Fig. 4. Fits of the standard (A, B) and enhanced critical-volume (CV) model (C) to datasets excluding (A) and including (B, C) heart irradiation. (A) The best fit of the CV model to data obtained after lung-only irradiation. The differences between model and data are not significant ($p = 0.19$). (B) The model predictions from fit parameters determined in (A), for data including heart irradiation (solid line). The dashed line indicates the best fit of the CV model to all data. Both sets of curves deviate significantly from the data ($p < 0.001$). (C) The best fit of the improved CV model to all data. The model curves do not differ significantly from the data ($p = 0.24$).

Table 1. Fit parameters and model characteristics

Fit/data	Goodness of fit	Area under ROC curve	Critical-volume model parameters			
			ED_{37} (Gy)	m (Gy^{-1})	r	σ
A: CV model/lung-only data	0.19	0.94	12.6	0.056	0.32	0.048
B: CV model/all data	<0.001	0.78	12.6	0.056	0.32	0.048
C: CV model/all data	<0.001	0.89	13.3	0.077	0.32	0.089
D: Modified CV model/all data	0.24	0.93	12.7	0.056	0.32	0.051

Abbreviation: CV = critical-volume.

In fit D, the decrease in functional reserve (r) from dose to the heart >18.5 Gy was found to be c = 0.10.

of this added parameter, obtained from the best fit to the data, indicates that the reserve capacity of the lung is reduced by one third after heart irradiation (Table 1; fit D, $c/r = 0.31$).

DISCUSSION

Using functional reserve as predictor of morbidity

In the current study, the impact of dose to the heart on the dependence of the tolerance dose for SRILF on irradiated volume was measured. It was found that the enhancement of loss of lung function is subject to a threshold heart dose. In addition, it was observed that the influence of heart irradiation on loss of lung function increases steeply as the size of the irradiated volume decreases.

In the current study, the concept of functional reserve was used to estimate the risk of SRILF, as has been proposed by others (18–20). Even though pulmonary functional reserve is a rather abstract concept, it is being used in surgery (32) for risk assessment.

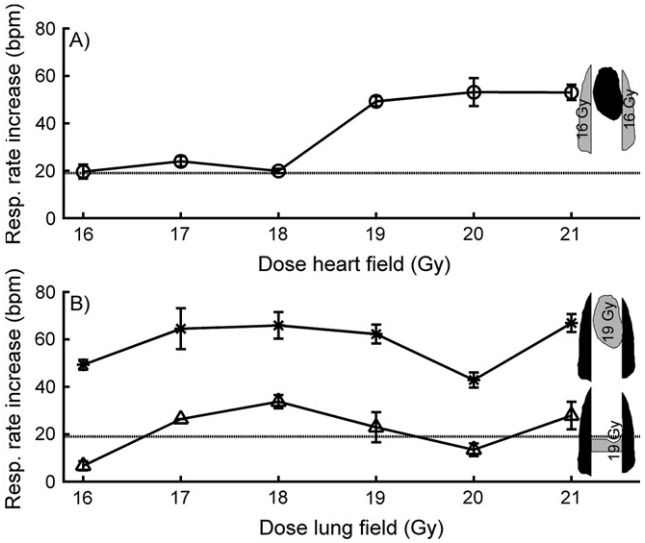

Fig. 5. Heart- and lung-dose dependence of the effect of heart irradiation on lung function loss. (A) The heart-dose dependency of loss of pulmonary function. A distinct increase in breathing rate above the threshold is observed after doses >18 Gy. (B) The lung-dose dependence of the breathing rate increase for animals receiving heart irradiation and animals whose hearts are spared. In both series, 50% of the total lung volume was irradiated. The increase from heart irradiation is lung-dose independent. Error bars indicate the standard error of the mean.

It has also been recognized that interactions between various comorbidities may influence the outcome of a treatment. Birim *et al*. (33) use the Charlson comorbidity index (34), which is a weighted combination of various comorbidities, identified as risk factors for pulmonary surgery and conclude that this combined index is a better predictor for mortality than individual risk factors. Moreover, in their specific application, they increased the Charlson comorbidity index by 1 point if any preexisting coronary artery disease was present. The Charlson comorbidity index already contained pulmonary and myocardial comorbidity. Thus this is another example of a model that uses an interaction between cardiac and pulmonary comorbidity to predict adverse effect (mortality) of a treatment.

Fully optimized radiotherapy requires detailed information on the relation between treatment and risk of morbidity. The only factor taken into account is irradiated volume, expressed in mean lung dose (35) or lung volume receiving more than a certain dose (*i.e.*, V_{13} or V_{20} for 13 Gy or 20 Gy). Even though these quantities correlate significantly to the risk of SRILF, correlations are generally weak (36, 37). Several studies showed that the incidence of symptomatic radiation pneumonitis depends on the location of the irradiated volume (16, 17, 21–23, 25). Because dose–volume histogram–based predictors do not take into account spatial information, inclusion of spatial information in predictive models may lead to improved predictive power.

In the present study, the physiologic meaning of the functional reserve is not specified. Through the critical volume model, it is related to irradiated volume and local loss of ''function'' without specifying which process or processes are critical to the development of SRILF. Although this lack of detailed biologic information causes a lot of reluctance in using these models, it is also an advantage of the approach. In the present study, it allowed the characterization of the nature of the interaction between heart and lung and the processes leading to SRILF, without the need of explicitly identifying the underlying physiologic or cell-biologic mechanisms. Any mathematical model uses global assumptions to describe gross effects. Because these models are the only tools to optimize treatments quantitatively, they need thorough testing, such as in this work.

The enhanced model is better capable of separating responders from nonresponders than models and predictors used on clinical data, indicated by the area under the receiver-operator characteristic curve (0.93 vs. 0.5–0.7) (31). This difference is partly explained by the fact that in preclinical studies all subjects are identical. This is a clear advantage for mechanistic studies, but also implies that parameters that are controlled in preclinical studies still need to be added in the model before it can be used clinically. Examples of such confounders are preexisting heart (current study) and related disorders such as lower pulmonary arterial blood flow (38) and lung morbidity as in chronic obstructive pulmonary disease (35), which is often present in non–small-cell lung cancer patients. In the current model, different forms of pretreatment morbidity may be incorporated as additional factors modulating either the functional reserve or the development of local loss of function. Additional research is needed to find the relation between preexisting morbidity and symptomatic radiation-induced function loss.

Sparing the heart and the potential for dose escalation

Radiation-induced pulmonary toxicity is still limiting the dose that can be administered to many thoracic tumors. Recent improvements in treatment techniques are resulting in better conformation of the highly dosed region to the tumor and consequently a smaller amount of coirradiated lung tissue.

In a study on regional variations on the effect of irradiation on lung function (9, 23), it was found that, in addition to local damage in the lung (24), the occurrence of SRILF may be determined by extrapulmonary factors, such as radiation dose in the heart (23). In the current study, the impact of this interaction on the dependence of the tolerance dose for SRILF on irradiated volume was measured and it was found that the gain of sparing the heart increases steeply as the size of the irradiated lung volume decreases towards and below the functional reserve of the lung. As a result, the gain of reducing the amount of coirradiated lung tissue is increased strongly when the heart is spared. Therefore, it is expected that this effect will become more important as improving treatment techniques result in better conformation of the high-dose region to the target volume resulting in less coirradiated lung tissue.

CONCLUSIONS

In the current study, it was found that the CV model describes the risk of SRILF if the heart is not spared. If the heart is coirradiated, however, the functional reserve is reduced and, to accurately describe and eventually predict SRILF, the CV model needs to be modified. The present study shows that the impact of dose to the heart depends strongly on the irradiated lung volume and that the gain of sparing the heart increases steeply for decreasing irradiated volumes. A modified CV model was described that takes these effects into account and describes the data accurately.

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APPENDIX

MODIFIED CRITICAL-VOLUME MODEL

The critical-volume model is based on the hypothesis that the risk of symptomatic loss of function is given by the probability that the total amount of local loss of function exceeds a functional reserve.

The total capacity lost due to lung irradiation, c_l, is given by:

$$c_l = \sum_i \gamma_i \cdot P(D_i) \qquad \text{Eq. 1}$$

where γ_i is the local capacity in subvolume i and $P(D_i)$ the probability of loss of capacity in subvolume i as a function of local dose. In the current work, no information is available on the local capacity. Therefore all subvolumes are assumed to contribute equally to global function. In the current study, the following parameterization of a sigmoidal curve was used to describe the probability of local loss of function:

$$P(D_i) = \left(1 - e^{-a \cdot D_i}\right)^b. \qquad \text{Eq. 2}$$

The capacity lost after heart irradiation is denoted c_h. The data shown in Fig. 5 indicate that the value of c_h is subject to a threshold dose to the heart. The capacity lost when exceeding this dose on the heart is denoted c. Thus c_h is given by:

$$c_h = \begin{cases} 0 \ (D_{heart} < 18.5) \\ c \ (D_{heart} > 18.5) \end{cases}. \qquad \text{Eq. 3}$$

The final assumption is that an animal becomes symptomatic if it looses more capacity than its functional reserve. Assuming that the probability distribution of the functional reserve is the normal distribution, the probability of a symptomatic response is given by:

$$NTCP = \frac{1}{2} \cdot \left(1 + \text{erf}\left(\frac{c_l + c_h - r}{\sigma \cdot \sqrt{2}}\right)\right) \qquad \text{Eq. 4}$$

where r and σ denote the population mean of the functional reserve of the lung and the population spread respectively. Both are normalized on the total capacity of the lung (*i.e.*, the total capacity of a healthy lung is set to 1).