Radiation Damage to the Heart Enhances Early Radiation-Induced Lung Function Loss

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Abstract

In many thoracic cancers, the radiation dose that can safely be delivered to the target volume is limited by the tolerance dose of the surrounding lung tissue. It has been hypothesized that irradiation of the heart may be an additional risk factor for the development of early radiation-induced lung morbidity. In the current study, the dependence of lung tolerance dose on heart irradiation is determined. Fifty percent of the rat lungs were irradiated either including or excluding the heart. Proton beams were used to allow very accurate and conformal dose delivery. Lung function toxicity was scored using a breathing rate assay. We confirmed that the tolerance dose for early lung function damage depends not only on the lung region that is irradiated but also that concomitant irradiation of the heart severely reduces the tolerance of the lung. This study for the first time shows that the response of an organ to irradiation does not necessarily depend on the dose distribution in that organ alone. (Cancer Res 2005; 65(15): 6509-11)

Introduction

Many frequently occurring malignant tumors in the thoracic region are routinely treated by radiotherapy, often in combination with chemotherapy. The tolerance dose of normal tissues surrounding the target volume, such as the lung in the case of breast and lung cancer, poses a limit on the dose that can be given safely to the tumor. This in turn determines the maximum probability of cure (1–3).

Technological improvements to the radiotherapy treatment, such as intensity-modulated radiotherapy and the use of particles such as protons (4) or carbon ions (5) have resulted in a decrease in the amount of normal tissue that is irradiated to the same dose as the tumor. With protons and carbon ions, an additional advantage is that dose is only deposited to the tumor and proximal to the tumor. This means that by choosing a beam angle one can choose to spare specific (distally located) parts of the normal tissue surrounding the target volume. High-precision information on the effect of irradiation on different regions of the thorax is needed to be able to fully exploit these advances for the treatment of thoracic tumors.

Using rats (6) or mice (7), it has been shown that there are large variations in radiation-induced lung morbidity depending on the location irradiated. Our recent data on rats (6) not only revealed that more sensitive regions encompassed the largest amount of alveolar tissue but also suggested that including the heart in the radiation field enhanced loss of lung function. Classically, clinically and experimentally, radiation-induced heart damage is considered to be a late effect (8, 9). Surprisingly however, irradiating the heart not only resulted in late (>34 weeks) radiation-induced lung function loss but also a trend for increased early (<12 weeks) lung function loss was found. The finding that dose to the heart adds to early function loss of the lung would suggest that radiation-induced heart damage also has a highly relevant early component, which may manifest itself in combination with early (subclinical) lung damage. As such it would be necessary to consider functional damage to the lung in terms of multiorgan damage.

However, in our previous study (6), the effect of the heart just did not reach statistical significance. This was most likely due to the field design, which was not tailored to include or exclude the entire heart, thereby diluting the possible influence of the heart. For the present study, we therefore developed a high-precision proton irradiation to further optimize uniformity in the irradiated regions and to minimize the dose to shielded regions. Next, irradiation fields were designed to specifically include or exclude the entire heart and/or most alveolar tissue. We now conclusively show that the early radiation-induced function loss of the lung is greatly enhanced when the heart lies within the radiation field. This result implicates that the function loss of an organ does not necessarily depend on the dose distribution in that organ alone and has significant implications for treatment planning with high-precision radiotherapy modalities.

Materials and Methods

Wistar rats were irradiated with 150 MeV protons from the cyclotron at the Kernfysisch Versneller Instituut, Groningen, using the shoot-through technique as previously published (10). 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.) Four different irradiation fields were used. The shape of each field is shown in Fig. 1*A*. The irradiation ports were designed using CT scans of animals of the same age and weight, by a previously described procedure (6). For both the heart and the lung, separate contours were designed based on multiple individually positioned animals. 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 3% spread in the irradiated lung volume. Each dose group (16-21 Gy, single dose) consisted of five to seven animals.

The first field (Fig. 1*A*, *red*) contained the heart with the smallest possible amount of lung tissue (25 ± 4% of the lung). The second field (Fig. 1*A*, *black*) contained the heart with a portion of the mediastinal located lung tissue. The total lung volume in this field was 50 ± 2%. The third field (Fig. 1*A*, *blue*) also contained the heart but now combined with laterally located lung tissue, again adding up to 51 ± 3% of the total lung

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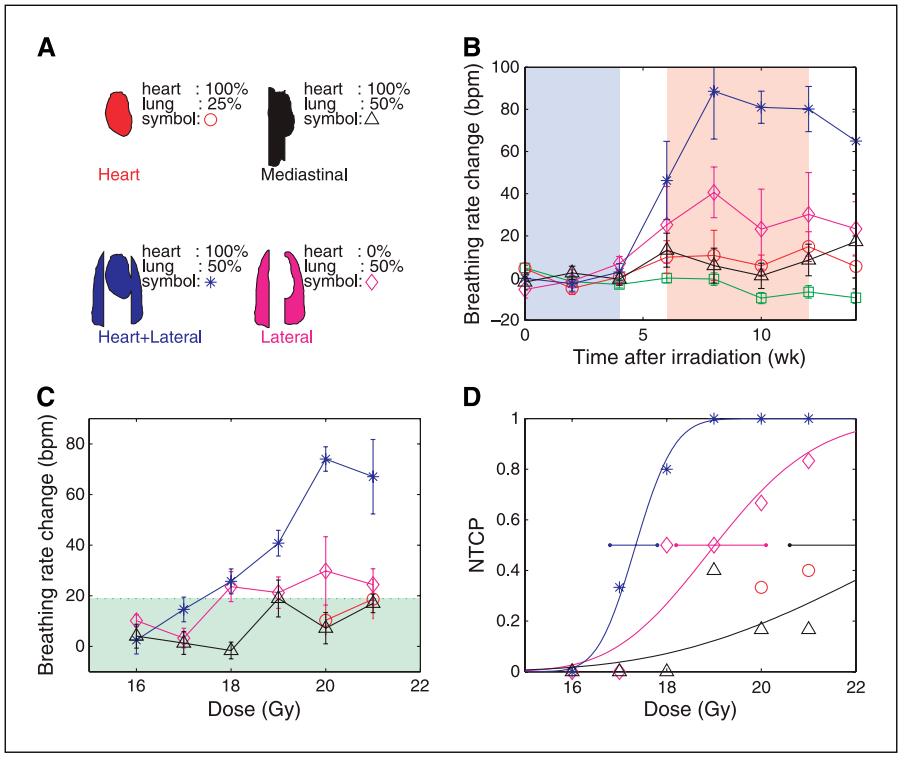

Figure 1. *B,* breathing rate as a function of time after irradiation using 20 Gy with different radiation fields shown in (*A*). The time span of the early radiation-induced function loss phase (weeks 6-12) is indicated in red. Increase in the mean breathing rate in this phase with respect to the latent phase (*blue*). An increase above the green region in (*C*) indicates pneumonitis. *D,* fraction of animals manifesting symptomatic lung function loss. *Horizontal lines,* 95% confidence limits of ED_{50}. *Bars,* SE (*B* and *C*).

volume. In the last field (Fig. 1*A, purple*), the heart was fully spared. To obtain 50 ± 2% irradiated lung volume, part of the mediastinal located lung tissue was spared as well.

After the irradiations, breathing rate measurements were done biweekly as described before (6). In our previous study, it was found that the early (weeks 6-12 after irradiation) increase in breathing rate is mainly characterized by inflammation. Therefore, the increase of the mean breathing rate in this period, relative to the mean breathing frequency in weeks 0 to 4 after irradiation, was used as an indicator of the functional status of the lung. To distinguish between animals showing 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 SD was calculated. The mean value plus 2 SDs was used. An increase of breathing rate above this threshold was defined as functional impairment.

For each dose group, the fraction of symptomatic animals was determined. This fraction equals the normal tissue complication probability (NTCP). To these NTCP data, probit curves were fitted (11). Lastly, the dose for which 50% of the animals responded (ED_{50}) was predicted, as well as its 95% confidence limits.

Results and Discussion

To assess the effect of the heart on regional differences in lung function damage after irradiation four different dose distributions, either including or excluding the heart (Fig. 1*A*), were delivered to the thorax of the rat. The time course of the change in breathing rate as a measure of lung function after a dose of 20 Gy is shown in Fig. 1*B*. The radiation-induced lung function loss, starting at week 6, is clearly visible and the data show large heterogeneity in response depending on the dose distribution used. This was confirmed for all doses as depicted in Fig. 1*C* where the mean increase in breathing rate during weeks 6 to 12 is plotted as a function of dose. Increases larger than the threshold (+19 bpm) calculated from the controls (i.e., higher than the range marked in green in Fig. 1*C*) indicate symptomatic radiation-induced function loss. Irradiation of the heart alone results in a low response similar to whole mediastinal region irradiation including the heart (Fig. 1*C*). Irradiation of a similar volume of lateral lung tissue alone, excluding the heart, resulted in a larger breathing rate increase and a lowering of the ED_{50} dose from 23.5 Gy [20.6-700 Gy, 95% confidence interval (95% CI), mediastinal] to 19.0 Gy (18.2-20.1 Gy, 95% CI, lateral; Fig. 1*D*). This confirms our previous findings that the severity and the ED_{50} for radiation-induced lung function loss are determined by the amount of alveolar tissue that is irradiated. If, however, the heart is irradiated together with lateral parts of the lung (same lung volume with even slightly less alveolar tissue), a much more pronounced response is seen compared with the lateral field in which the heart was spared (Fig. 1*C*). Including the heart in the irradiation field resulted in a pronounced reduction of the ED_{50} from 19.0 (lateral without heart) to 17.3 Gy (16.8-17.8 Gy, 95% CI; lateral with heart, Fig. 1*D*).

These data are the first to conclusively show that coirradiation of the heart has a strong effect on the clinical manifestation of radiation-induced lung function loss early after radiation. Local heart irradiation is known to affect respiratory function (12), whereas lung irradiation induces changes in pulmonary vascular bed that cause pulmonary hypertension and lead to a congestive right cardiac failure in humans (13) and several animal models (14, 15). Also in our previous study, it was clearly shown that irradiation of the heart results in late radiation-induced pulmonary toxicity (6). The late time point (>38 weeks after irradiation) coincides with occurrence of late radiation toxicity of the heart, similar to the situation in humans. Yet, early effects of heart irradiations on lung function have not been reported before.

In animal studies, however, morphologic changes to the heart were already observed around 10 weeks after irradiation (16). An early decline in cardiac function after heart irradiation followed by

a period of recovery that precedes the onset of late symptoms was reported for rats, dogs, and even humans (16–18). Early heart damage, however, has never received that much attention, as it was not recognized as a clinical problem. In our current study, however, we show that early damage to the heart can have severe consequences on the radiation-induced function loss of the lung. This may be due to loss of functional reserve capacity of the cardiopulmonary system, leading to enhanced manifestation of respiratory function loss. Therefore, when looking at early morbidity of the lung, also radiation dose given to the heart should be regarded.

It has been suggested that a dose up to 102.9 Gy (in 2.1 Gy fractions) can be safely delivered to limited lung volumes with minimal toxicity (19). In this study, 70% freedom of local progression (stage I, non–small cell lung cancer, NSCLC) was obtained when >92.4 Gy was given. For larger irradiated lung volumes, the maximum tolerated dose was established at 65 Gy with very poor freedom of local progression (20). New techniques that are currently being introduced in radiotherapy aim at reducing the dose to and volumes of normal tissues irradiated to subsequently allow dose escalation. Exploiting regional differences in radiation response and avoidance of function loss enhancement due to heart irradiation may allow for dose escalation even for somewhat larger volumes. Extrapolation of data from this study suggest that when the heart would be completely avoided a gain of ~10% lung tolerance dose might expected, thus allowing a significant dose escalation. This may have important implications for radiotherapy for NSCLC, where the early lung morbidity (radiation pneumonitis) is the main dose-limiting complication. Moreover, as previously shown (6), excluding the heart from the radiation field will also reduce late effects after thoracic irradiation because the occurrence of radiation pneumonitis predisposes to late radiation fibrosis.

In summary, using high-precision proton irradiations of the rat lung, we established that radiation damage to the heart combined with damage to the lung may result in a symptomatic lung function loss early after radiation. Therefore, when irradiating the thorax, it is important to prevent irradiating the heart. This finding stresses the importance of newly developed high-precision irradiation techniques that allow the clinician to keep specific regions dose-free.

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