Published in final edited form as:
Int J Radiat Oncol Biol Phys. 2010 March 1; 76(3 Suppl): S70–S76. doi:10.1016/j.ijrobp.2009.06.091.

Radiation Dose Volume Effects in the Lung

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Abstract

The three dimensional dose/volume/outcome data for lung are reviewed in detail. The rate of symptomatic pneumonitis is related to many dosimetric parameters, and there are no evident threshold “tolerance dose/volume” levels. There are strong volume and fractionation effects.

Keywords

Lung injury; radiation; QUANTEC; pneumonitis

1. Clinical significance

Radiation therapy (RT) plays an important role in the treatment of several tumors in and around the thorax. Clinically-significant symptomatic pneumonitis (RP) occurs in ≈5–50%, ≈5–10%, and ≈1–5% of patients irradiated for cancers of the lung, mediastinal lymphatics, and breast, respectively (1, 2), and is one of the most common clinical toxicities in these patients. The risk of RP limits the delivered dose for some and may thus hamper tumor control. A large fraction of patients experience sub-clinical RT-induced injury (e.g., reductions in formal pulmonary function tests [PFTs], and/or radiologic changes) that may be chronic and reduce the patient’s reserve to deal with future cardio-pulmonary stresses.

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Conflict of Interest: The authors report no conflicts.

2. Endpoints

Several endpoints can be used to define RT-induced lung injury (Table 1). In the context of QUANTEC, consideration is limited to the endpoint of symptoms; arguably the most clinically meaningful endpoint for patients. Approximately 80% of RP is clinically manifest within 10 months of RT. The scoring of symptomatic RP presents several challenges:

- **a.** Dyspnea is non-specific and can also be caused by anemia, cardiac arrhythmia, infection, tumor, etc. In a prospective clinical study, 28% of patients suspected of having RP also had ongoing medical conditions confounding the diagnosis (3).
- **b.** Toxicity grading systems often consider the medical interventions (e.g., steroid use). Therefore, physicians that are more apt to prescribe steroids may note a higher reported rate of pneumonitis. Steroid use is grade 3 for RTOG, but grade 2 in several other systems. Requirement of steroids has been omitted from the CTCAE 3.0.
- **c.** Treatment-induced tumor shrinkage may improve overall lung function (especially for central lesions compressing regional airways/vessels), thus maybe masking the effects of RT on the normal lung.
- **d.** The relevant grade of symptoms is controversial. Grade I RP is common, and is often not clinically significant. More severe RP is more clinically relevant, but its lower incidence limits the statistical power of analysis based on severe events.

3. Challenges Defining Volumes

The lung is usually considered as a single, paired-organ (total lung tissue) rather than as separate ipsi- and contra-lateral lungs. Since lung volumes vary with breathing, there is ambiguity in defining its DVH-based parameters. In the articles herein reviewed, dosimetric information was mostly based on CT images obtained during free breathing. The dosimetric parameters would change had these scans been obtained at specific phases of the respiratory cycle. Segmentation of a thoracic scan can be challenging. There is uncertainty defining how much of the bronchus should be defined as “lung”, and the lung edges may vary with the window/level setting. Thus, volume-based parameters will vary between investigators. The accuracy of any auto-segmenting tools should be carefully assessed, especially to ensure that portions of atelectatic lung or tumor at soft tissue interfaces are not inadvertently omitted from the lung.

During RT planning, the total lung volume is usually defined to exclude the gross tumor volume (GTV). Excluding the planning target volume (PTV), rather than the GTV from the lung volume, may reduce the apparent lung exposure (as normal lung within the PTV, but outside the GTV, will be excluded), and may increase inter-institutional variations (as PTV margins may vary).

During treatment, there may be changes in GTV-volume, with corresponding changes in normal tissue anatomy. Thus, plans defined based on pre-RT imaging may not accurately reflect the degree of normal lung exposure. While this effect has not been systematically assessed, presumably tumor shrinkage (with movement of normal lung into to previously-occupied GTV) will increase normal lung exposure relative to pre-RT plans. Similarly, changes in pleural effusions, and re-aeration of lung regions can cause anatomic and functional changes. Indeed, the ability to predict changes in lung function based on pre-RT dosimetric data is reduced in patients with tumor-associated airway obstruction (i.e., those most likely to experience re-aeration during therapy) (4).

4. Review of dose/volume data

The literature on dose-volume-pneumonitis is extensive: for this review we identified >70 published papers. The results are inconsistent, both for the best predictive metrics and significant co-morbid factors.

4.1 Lyman-Kutcher-Burman (LKB) DVH-reduction scheme and Mean Lung Dose (MLD)

The most widely used NTCP model for RP is the LKB model. This model has three parameters, a position parameter, TD_{50}, a steepness parameter, m, and the volume exponent, n (where n=1 the model reverts to mean lung dose; MLD). While TD50 is strongly dependent on the grade of RP being considered, n is often regarded as a tissue characteristic. Figure 1 shows a meta-analysis of reported n-values, it does not include the study by Rancati (39), which used only the ipsilateral lung. The best estimate for n is 1.03 with standard deviation 0.17 (95% conf interval: [0.67–1.39]), the test for heterogeneity of the data sets is not significant, and I^2 is zero. The TD50 values cannot be pooled in a meaningful way, as the various reports analyzed considered varying grades of RP.

The MLD model is widely considered due to its simplicity and effectiveness. It was the metric used by the large multi-institutional analysis of Kwa (5), and often performs as well as more complex models. Figure 2A shows a logistic regression fitted to RP vs. MLD data from all published studies of a significant size that had extractable complication rates binned by mean dose. Some of the variation around the fitted curve is possibly explained by differences in patient selection as well as differences in the grade of RP reported in the various studies. Nevertheless, there is a relatively small 68% confidence interval (stippled lines). A similar fit using the probit model (equivalent to fitting the Lyman model with n fixed at 1) gives an essentially identical response function in the region of the data. The gradual increase in dose response suggests that there is no absolute ‘safe’ mean lung dose below which there is no pneumonitis. The clinically acceptable risk of RP –and therefore the associated planning constraint on MLD– will depend on the risk: benefit ratio in the individual case. A number of non-DVH-based factors may affect the risk of RP (section 5). Finally, it is likely that the MLD-RP relationship may have lower predictive power for ‘non-standard’ dose distributions not included in these analyses, for example after stereotactic body radiotherapy (SBRT) or proton therapy.

4.2 Dose-volume threshold analyses

Various Vx values (% lung volume receiving ≥X Gy) are associated with RP risk (Fig. 2b) The observation that a variety of dose levels are predictive suggests that there is no sharp dose threshold, below which there is no risk. Within individual data sets, there are usually strong correlations between the different dosimetric parameters (e.g., V5 and V20); and thus there are probably no “optimal” thresholds. Further, the correlations between dosimetric parameters are technique dependent, and readers should carefully assess the similarity of their treatment technique before using any of these limits as clinical constraints.

RT-induced dyspnea appears more commonly in patients with lower- vs. upper-lobe tumors, and may be better correlated with RT doses to the lower- vs. upper-lung (7–11). An analysis that combined institutional data with RTOG 93-11 (n=324) concluded that RP is much better predicted (at least for that dataset) based on mean lung dose and positional dependence of the high dose region as opposed to mean lung dose alone (12). The cause of this correlation is presently unknown and requires further investigation.

5. Factors affecting risk

Several patient and treatment-related factors have been inconsistently reported to correlate with the risk of developing RP. Vogelius and Bentzen (70) applied standard meta-analysis methodology to eight factors with meaningful data. In summary, there was no significant evidence for an association between RP and *laterality* (left vs. right lung), *co-morbidity* or *gender*. *Younger patients*, typically defined as <60 or <70 years of age, have a lower risk of RP than older patients. *Surgery* had a just-significant p-value, but the test for heterogeneity was significant (p=0.03) suggesting that the variation among studies cannot be explained by chance alone. Thus, at present, the reduced rate of RP in patients undergoing surgery remains controversial. Interestingly, current smokers have a significantly *reduced* risk of developing RP.

Chemotherapy

Many systemic agents have known pulmonary toxicities (13) and may exacerbate RT-induced injury. The varying drugs, doses and schedules (e.g., sequential, concurrent) make any synthesis of data from multiple studies generally not feasible. Based on general experience, adding chemotherapy should be expected to increase the risk of RP. Nevertheless, the agents most commonly utilized with RT for lung cancer, such as cisplatin, carboplatin, paclitaxel, and etoposide, have not been consistently shown to increase the risk of pneumonitis (7, 11, 14, 15, 66). More modern agents have been associated with high rates of pulmonary toxicity when used concurrently with thoracic RT (e.g., docetaxel and gemcitabine; 1, 16, 64).

Radiation dose-time-fractionation

RP has a relatively high fractionation sensitivity, the best current estimate (±1 standard error of the estimate) of the α/β ratio of the linear-quadratic model is 4.0±0.9 Gy (65). For comparison, the upper bound on the 95% confidence interval for α/β for pulmonary fibrosis is 3.5 Gy. There is also a significant time factor for pneumonitis, with an overall best estimate of the dose recovered per day, D_p, of 0.54±0.21 Gy/day. Several have suggested methods to adjust the DVH to reflect the impact of fraction size (6, 17).

6. Mathematical/biologic models

The association between RP risk and MLD (logistic fit to the data in Figure 2B) can be expressed as:

$$p=\frac{\exp(b_0+b_1\cdot MLD)}{1+\exp(b_0+b_1\cdot MLD)}$$

Best fit parameters [95% confidence intervals] are $b_0=-3.87$ [−3.33, −4.49], $b_1=0.126$ [0.100, 0.153] Gy^{-1}. These estimates yield a predicted $TD_{50}=30.8$ [28.7, 33.9] Gy and $\gamma_{50}=0.97$ [0.83, 1.12] (this parameter represents the increase in response [measured in %] per 1% increase in dose, near the 50% dose response level.) A fit using the probit response function (equivalent to a fit of the Lyman model with n= 1) yields TD50 = 31.4 Gy, 95% conf.: [29.0–34.7 Gy], and m = 0.45 95% conf.: [0.39–0.51]. The resultant response function is essentially identical to that of the logistic fit in the region occupied by the data. The curvature is slightly smaller, resulting in the slightly larger TD50 value.

7. Special situations

The data reviewed here are largely derived from patients who received partial lung irradiation using conformal 3D-planned external beam RT with conventional fractionation (e.g., 1.8–2.0 Gy/fraction). Several special situations are discussed:

7.1 Whole Lung Irradiation

Near-uniform irradiation of both lungs occurs during total body irradiation (TBI) as conditioning for stem cell transplants, hemibody RT for diffuse metastases, and whole lung irradiation (WLI) for prophylaxis or treatment of pulmonary metastases from various malignancies. The risk of RP depends on total dose and fraction size (Fig 3). The development of RP in these settings is an ominous sign, proving fatal in up to 80% of patients (18). The pathogenesis of RP, in particular after TBI, is relatively complex and depends on multiple patient and treatment-related factors (19). There are consistent data supporting a protective effect of low dose rate and low dose per fraction. For a recent comprehensive review see Sampath (20).

7.2 Hypofractionation

Stereotactic body radiation therapy (SBRT) generally involves 1–5 large fractions (e.g. 14–30 Gy) given over 5–20 days (21, 22). The high-dose volumes are small, and dose gradients are steep, minimizing dose to surrounding critical structures. However, because numerous beams are used, there are large areas of lung receiving low-medium doses (22). Thus, the dose volume characteristics of SBRT are quite different from conventional lung RT, and deserve special consideration. RP is relatively uncommon after SBRT, usually <10% (23, 24), but as high as 25% (25). Bronchial injury/stenosis, an unusual complication with conventional doses (26), has been associated with SBRT of perihilar/central tumors (22).

7.3 Intensity Modulated Radiation Therapy (IMRT) for lung cancer

M.D. Anderson reported a lower rate of symptomatic grade ≥3 pneumonitis in 68 patients treated with IMRT, vs. a historical control group of 222 receiving conventional 3D (27). Memorial Sloan Kettering recently noted an acceptable 11% rate of grade ≥3 pneumonitis in 55 patients treated with IMRT (28). Postoperative IMRT for mesothelioma has been associated with a high rate of lethal pneumontis (8–46%) (29–31), and extreme care should be used to limit lung irradiation in these cases (see section 8).

8. Recommended dose/volume limits

Recommending dose/volume limits is challenging since there are no clear/consistent “thresholds” for candidate metrics (i.e., the response function is often gradual), and the “acceptable” risk level varies with the clinic scenario. RT fields for lung cancer may be appropriately-large for target coverage; physicians and patients often need to accept the significant pulmonary risks. Further, there are marked inter-patient variations in pre-RT lung function that may impact symptom development, and tumor-related dysfunction may improve after RT.

Despite these caveats, it is prudent to limit V20 to ≤30–35 %, and MLD to ≤20–23 Gy (with conventional fractionation), if one wants to limit the risk of RP to ≤20%, in definitively treated patients with non-small cell lung cancer. Similar guidelines for other parameters can be extracted from the figures. Limiting the dose to the central airways to ≤80 Gy may reduce the risk of bronchial stricture (26). In patients treated post-pneumonectomy for mesothelioma, it is prudent to limit the V5 <60%, the V20 <4–10%, and the MLD to <8 Gy (see Miles [31] for detailed review).

9. Future toxicity studies

Progress regarding the predictors of RT-induced lung injury requires further understanding of:

- **a.** Endpoint interaction: The study of RT-induced lung injury is confounded by the use of ambiguous endpoints. Many scoring systems combine radiologic, functional, and symptomatic criteria to define a "global score". Since each endpoint may have different dose/volume dependence, this approach maybe counter-productive. Therefore, we recommend that further study of lung injury explicitly consider symptomatic, functional and radiographic endpoints separately.
- **b.** The impact of clinical factors (e.g., pre-RT functional status, tobacco use) and systemic agents (e.g., chemotherapy) on the risk of RP needs further study.
- **c.** Organ interactions: Some data suggest that there may be interactions between the lung and heart in the development of RT-associated dyspnea. In rats, the respiratory rate following thoracic RT was related to the volume of lung *and* heart irradiated (32–34).
- **d.** The impact of an in situ lung cancer on the risk of radiation-induced lung injury: The data for whole lung radiation is derived essentially from patients *without* primary lung cancers (e.g., elective lung RT for sarcoma), vs. fractionated partial lung radiation, often derived from patients with gross lung cancers. The confounding effect of tumor in the lung makes the study of RT-induced lung injury extremely challenging. Indeed, in several studies, the ability to predict for RT-induced lung injury is improved in patients without large central/occluding tumors. Thus, it might be relevant to develop separate useful predictive models in patients with intact intra-parenchymal lung tumors vs. those without such a lesion (i.e. post-resection RT for lung cancer, or RT for other thoracic tumors).
- **e.** Radiation response modifiers: Amifostine is a thio-organic pro-drug believed to scavenge harmful free radicals mediating RT-induced injury. Several randomized studies in patients receiving RT for lung cancer note a reduction in RP in the amifostine arm although the largest study (from the RTOG) was negative (35). However, this study has been criticized because the drug was administered *once* daily (4 days/week) and the RT was delivered *twice* daily (5 days/week), and thus 60% of the RT fractions were delivered *without* the protector. Such mixed results, combined with the acute toxicities of amifostine (nausea/vomiting, hypotension, infection, rash), have dissuaded many from using it in routine practice. One small randomized study demonstrated a protective effect of pentoxifylline, but pentoxifylline is not currently utilized in routine clinical practice (36).
- **f.** Biomarkers: Additional work is needed to assess the predictive ability offered by biomarkers such as TGFβ (measured before and/or during RT).

10. Toxicity scoring

A SOMA-LENT-type scoring system is recommended since it explicitly considers symptomatic, functional and radiographic endpoints individually. A global score can be generated, but the granular data can be maintained.

Acknowledgments

Partially supported by NIH grant 85181 (JOD), NIH grant CA69579 (LBM), and a grant from the Lance Armstrong Foundation (LBM).

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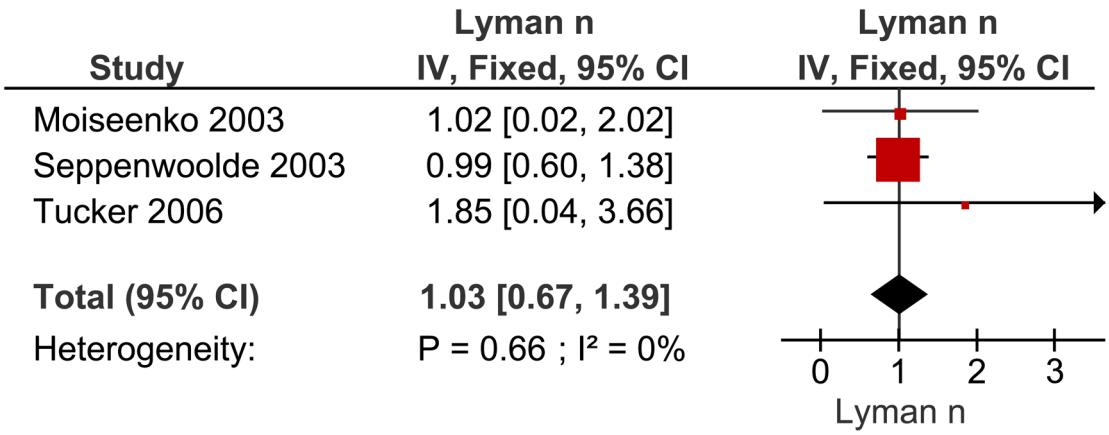

Figure 1.

Meta-analysis of reported *n*-values (volume parameter) for the LKB model using an inverse-variance (IV) weighting method. Recovery of variance estimates from the 95% confidence intervals (CI) and use of ~± 2*sigma instead of 1.96*sigma gave rise to small deviations in the derived 95% CI as compared to the literature reported values. Data estimated from (38, 40–41). Abbreviations: n = *n*-values for the LKB Model, IV = inverse variance, Fixed = fixed effect model CI = confidence interval. The *n* value reflects the manner in which dose/volume parameters lead to complications. A lower value of *n* suggests that the tissue is sensitive to hot spots (e.g., an organ structured in "series"), while a higher value of *n* (closer to 1.0), suggests that the risk is more related to the volume of an organ irradiated (e.g., "parallel" structure).

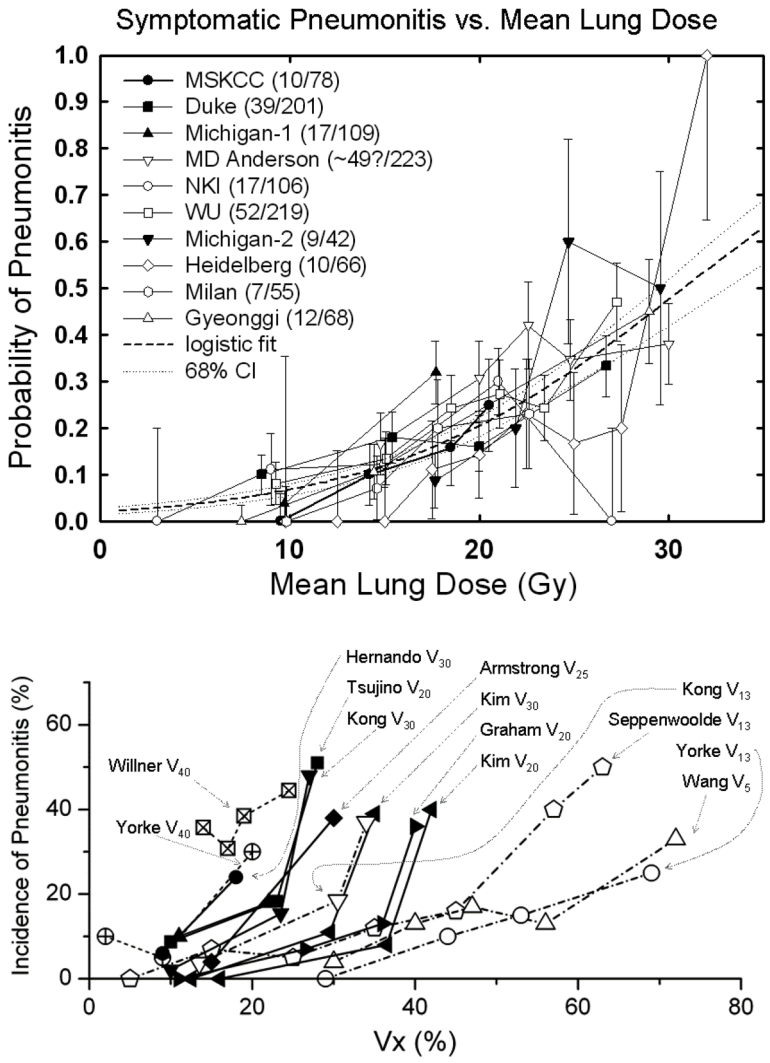

Figure 2.

Rate of RP following fractionated partial lung RT related to:

Panel A: Mean lung dose. Confidence intervals shown are ±1 standard deviation.

.Mean dose response data from: **MSKCC**, (10) from Fig 4a; (≥RTOG grade 3, 6 months); **Duke**, (15) from Table 4; (≥CTC grade 1, 6 months); **Michigan**, (43) from Table 4 and Fig 2a; (≥SWOG grade 2, 6 months)—bin location and time from authors; **MD Anderson**, (44) from Fig 2; (≥CTC grade 3, 1 year actuarial—includes concurrent chemo patients); **NKI**, (9) from Fig 3a; (≥SWOG grade 2, 6 months); **Washington University**, (11) from Fig 9c; (≥SWOG grade 2—no time limit) with bin locations from authors, increased by 11% to ~account for inhomogeneity corrections; **Michigan**, (45) from Table 1; (≥SWOG grade 1) with mean doses calculated from relationship between EUD (n=0.87) and mean dose from Kwa et al. (42), Fig 2a); **Heidelberg**, (46) from Fig 2 and text (≥RTOG acute grade 1); **Milan**, (47) from Fig 3; (≥SWOG Grade 2—no time limit, patients without COPD – includes induction chemo patients); **Gyeonggi**, (48) from Table 5; (≥RTOG grade 3, 6 months—includes concurrent chemo patients)—median values of mean dose in each bin provided by the authors. Dashed line is logistic fit: data fit to the form (f/(1+f)), where f=exp(b0+b1*dmean). Best fit values [95% confidence intervals] are b0 = −3.87 [−3.33–−4.49], b1 = 0.126 [0.100–0.153], corresponding to TD_{50} = 30.75 [28.7–33.9] Gy and γ_{50} =

0.969 [0.833–1.122], where γ_{50} represents the increase in response [measured in %] per 1% increase in dose, near the 50% dose response level.

Panel B: The rate of RP is shown for different values of Vx.

V_x response data from: Yorke V_{13}, V_{40}, (10) from Fig 4d; **Willner** V_{40}, (68) from Fig 4; **Hernando** V_{30}, (15) from Table 6; **Tsujino** $V_{20,}$ (56) from Fig 1; **Kong** V_{13}, V_{20}, (43), from Table 4; A**rmstrong** V_{25}, (59) Fig 3; **Kim** V_{20}, V_{30}, (69) from Table 5; **Graham** V_{20}, (7) from Table 4; **Seppenwoolde** V_{13}, (40) from Fig 2; **Wang** V_5, (44). Some data estimated from published reports.

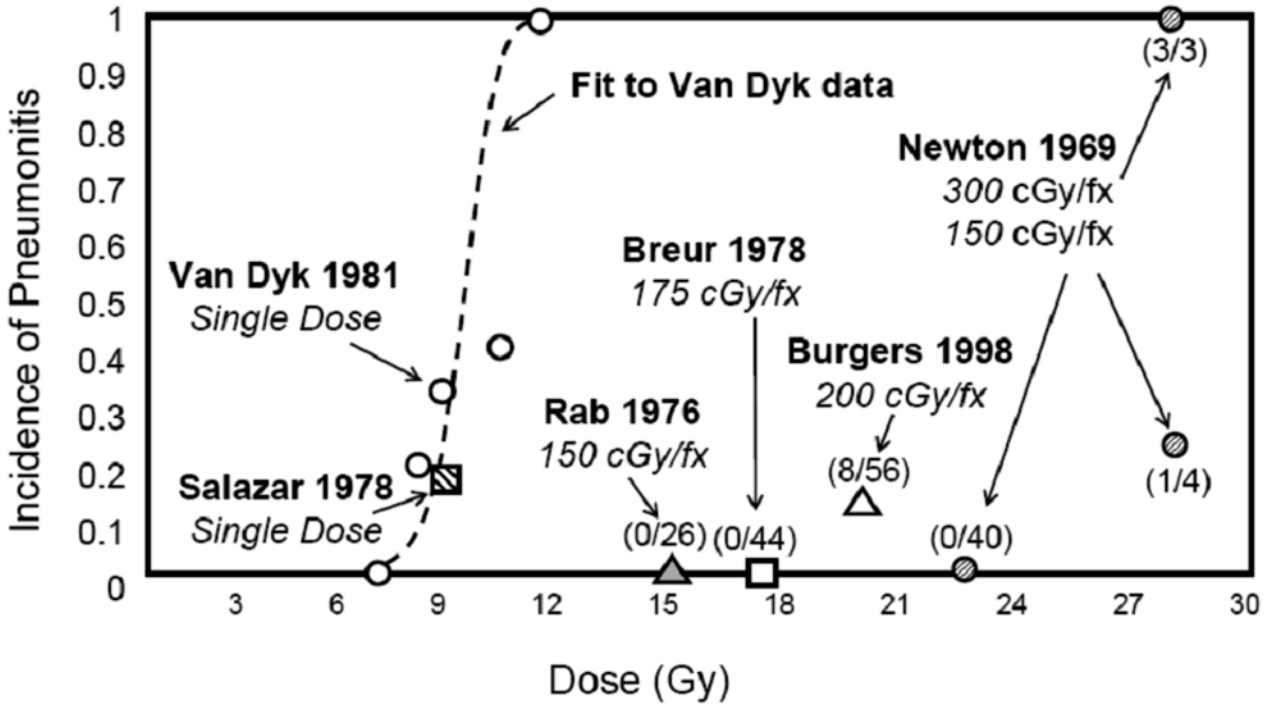

Figure 3.

Whole lung irradiation for diffuse lung or boney metastases, or prophylaxis for occult metastatic disease (18, 60–63). Numbers in parentheses give the incidence of pneumonitis divided by the population at risk for each fractionation scheme in each study. Some data estimated from published reports.

Table 1

Example end points for RT-induced lung injury (and approximate incidence)

	Regional	Global
Clinical	Bronchial stricture (<3% *)	Shortness of breath (5–50%)
Subclinical	Radiologic abnormalities (e.g. computed tomography, perfusion/ventilation scans) (20–80%)	Pulmonary Function Tests, Six-minute Walk Test, Blood gases, exercise capacity#

Example endpoints used to study RT-induced lung injury can be broadly segregated as shown.

*Uncommon with conventional fractionation and doses. More common with brachytherapy, high total doses and/or hypofractionation.

#Many patients experience declines in functional assessments, but the magnitude of the decline is variable.