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IMRT may increase pneumonitis risk relative to 3D-CRT in patients receiving combined chemotherapy and radiation therapy: a modeling study of dose dumping

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Abstract

Purpose—To model the possible interaction between cytotoxic chemotherapy and radiation dose distribution with respect to the risk of radiation pneumonitis (RP).

Methods and materials—Eighteen non-small cell lung cancer patients previously treated with helical tomotherapy at the University of Wisconsin were selected for this modeling study. Three treatment plans were considered in the study: (1) the delivered tomotherapy plans; (2) a 3D conformal radiotherapy (3D-CRT) plan; and (3) a fixed field intensity modulated radiotherapy (IMRT) plan. The IMRT and 3D-CRT plans were generated specifically for this study. Plans were optimized without adjusting for the chemotherapy effect. The effect of chemotherapy was modeled as an independent cell killing process by considering a uniform chemotherapy equivalent radiation dose (CERD) added to all voxels of the organ at risk. Risk of radiation pneumonitis was estimated for all plans using the Lyman and the Critical Volume models.

Results—For radiation therapy alone, the Critical Volume model predicts that the two IMRT plans are associated with a lower risk of RP than the 3D-CRT plan. However, when the CERD exceeds a certain threshold, the RP risk after IMRT is *higher* than after 3D-CRT. This threshold dose is in the range estimated from clinical chemo-radiation data sets.

Conclusions—Cytotoxic chemotherapy may affect the relative merit of competing radiation therapy plans. More work is needed to improve our understanding of the interaction between chemotherapy and radiation dose distribution in clinical settings.

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Conflict of interest statement. T. R. Mackie is Co-Founder and Chairman of TomoTherapy, Inc. and M.P.Mehta is a part-time consultant for TomoTherapy, Inc.

Keywords

radiation therapy; chemotherapy; pneumonitis risk; functional damage model; Lyman model

Introduction

Highly conformal radiation therapy techniques, such as intensity modulated radiation therapy (IMRT), can deliver therapeutic doses of radiation to complex target volumes with improved sparing of adjacent normal tissues when compared with conventional radiotherapy techniques[1-3]. This may potentially lead to reduced toxicity, and also opens up the possibility of escalating the radiation dose to the target volume. In some cases, the avoidance of defined organs at risk can lead to dose deposition – dose dumping – in areas not delineated that may not receive significant doses with conventional techniques, and may therefore cause unexpected toxicity [4]. In addition, the improved target dose homogeneity and conformity associated with IMRT often results in larger volumes of normal tissue receiving medium to low doses[5].

In parallel with the introduction of IMRT, there has been a move towards combined modality therapies in the management of many solid malignancies. This shift is supported in part by pre-clinical studies that provide mechanistic rationales for combining drugs and radiation[6,7], and also by the outcome of clinical trials. Although the quality of normal tissue toxicity data are often less than optimal in such clinical trial reports, the overall experience suggests that combined modality regimens are most often associated with increased toxicity. An open question is whether the presence, type, and intensity of chemotherapy administered influence the toxicity ranking of alternative radiation techniques delivering the same tumor dose, but different normal tissue dose distributions. In particular, whether the addition of chemotherapy could make an IMRT plan, that is estimated to be superior to a simple 3D-CRT plan in case of single modality radiotherapy, become inferior in terms of normal tissue side effects.

Non-small cell lung cancer (NSCLC) is a challenging disease from a management point of view. Optimal non-surgical therapy consists of combined chemotherapy and radiotherapy[8]. As the target volume is surrounded by healthy lung and as lung is relatively sensitive to cytotoxic therapy, it is virtually impossible to deliver effective therapy without some risk of pulmonary side-effects.

This study applies the Lyman and Critical Volume models to evaluate the effect of adding chemotherapy. Chemotherapy was assumed to act independently and isotropically throughout the organ at risk, in this case the lung, i.e it is seen as equivalent to adding a uniform equivalent dose to all voxels.

Methods and Materials

Patient selection and treatment planning

Eighteen patients with non-small cell lung cancer (NSCLC) previously treated at the University of Wisconsin with helical tomotherapy were selected for this study[5]. For all patients, planning CT images were acquired with a dedicated GE Discovery LightSpeed™ CT scanner. Planning images were transferred to the Pinnacle™ treatment planning system (Phillips, Milpitas, CA) so that contours could be delineated. Once all regions of interest had been identified, the images and contours were pushed to the TomoTherapy treatment planning system (TomoTherapy Inc., Madison, WI) for planning.

The TomoTherapy Hi-Art II™ unit combines a 6 MV linac with a CT ring gantry to allow for the delivery of image guided IMRT in a helical fan-beam geometry. Of the 18 patients in this study, 17 were planned using a 2.46 cm field width, while the remaining patient, who had less extensive disease, was planned using the 1.04 cm field width. The average pitch for these plans was 0.212 (range: 0.172-0.287) while the average planning modulation factor was 3.14 (range: 1.8-4.4). The planning modulation factor effectively sets an upper limit on the degree of modulation that can be utilized during optimization, and so is often not realized. For the tomotherapy plans in this study, the average modulation factor realized was 2.09 (range: 1.5-2.8). Plans were optimized to deliver the prescription dose to at least 95% of the target volume while simultaneously meeting dose-volume constraints placed on the residual lung, esophagus, and spinal cord and approved by the radiation oncologist.

For all patients planned on tomotherapy, the original CT image and contour data were restored into the Pinnacle™ TPS and both 3D-CRT and fixed field IMRT plans were generated for the purpose of this study. The 3D-CRT plans typically used a four field technique to provide sufficient coverage of the target volume while limiting the maximum dose delivered to the spinal cord to less than 45 Gy. In two cases, extra fields were used to ensure adequate target coverage. Conformal blocking was achieved using a Varian 120 leaf mMLC with a minimum leaf resolution of 5 mm and a maximum resolution of 2.5 mm over the central 80 leaves. Hard wedges were also used where necessary to improve dose homogeneity in the target and to reduce hot spots in the entrance regions.

The conventional (static) IMRT plans for all patients were generated using a seven field technique with beams evenly spaced about 180 degrees (the AP field) in 40 degree intervals. Optimization was performed using constraints and objectives similar to those used in the tomotherapy plans. After planning, dose volumes were extracted from the treatment planning systems and read into Matlab™ for analysis using CERR [9] as well as in-house routines. Dose-volume histograms (DVHs) were obtained for each plan, and while various fractionation schedules were originally used (as patients were enrolled on a Phase I dose escalation trial with a fixed number of total fractions[5]), all plans were renormalized so that 95% of the PTV received 60 Gy for the purpose of this study.

Radiobiological modeling

After planning, dose-volume information from all plans were converted to 2 Gy equivalent doses using the linear-quadratic formalism with an assumed alpha-beta ratio for healthy lung and tumor of 3 and 10 Gy, respectively. Two different normal-tissue complication probability (NTCP) models were used to predict the risk of developing pneumonitis; the Lyman model with a generalized equivalent uniform dose[10,11] and the Critical Volume model [12,13]. In the Critical Volume model, the lung is assumed to consist of a number of functional subunits (FSUs). The probability of inducing damage in a single FSU, P_{dam}, is assumed to be a function of the local dose D_i, described as a logistic dose-response function with two parameters: the dose resulting in 50% local damage probability, D_{50}, and a steepness parameter, k.

$$P_{dam} = \frac{1}{1+(D_{50}/D_i)^k}.$$

The probability of a clinical complication is again a function of the damaged volume $f_{dam} = \sum_i P_{dam}(D_i) v_i$ through a logistic function:

$$NTCP = \frac{\exp(b_0 + b_1 f_{dam})}{1 + \exp(b_0 + b_1 f_{dam})}$$

Here, v_i is the volume of the voxel receiving dose D_i. In choosing the model parameters b_0 and b_1, we used the established NTCP fits of Yorke *et al* [14]. For grade 3 or higher NTCP vs. damaged volume we find b_0=-5.2 and b_1=13.3. The local steepness parameter k is left variable, but is often omitted completely by setting it to infinity. In this case, the local dose response is a step function with the local dose damaging the FSU if and only if it exceeds D_{50}. The advantage of this approach is to reduce the number of model parameters from four to three.

Application of the Lyman model requires as a first step the calculation of an equivalent uniform dose (EUD) from the inhomogeneous dose distribution in the organ at risk, $EUD = \left(\sum_i v_i (D_i)^{1/n} \right)^n$, where n is a model parameter. The normal tissue complication probability (NTCP) is then assumed to be linked to the EUD through a sigmoidal link function, $NTCP(EUD) = \frac{1}{\sqrt{2\pi}} \int_0^k \exp\left(-\frac{t^2}{2}\right) dt$, where $k = \frac{EUD - TD_{50}}{mTD_{50}}$ and m is a parameter defining the steepness of the curve. Based on literature reports (12), the three parameters of the Lyman model, TD_{50}, m and n, were chosen at 20 Gy, 0.37 and 0.81, respectively in the modeling presented here,.

NTCP values from both models were computed in Matlab using the extracted DVH data for the residual lung, which was defined as the whole lung (both sides) minus the PTV. The effect of chemotherapy was modeled by adding a chemotherapy equivalent radiation dose (CERD) in 2-Gray fractions to all voxels in the organ at risk.

The mean NTCP for the 18 IMRT, 3D-CRT and tomotherapy plans were computed with varying CERD. The uncertainty of the mean values was estimated using a bootstrap method whereby 5000 simulated patient cohorts with 18 individuals in each cohort were randomly sampled from the original population. The Monte Carlo 68% confidence interval of the mean (~ 2 SD) was then estimated from the 5000 samples as the 16th and 84th percentile of the simulated means.

Results

The mean and range of important dose-volume metrics for the three plan types are given in Table 1 for CERD=0 and 10 Gy along with the mean and range of the NTCP estimates using the critical volume model.

Illustrative case study

Figure 1 shows an individual example of a dose distribution representative of the tomotherapy and 3D-CRT plans used for this study along with the corresponding dose volume histograms for these two plans as well as the fixed-field IMRT plan. The tomotherapy plan delivers a highly conformal dose to the target while simultaneously minimizing the volume of residual lung receiving high radiation dose. The conformality of the tomotherapy plan results in a larger volume of normal lung irradiated to a low dose (< 15 Gy), in the range that is normally regarded as “safe” and not associated with clinically significant pulmonary toxicity.

While the low dose volumes may be of little consequence on their own, they could potentially become important when radiation is combined with chemotherapy that is additive or synergistic in terms of pulmonary toxicity. This is illustrated in Figure 2, where the effect of chemotherapy (described in terms of the CERD) is estimated by the Critical Volume model, using modeling parameters of D_{50} = 20 Gy and k = infinity. In the figure, the risk of grade 3 or higher radiation pneumonitis (RP) for each of the three plan types is plotted as function of CERD. This model predicts that the risk of grade 3 and higher radiation pneumonitis at CERD=0 Gy is lower with tomotherapy and IMRT than with 3D-CRT. This ranking of the three plans is preserved until the assumed CERD exceeds about 10 Gy, beyond which the tomotherapy and IMRT plans are estimated to yield greater toxicity than 3D-CRT.

Population results

The same simulation performed on the cohort of 18 patients. Figure 3 shows the population averaged results of simulations with the Critical Volume model using the same parameters as above. The statistical uncertainty is indicated by thin dashed lines representing the 68% confidence interval of the mean.

The observations in the above individual case also hold for the cohort; at CERD=0 Gy the IMRT and Tomotherapy plans are estimated to be superior to 3D-CRT with respect to pneumonitis risk. However, as the CERD is increased, the plan ranking changes and the 3D-CRT technique is predicted to be less toxic than the two IMRT techniques. Table 1 gives numerical mean and ranges of NTCP for CERD=0 and 10 Gy and further illustrates the change of ranking.

The results seen in Figures 1-3 depend on the parameters used in the model. A sensitivity analysis of the modeling parameters yield the following two general mechanisms; (1) The cross-over between 3D-CRT and tomotherapy plans appears at increasing CERD for increasing D_{50}. This can be understood from the model as the additional CERD required to bring the low dose areas of the conformal techniques to toxic levels increasing with increased tolerance of the functional subunits; as represented by the D_{50} parameter. (2) The influence of k is limited in comparison, but decreasing k results in decreasing CERD at the cross-over between 3D-CRT and tomotherapy NTCP values. For values of D_{50} below approximately 10-15 Gy (depending on k) or values of k significantly lower than approximately two (depending on D_{50}), the IMRT and tomotherapy techniques are predicted to be more toxic than 3D-CRT even at CERD=0 Gy. For most realistic values of D_{50} and k, however, the change of plan ranking above a certain critical CERD is consistent. Table 1 shows the mean and range of the NTCP predicted by the critical volume model with $k=3$ and $k=\infty$ and D_{50} fixed at 20 Gy.

Simulations were repeated with the Lyman NTCP model in order to estimate the possible model-dependence of the change in plan ranking. The Lyman model predicts increased toxicity with increasing CERD, in accordance with the Critical Volume model, but the ranking of the plans does not change.

Discussion

The present study shows that the toxicity ranking of radiation-only plans may change in the presence of systemic agents. If chemotherapy acts as a ‘priming’ dose throughout the organ at risk, low-dose regions of the organ may begin to contribute to reduced local function and ultimately to the risk of organ-level side-effects. Techniques irradiating a smaller total volume of lung tissue may thereby be less damaging than techniques spreading a relatively

low dose over a larger volume. The magnitude of this effect will vary with the actual drug or combination of drugs, drug dose and dose-intensity.

The changed ranking among radiotherapy dose-distributions depends on the chosen NTCP model parameters. However, for realistic parameter sets, the CERD where the NTCP of simple and highly conformal plans will cross ranges from 5 to 15 Gy. Estimates of the CERD of current clinical chemotherapy regimens can be derived from studies reporting pneumonitis incidence after radiotherapy with and without chemotherapy. There are limited data of this type, but in a recent report [5] from a dose-per-fraction escalation study at the University of Wisconsin, adjuvant chemotherapy was found to be a statistically significant (P=0.018) risk factor for grades 1 and 2 pneumonitis. Figure 4 shows the incidence of Grade 1 and Grade 2 radiation pneumonitis observed with neoadjuvant or no chemotherapy compared to adjuvant chemotherapy from this dataset. Note that no Grade 3 toxicity was observed. From the ordinal regression analysis, the CERD was estimated at 11.5 Gy. Hence, this estimate is in the range where IMRT techniques are predicted to be more toxic than simpler techniques. It should be noted, however, that the 95% confidence interval for the CERD estimate is wide: from 1.1 Gy to 98 Gy, probably reflecting the small number of cases and the limited number of toxicities observed. Caution must be exercised in interpreting these data; patients in the University of Wisconsin trial had no grade 3 pulmonary toxicities, and the clinical relevance of the effect of chemotherapy on low grade radiation pneumonitis could be questioned. Further, the study specifically excluded concomitant chemotherapy, and therefore, the effect of concomitant administration cannot be deduced from it. Interestingly, neoadjuvant chemotherapy did not increase the risk of low grade pneumonitis, but adjuvant chemotherapy did; a possible explanation of this observation could be that chemotherapy agents in routine use in non-small cell lung cancer may have little or no untoward pneumocytocidal activity on their own, but once damaged by radiation subsequent chemotherapy yields a pneumocytocidal damage resembling the “radiation recall” phenomenon seen with agents such as doxorubicin. It is also possible that there is an interaction between the drugs and the continuing cascade of TGF-beta (and other cytokines) that mediate pulmonary damage [15] which would extend far beyond the end of radiotherapy.

The choice of an additive model is based on an assumption of no direct interaction between tissue damage from chemotherapy and from radiation. While increased toxicity of chemoradiation compared to RT alone has been documented in a number of studies, there is to our knowledge no clinical data allowing discrimination between different model of drug-radiation damage. The simplest possible assumption is that the two types of cytotoxics have additive independent effects. Alternative models could be that the drug acted as a dose-modifying factor or more elaborate models where, say, the drug only affected repairable damage. Empirically, it should be possible to find the best-fitting model from large clinical datasets, as it has been done in a study of second cancer induction where chemotherapy was concluded to have an additive effect [16]. However, the structural information in current clinical chemo-radiation datasets is insufficient to allow this kind of analysis.

A recent non-randomized study from MD Anderson Cancer Center[17], documented the incidence of pulmonary toxicity after concomitant chemoradiotherapy with conventional 3-D CRT or IMRT for lung cancer. In spite of a larger average PTV in patients receiving IMRT compared with 3D CRT, a lower rate of pulmonary toxicity was seen after IMRT. However, the IMRT planning technique used in the MDACC study resulted in a decreased lung volume exposed to the relatively low dose of 10 Gy in contrast to the optimization technique used in our study. Optimizing IMRT with very low dose objectives may circumvent the change in plan ranking observed in the present study, by pushing the crossover point between IMRT and 3DCRT plans to a higher CERD value. Provided data on

the interaction between radiation dose distribution and drugs become available, the chemotherapy effect could be directly represented in plan optimization. It is quite possible that an adequately optimized chemo-IMRT plan would still be superior to the corresponding 3D CRT plan.

Another set of interesting clinical data stem from studies of mesothelioma patients receiving tri-modality therapy: radical extrapleural pneumonectomy, chemotherapy and radiotherapy. The Dana-Farber cancer center reported an unexpected high rate of fatal (Grade 5) lung toxicity after IMRT; six fatal complications in thirteen patients treated [18]. Other groups have applied IMRT in the same setting [19,20] with an incidence of fatal pulmonary toxicity in the order of 10-15%. Comparing the three studies, there is no obvious explanation for the somewhat higher incidence of Grade 5 lung toxicity in in the Dana-Farber series, although an interaction between RT and the more aggressive intrapleural and systemic therapy has been suspected to play a role. Likewise it is unclear why mesothelioma patients in general are at a high risk of fatal pneumonitis when dose constraints that would be considered safe for NSCLC are applied. However, all three studies report large volumes of the lung exposed to low dose levels of 5-10 Gy. In contrast, the previously applied antero-posterior parallel-opposing field technique did not, in general, expose the contralateral lung to a significant radiation dose and did not produce such severe pneumonitis: 0 of 54 patients experienced grade 4 or 5 pneumonitis in a Memorial-Sloane-Kettering study [21]. This corresponds to an upper 95% confidence bound on the incidence of Grade 4+ pneumonitis estimated at 6.6%. Despite the relatively limited number of patients and the unique combination of pneumonectomy and intensive chemotherapy, the overall experience in mesothelioma patients is consistent with our hypothesis that combined IMRT with chemotherapy may lead to unexpectedly severe toxicity.

As shown here, the qualitative effect of chemotherapy depends on the choice of biomathematical model used to estimate the risk of radiation pneumonitis. This reflects fundamental differences between the Critical Volume and Lyman models. The Critical Volume model predicts a local dose response relationship that saturates with increasing local dose when unit probability of local damage is approached. In other words, when local function is completely lost, further irradiation of this region will not add to the overall loss of lung function and thereby the risk of RP. In contrast, in the Lyman model, EUD continuously increases with increasing local dose. As a result, high dose volumes will dominate the Lyman NTCP regardless of the CERD whereas high dose regions already predicted to be damaged in the critical volume model are insensitive to the added chemotherapy. Furthermore, in the Critical Volume model the added effect of the cytotoxic chemotherapy will ‘lift’ the lower dose regions into the range where the likelihood of local damage is no longer negligible which again will affect the predicted lung function and therefore the risk of developing RP. Table 1 illustrates this phenomenon as the volume receiving 20 Gy, which is monotonically related to NTCP in the critical volume model, with CERD=10 Gy is equal to the volume receiving 10 Gy with CERD=0 Gy. In contrast, the Lyman model prediction is related to MLD, which means that the ranking of plans will not change when adding a constant CERD. To the best of our knowledge, no studies have been able to show which of the two models is superior for predicting the risk of radiation pneumonitis after radiotherapy alone, despite the fundamental differences in the underlying pathogenic mechanisms of the models. However, the dissociation in the behavior of the two models in the presence of chemotherapy may provide a useful clue. In fairness, both models have shown a disappointing ability to reliably predict radiation pneumonitis risk for diverse dose distributions. Furthermore, our study demonstrates that it is necessary to include chemotherapy effects in the modeling process in order to improve the reliability of risk predictions. The approach taken here represents a simple way to model the effect of chemotherapy.

Other authors have suggested that if adding chemotherapy to radiation therapy increases toxicity, then reducing the irradiated volume could be one strategy to mitigate this effect [22]. What we show in the present modeling study is that there may even be a direct interaction between chemotherapy and radiation dose distribution, i.e. that the sparing seen from IMRT in the radiation alone scenario may be abolished if sufficiently toxic chemotherapy is given as well. The use of IMRT techniques with emphasis on reducing the volume of lung exposed to low doses of 5-10 Gy represent one way of getting around this effect. This may be achieved through careful selection of beam angles and the use of different dose objectives, but more clinical data are needed in order to improve the understanding of chemo-RT interactions and their influence on the optimal choice of dose plan. While the MDACC experience is positive, the mesothelioma experience and the data presented in Figure 4 suggest that further studies of the effect of low dose levels in the lung and the possible interaction with chemotherapy are required in order to define safe dose constraints when using a new delivery technique in multimodal therapy. The implementation of appropriate dose constraints could very possibly give rise to IMRT plans that are superior to 3D-CRT plans. Finally, we note that proton therapy plans would be expected to be largely insensitive to chemotherapy in the proposed model because of the ability to produce highly conformal plans with protons that do not have the extensive low-dose dose-dumping characteristic of photon IMRT.

Interactions between radiation dose-distribution and the combination of drugs with radiation therapy can also be expected for other organs at risk. One example may be the RTOG 0234 trial where an increased incidence of oral mucositis after was seen after IMRT as compared with non-IMRT when combined with cetuximab and cisplatin or docetaxel for head and neck cancer[23].

Conclusions

This modeling study shows that dose-plan toxicity ranking may change from favoring IMRT to favoring 3D-CRT techniques when a chemotherapy equivalent radiation dose is added to the healthy lung and the critical volume model is used to predict RP. This effect is not present with the Lyman model, which always favored the IMRT plans. The qualitative difference between the models suggests that systematic studies of toxicities occurring after chemoradiation may be informative for model selection. If reliable chemo-radiation dose-effect models were available, IMRT plans could be optimized in the presence of the drug-radiation combination. The present study illustrates the need to incorporate the effects of chemotherapy in our bioeffect modeling in all links of the clinical radiation research chain: outcomes analysis, radiation treatment planning and radiobiological modeling in order to improve patient-specific clinical decision making.

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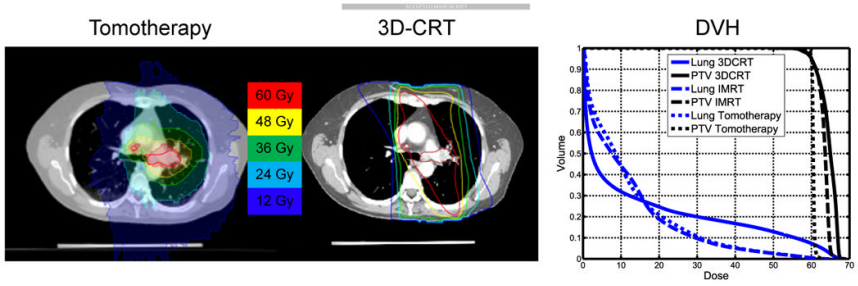

Figure 1.

Dose distribution representative for the tomotherapy (left) and 3D-CRT (middle) plans used for this study Right: Dose volume histogram for the three plans in the target and OAR. The IMRT plan is qualitatively similar to the tomotherapy plan.

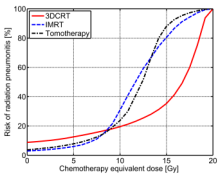

Figure 2.
NTCP versus added CERD in 2 Gy fractions calculated in the critical volume model using the plans depicted in Figure 1.

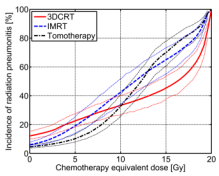

Figure 3.
Population averaged NTCP versus CERD estimated from the critical volume model. The dotted lines indicate the 68% confidence interval of the mean.

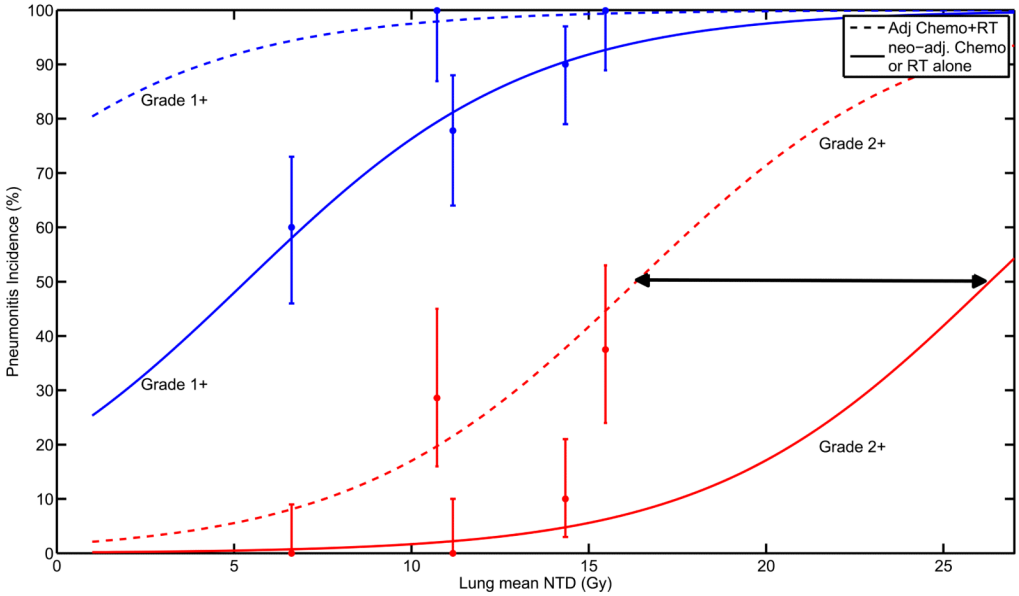

Figure 4.

Observed incidence of RP in a cohort of patients receiving either no chemotherapy or neoadjuvant chemotherapy compared to patients receiving adjuvant chemotherapy. The black arrow indicates the presence of a CERD around 10 Gy range when adjuvant chemotherapy is used. Estimation by a full ordinal logistic regression yields CERD=11.5Gy. NTD: normalized total dose in 2 Gy fractions. Data from [5].

Table 1

Dose volume metrics

Mean and range of dose-volume metrics for the three types of dose plans and the mean and range of the NTCP as calculated with the critical volume model with D_{50}=20 Gy and k=inf and k=3. CERD: Chemotherapy equivalent radiation dose, MLD: mean lung dose, Vx: volume of lung receiving x Gy. All values are corrected for fractionation with α/β=3 Gy for the residual lung. Bold font denotes the smallest dose-volume/NTCP values of the three plan types. Note that V20 is monotonically correlated with NTCP. Also, V10 with CERD=0 Gy is equal to V20 at CERD=10 Gy, explaining the change of ranking in the critical volume model. In contrast, the Lyman model is related to MLD which means that plan ranking will not change as CERD is a constant dose added to the MLD without chemotherapy.

Plan Type	CERD=0 Gy				
	MLD	**V10**	**V20**	**NTCP (k=∞)**	**NTCP (k=3)**
3D-CRT	11.7 Gy (3-19 Gy)	**30%** (12-49%)	21 % (8-37%)	12 % (1-45%)	12% (1-41%)
IMRT	9.9 Gy (3-18 Gy)	36% (9-72%)	14 % (1-30)	6% (1-23%)	10% (1-35%)
TOMO	**9.6 Gy** (2-17 Gy)	**30%** (3-60%)	**13 %** (1-26%)	**5%** (1-15%)	**7 %** (1-23%)
	CERD=10 Gy				
	MLD	**V10**	**V20**	**NTCP (k=∞)**	**NTCP (k=3)**
3D-CRT	21.7 Gy (13-29 Gy)	100%	**30%** (12-49%)	**33%** (3-78%)	**45%** (9-85%)
IMRT	19.9 Gy (13-28 Gy)	100%	36% (9-72%)	43% (2-99%)	51% (9-85%)
TOMO	**19.6 Gy** (12-27 Gy)	100%	**30%** (3-60%)	34% (1-95%)	51% (7-93%)