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CLINICAL INVESTIGATION **Breast**

RADIATION PNEUMONITIS AFTER BREAST CANCER IRRADIATION: ANALYSIS OF THE COMPLICATION PROBABILITY USING THE RELATIVE SERIALITY MODEL

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Background: Toxicity of the respiratory system is quite common after radiotherapy of thoracic tumors; breast cancer patients represent one of the groups for which there is also a long expected survival. The quantification of lung tissue response to irradiation is important in designing treatments associated with a minimum of complications and maximum tumor control.

Methods: The study population consisted of 68 patients who received irradiation for breast cancer at Stage II. Radiation pneumonitis was retrospectively assessed on the basis of clinical symptoms and radiological findings. For each patient, a measure of the exposure (i.e., the lung dose-volume histogram [DVH]) and a measure of the outcome was available. Based on these data, a maximum likelihood fitting to the relative seriality model was performed. The uncertainties of the model parameters were calculated and their impact on the dose-response curve was studied. The optimum parameter set was then applied to 5 other patient groups treated for breast cancer, and the normal tissue complication probability (NTCP) was calculated. Each group was individuated by the radiotherapy treatment technique used; the dose distribution in the lung was described by a mean DVH and the incidence of radiation pneumonitis in each group was known. Lung radiosensitivity was assumed to be homogeneous through all of the calculations.

Results: The relative seriality model could describe the dataset. The volume effect was found to be relevant in the description of radiation pneumonitis. Age was found to be associated with increased risk of radiation pneumonitis. Two distinct dose-response curves were obtained by splitting the group according to age. The impact of the parameter uncertainties on the dose-response curve was quite large. The parameter set determined could be used predictively on 3 of the 5 patient groups.

Conclusion: The complication data could be modeled with the relative seriality model. However, further independent datasets, classified according to the same endpoint, must be analyzed before introducing NTCP modeling in clinical practice. **© 2000 Elsevier Science Inc.**

Radiation pneumonitis, Breast cancer radiotherapy, NTCP, Lung complications

INTRODUCTION

Lung complications and in general toxicity of the respiratory system are relatively common after radiotherapy of thoracic tumors. A quantitative description of the lung response to radiation is of importance for designing treatments with a minimum of complications while maximizing the frequency of patients with tumor control. Of the patients treated with radiotherapy for tumors close to the lungs, breast cancer patients form one of the largest groups for which there is also a long expected survival. Because of the adjuvant nature of postoperative radiotherapy in breast cancer, the extent and the severity of the side effects should be kept low. In breast cancer patients, lung complications, grouped according to two major clinical syndromes: i.e., an early effect, radiation pneumonitis; and a later effect, lung fibrosis (1–4) have been reported in several studies (5–12).

To introduce and to use, in the clinical routine, information about normal tissue reaction to irradiaton, it is necessary to quantify it. The quantification of the normal tissue

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response to irradiation, which translates the dose delivered to the tissue into the tissue biological response, is done by using biophysical models. The extension of the models describing dose-response relationships to include data from three-dimensional (3D) treatment plans represents an important tool in the calculation of normal tissue complication probabilities (NTCP), and consequently, in the evaluation and comparison of treatment plans. However, despite the potential impact of NTCP modeling in radiotherapy, the data available for NTCP modeling is still scarce, and a consensus on the dose-response curves describing a specific endpoint for a specific organ has not yet been reached.

The two aims of the present analysis were as follows. First, the goal was to parameterize the dose-response curve for radiation pneumonitis following radiotherapy for breast cancer at Stage II. A 68-patient dataset, consisting of the individual outcomes and the individual lung dose-volume histograms (DVHs), was analyzed by using the relative seriality model (Appendix A). The optimum parameters were determined by a maximum likelihood fitting. Second, the optimum parameter set was then used to calculate the probability of radiation pneumonitis, following breast cancer irradiation, for five patient groups treated with different techniques. The predicted probability of lung complication was compared to the known incidence of radiation pneumonitis for these five groups.

METHODS AND MATERIALS

Study population

The patient group consisted of 68 consecutive patients treated with postoperative radiotherapy for locoregional breast cancer between January 1993 and March 1994 at Radiumhemmet. Eighteen patients received chemotherapy prior to radiotherapy; 43 of 68 patients were treated with tamoxifen during radiotherapy.

The endpoint in the present study was radiation pneumonitis, with the assessment done retrospectively by clinical diagnosis, together with radiological findings. The symptoms underlying the clinical diagnosis were cough/dyspnea/fever, as reported in the clinical charts. The patients' medical records were examined up to 1 year after the completion of radiotherapy. In the present study, smoking history and respiratory history before radiotherapy were not regularly described in most of the patients' records. As a consequence, the data could not be analyzed for these factors.

Treatment technique and dose planning

The clinical target volume (CTV) consisted of the breast parenchyma (chest wall in case of postmastectomy treatment) and of the lymph nodes in the internal mammary chain, in the fossa, and in the axilla. A margin of 5–7 mm was added isotropically to the CTV, defining the planning target volume (PTV). The patient lay on a wedged couch, fitting the computed tomography (CT) aperture, with the arm on the affected side abducted ideally at 90° from the body. This position was kept at the simulator and during the treatment for all patients, while in the majority of the cases, the arm was abducted less than 90° at the CT, in order for the patient to fit the aperture.

The treatment technique (for simplicity, denominated here as "five-field technique") was based on an oblique electron field covering the internal mammary chain and tangential photon fields for the treatment of the chest wall, as originally suggested by Woudstra *et al.* (13). The lymph nodes in the fossa and axilla were irradiated with two anterior adjacent photon fields; the energies used were 6 and 16 MV, respectively, in accordance with the depth of the respective target. Matching between all of the fields was performed by asymmetric collimation. A special electron collimator, permanently mounted on the accelerator, was developed for this treatment. In this way, the need to reposition the patient when mounting and dismounting the collimator was eliminated. Furthermore, asymmetric collimation of the electron beam was possible. Two isocenters were used, one for the four photon beams and one for the electron beam (14). The isocenter setup was made from an external reference point, defined before the CT, situated at the intersection between the mamillary plane and the sternum midline, and tattooed on the skin. This reference point was then used to define a local patient coordinate system, in which the isocenter coordinates were determined at the dose planning and for the setup at the treatment unit (15). The treatment planning was made on a 3D treatment planning system (TMS, Helax), based on approximately 30 CT slices with 1-cm spacing, using tissue inhomogeneity corrections. A block protecting the apex of the lung was used for some treatments. The dose distribution was generally specified so that the minimum dose to PTV was 95% of the specified target absorbed dose. The dose was delivered with 2 Gy per fraction, 5 days a week, the total dose of either 46 Gy (chest wall and locoregional lymph nodes) or 50 Gy (breast parenchyma). This treatment technique has been routinely used at the Radiumhemmet since 1993 for both partially and radically mastectomized patients. DVHs were calculated for the lung volume on the affected side.

Determination of parameters and uncertainties

The NTCP model applied in this study was the relative seriality model (Appendix A). The fractionation schedule was taken into account in the calculations as follows: each lung DVH was corrected using the linear quadratic model to a 2 Gy per fraction schedule (16). Thus, each dose step in the histograms was corrected separately. The α/β value assumed in the linear quadratic model correction was 3 Gy (17, 18). However, a sensitivity test was performed and the calculation was also performed using an α/β value of 8 Gy. The radiation sensitivity was assumed to be homogeneous throughout the lung volume.

The parameter values and their uncertainties were determined by a fit of the theoretical predictions of complication, using the DVHs, to the clinical data of complication. For the fitting of the parameters, the maximum likelihood method was chosen (i.e., a method which determines the optimum

Table 1. Best fitting parameter values for the whole group of patients (n = 68)

Parameter	Calculated value	68% Confidence limits
D_{50} dose giving 50% of complication probabilities (Gy)	30.1	(−2.17; +2.43)
γ maximum relative slope of the dose response curve	0.966	(−0.198; +0.242)
s-relative seriality factor	0.012	(at limit; +0.145)

values of the parameters by maximizing the likelihood of the given observations) (19, 20).

The fit calculations were performed by means of a CERN minimization package, MINUIT (21), previously used in applications similar to the present one (22, 23). For the present calculations, the parameter space was unrestricted except for the constraint imposed by the model ($0 \leq s \leq 1$). Once the minimum had been obtained, in order to check its stability, calculations were performed changing both the initial values and the allowed range of the parameters.

The goodness of the fit was estimated according to the method described by Jackson *et al.* (24): given D_{50}, γ, and *s* from the minimization, the average of the likelihood function and its variance were calculated assuming a Gaussian distribution for the likelihood function. The expected mean value and standard deviation were then compared to the likelihood function value observed in the minimization.

An evaluation of the parameters errors was done by calculating the 68% confidence interval. This was obtained, in a first approximation, by considering the monodimensional likelihood profiles, i.e., by studying the variation of the likelihood function in the minimum region while keeping constant the other parameters at the optimum value (22).

In a second approximation, the bidimensional 68% joint confidence region of the parameters D_{50} and γ was analyzed, i.e., the region in the D_{50}-γ plane, in which we estimate there is 68% probability of finding the true values of the two parameters. The D_{50}-γ plane was selected with the parameters fixed at its optimum value. To study the impact of the uncertainties in the parameters on the dose-response curve, a bundle of dose-response curves was calculated using the parameter values on the contour. The described procedure represents a first step in quantifying the uncertainty in the dose-response curve, due to the uncertainties in D_{50} and γ, imposed by the fitting procedure.

NTCP predictions on the basis of the optimum parameter set

To test the validity of the obtained results and the possibility of using the optimum dataset as determined by the fitting in a predictive way, NTCP was calculated for different groups of breast cancer patients treated with radiotherapy at Radiumhemmet between 1987 and 1989 (8) and at Söder Sjukhuset (11). For these patients, lung complication was assessed according to the same criteria applied in the present study. Radiumhemmet's study population consisted of 273 consecutive breast cancer patients, grouped according to the treatment technique: Group 1 consisted of 109

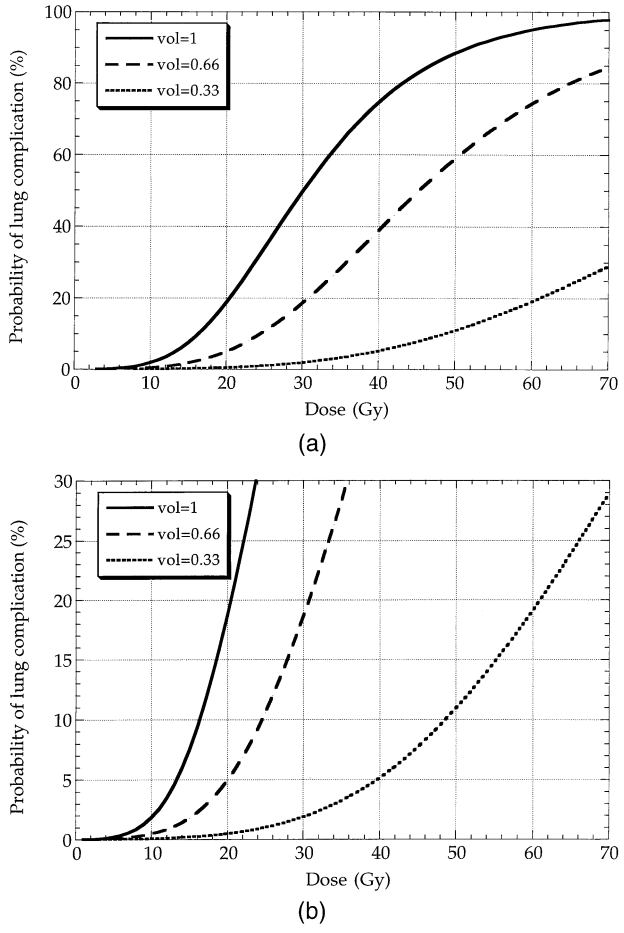

Fig. 1. Probability of radiation pneumonitis versus dose. The relative lung volumes are 100%, 66%, and 33%. The curve parameters are D_{50} = 30 Gy, γ = 1.01, s = 0.01. The curve covers the probability range up to 100% (a), and up to 30% (i.e., within the interval of the clinical data) (b).

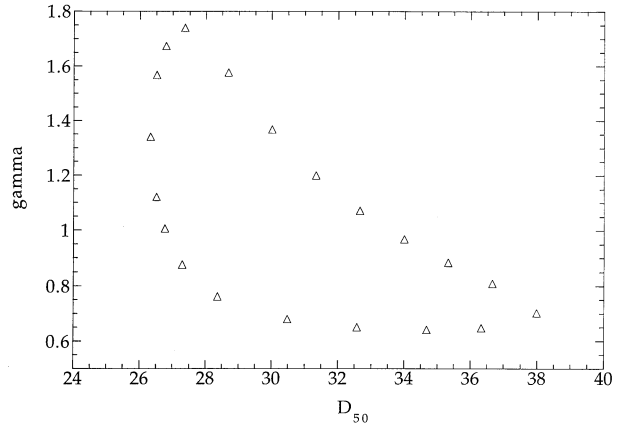

Fig. 2. Joint probability region for D_{50} and γ, obtained by fixing *s* at its optimum value. The probability statement for this region is that the probability that parameters one and two simultaneously assume values within the 1-SD likelihood contour is 68%.

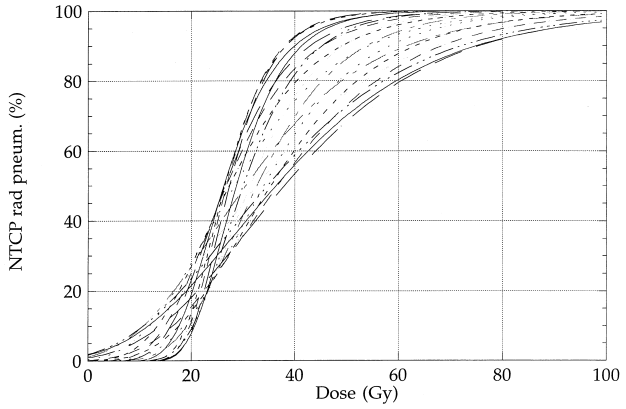

Fig. 3. Bundle of dose-response curves obtained from the sets of parameters defining the contour of the D_{50}-γ joint probability region. The D_{50}-γ plane was chosen with s fixed at its optimum value, $s = 0.01$.

patients who received local treatment, consisting of tangential photon fields (6 MV or ^{60}Co), while Groups 2 and 3 consisted of patients who received locoregional treatment with two different techniques. In Group 2 (56 patients), the breast/chest wall and the lymph nodes of the internal mammary chain were treated with extended tangential photon fields (^{60}Co or 6 MV), while the lymph nodes of the clavicular region and of the axillary region were treated with an anterior photon field; a posterior photon field was added to the axillary region. In Group 3 (108 patients), the chest wall was treated with an oblique electron field (9–14 MeV). The lymph nodes located in the internal mammary chain, in the fossa, in the clavicular region, and in the axillary region were treated with an anterior photon field (4 MV or ^{60}Co) with a posterior photon field added to the axillary region. A block protecting the lung apex was used for most patients in Groups 2 and 3. For Group 1, the target dose (the target had to be encompassed by the 95% and 105% isodoses) was 50 Gy, while for Group 2, the target dose was 46 Gy to the chest wall and locoregional lymph nodes, and 50 Gy to the breast parenchyma. In Group 3, the target dose was 46 Gy. The fractionation schedule was 2 Gy/fraction, 5 fractions per week. A fourth group was included; it consisted of 138 patients, treated at the Söder Sjukhuset in Stockholm between 1990 and 1993. These patients, who had gone through a radical mastectomy before radiotherapy, were treated with an anterior electron field, covering the whole chest wall and the caudal part of the internal mammary lymph nodes. A complementary anterior photon field was used for the cranial part of the internal mammary, axillary, and supraclavicular lymphnodes.

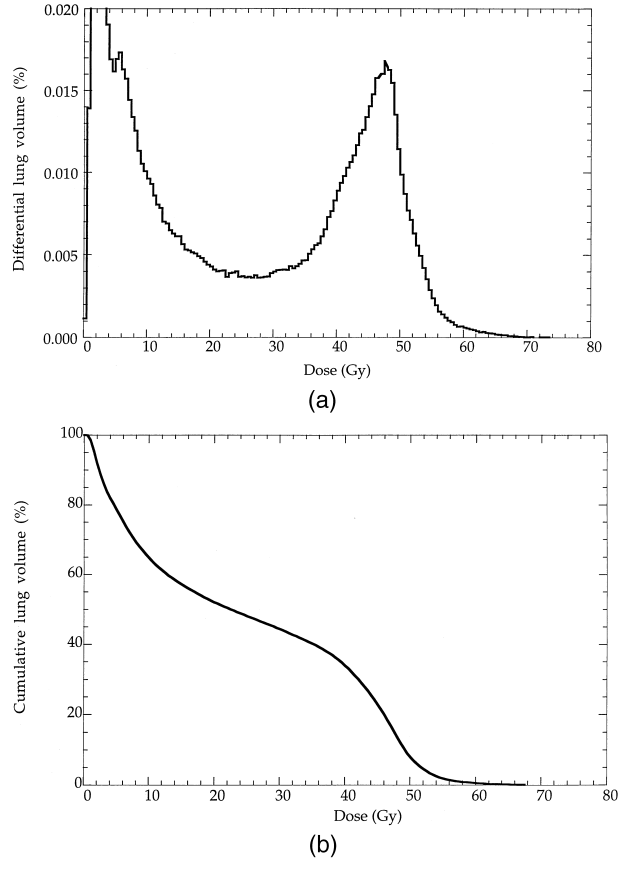

Fig. 4. Mean differential (a) and cumulative (b) lung DVH for the five-fields treatment technique.

For these 4 groups, 3D dose distributions in the lung were not available from the dose planning. Thus, each treatment technique was simulated in 3D on 10 model patients using the treatment planning system TMS. The selection of the model patients and the radiotherapy data used in the reconstruction was based on the information collected from the original individual 2D treatment planning, from the individual radiotherapy cards, and from other available sources (22). In the reconstruction, the dose planning was calculated on about 30 CT slices, spaced 1 cm apart. Differential and cumulative DVHs were obtained for each reconstruction, where each DVH was normalized in volume to its total lung volume. A fifth group, consisting of the patients treated with the five-field technique, was also analyzed with respect to NTCP calculation; in this case, the individual lung DVHs were available. For each treatment technique, a mean DVH (i.e., the mean of the volume) for each dose step was calculated. For the NTCP calculation, the mean lung DVH was corrected for fractionation, using the same procedure as described above (22).

RESULTS

Of the 68 patients in the study, 20 developed radiation pneumonitis according to the above definition (group incidence 29%). The average appearance time of the symptoms was between 2 and 3 months after the completion of radiotherapy. Fisher's exact test showed no significant association between the incidence of radiation pneumonitis and chemotherapy (p-value of two-sided test = 0.23); neither was a significant association found between tamoxifen and lung complication (p-value of Pearson test = 0.085). The mean age of the patients at radiotherapy time in the com-

Table 2. Best fitting parameter values for the groups divided according to age

Parameters	Calculated value (68% confidence limits)	
	Below 57 years ($n = 33$)	Above 57 years ($n = 35$)
D_{50} dose giving 50% of complication probabilities (Gy)	40.6 (−5.4; +7.0)	26.9 (−2.6; +3.0)
γ maximum relative slope of the dose response curve	0.87 (−0.2; +0.4)	0.91 (−0.5; +0.5)
s-relative seriality factor	0.15 (at limit; +0.4)	0.006 (at limit; +0.2)

plication group was found to be 62 years, versus 56 years in the group without complication. A statistically significant positive association, although at the borderline, of radiation pneumonitis with age was found (Pearson test, $p = 0.048$; odd ratio [O.R.] = 3.0, 95% confidence interval [CI] 1.0–9.1). The higher risk for older patients still remained after adjustment for chemotherapy and tamoxifen, but was not statistically significant (O.R. = 2.6, 95% CI 0.8–8.2, $p = 0.12$).

Parameter determination

The optimum parameter values with the 68% confidence intervals are given in Table 1. The correlation coefficients from these calculations were 0.62 between D_{50} and γ, 0.96 between γ and s, and 0.7 between D_{50} and s. As described above, these calculations were performed by correcting each step of the DVH with the linear quadratic model and assuming an α/β value of 3 Gy. The sensitivity test performed by using an α/β value of 8 Gy in the fitting procedure provided parameter values very close to the ones obtained with α/β value of 3 Gy, showing that the present evaluation is not strongly dependent on the fractionation correction. The optimization did not show any dependence on the choice of the initial value of the parameters and on the parameter range chosen for the calculation.

The goodness of fit was determined as described in the previous section. The expected value of the log-likelihood function obtained from the patient's complication probabilities, calculated using the fitted parameters, resulted to be −39.63, with a variance of 12.44. The observed value of M for the fit was −39.88. By assuming a Gaussian distribution of M, these results indicate that the probability of having a worse fit was 48%.

The dose-response curves obtained with the optimum parameter set (Table 1) are given in Fig. 1a, where the curves are plotted for different values of the irradiation volume (Appendix B). A blow-up of the dose-response curve is shown in Fig. 1b, where the curves are plotted up to a complication probability of 30%, i.e., in the interval of the observed clinical complication. The large spread among the dose-response curves corresponding to whole and partial lung irradiations indicates that lung response to irradiation varies strongly with the irradiated volume. In other words, from a functional point of view, the lung shows a parallel architecture, mathematically expressed in the relative seriality model by the value of the parameter s, which is close to 0.

The 68% joint confidence region for D_{50} and γ, obtained by keeping the s-value at its optimum value, was calculated; the result is shown in Fig. 2. The bundle of dose-response curves calculated from the parameter values of the D_{50} and γ joint confidence region, and for whole volume irradiation, are depicted in Fig. 3. The parameter sets were chosen as the points defining the contour in Fig. 3. The choice of representing the bundle of dose-response curve from the D_{50}-γ joint confidence region was based on the consideration that a value of $s = 0.01$, indicating a possible parallel behavior of the lung from a functional point of view, was clinically realistic.

The mean differential and cumulative lung DVHs obtained with the five-field technique is depicted in Figs. 4a and b, showing that a relatively large volume receives a low dose with a peak at 4 Gy, while the volumes with a high dose have a peak at 48 Gy.

Based on the association between age and lung pneumonitis found in the present material, the patients were divided into two groups, according to the median age (57 years). The first group, below the median, consisted of 33 patients, 6 of them with diagnosed radiation pneumonitis. Of the 35 patients belonging to the second group (above the median), 14 had radiation pneumonitis. The two patient groups di-

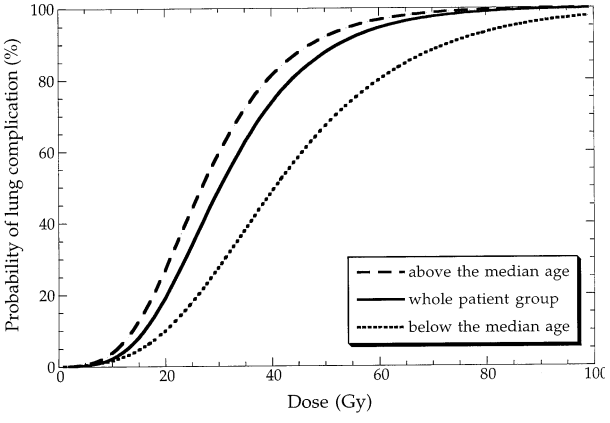

Fig. 5. Dose-response curves obtained by dividing the patients into two subgroups, according to the median age. The dashed line represents the group above the median age, the solid line represents the whole patient group, while the dotted line represents the group below the median age.

Table 3. Clinical incidence and calculated probability of lung complication

	No. patients	No. complications	Clinical incidence (%) (95% CI)	NTCP (%)
Group 1 (tangential fields)	109	2	1.83 (−0.69; +4.36)	0.5
Group 2 (photons, photons)	56	3	5.35 (−0.59; +11.3)	25.5
Group 3 (electrons, photons)	108	13	12.0 (−5.87; +18.2)	22.4
Group 4 (Söder Sjukhuset)	138	31	22.0 (+15.4; +29.4)	20.7
Group 5 (5 fields)	68	20	29.0 (+18.; +40.0)	32.9

vided according to age distribution were then separately modeled. The optimum parameter values obtained for the first group (i.e., for the group below the median age) were $D_{50} = 40$ Gy, $\gamma = 0.87$, $s = 0.15$; the parameter values for the second group (above the median age) were $D_{50} = 26.9$ Gy, $\gamma = 0.91$, $s = 0.006$, as shown in Table 2. The dose-response curves for the whole volume for the age subgroups are plotted in Fig. 5, together with the dose-response curve for the whole material; the first group of patients (i.e., below the median age) shows a higher response to irradiation compared to the patient group above the median age.

The NTCP calculations, based on the optimum parameter set, for the five patient groups are reported in Table 3, together with the observed clinical incidences. The predicted values fall within the 95% CI of the clinical incidence for Groups 1, 4, and 5; the main difference between clinical and predicted incidence was instead found for Group 2. The mean differential DVHs, representative of the mean dose distribution delivered with each treatment technique, are shown in Fig. 6.

DISCUSSION

The treatment described in the present study resulted in a large portion of lung volume irradiated, mainly due to the extension and to the irregular shape of the target. Although tumor control data from the present material are not yet available, the incidence of side effects on the lung in our dataset is high. This could, however, be more acceptable, considering the recent results on improved survival after breast cancer radiotherapy which may increase the threshold of acceptance of complication (25, 26).

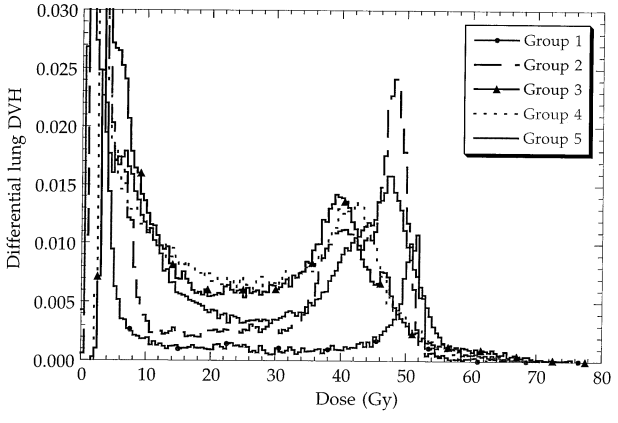

Fig. 6. Mean differential lung DVHs representing the five treatment techniques analyzed with the relative seriality model by using the optimum parameter set.

Radiation-induced lung injury, both early as radiation pneumonitis and late as radiation fibrosis, has been and is extensively investigated by several groups. However, the different structures of the underlying datasets (endpoint definition, assessment, dosimetric data available) and of the biophysical models used for the analysis make comparisons a complicated task. The lack of uniformity in the data modeling is partially explained by the fact that most studies, including the present one, are based on a retrospective assessment of the outcome. The quality and the amount of available information have thus become limiting factors in the definition of the endpoint and in its measure. Quantification of the dose distribution in the lung has often been approximative because of the absence of 3D dose planning. In addition, comparisons between single parameter values obtained from modeling different materials are questionable; the result of the minimization is a parameter set, combined with the uncertainties in the individual parameters, and should not be given as a single parameter value.

The quantification of the dose-response curve uncertainty as a function of the parameters uncertainties (see Fig. 3), as presented above, takes into account the contribution from a selected plane in the parameter space, not from the whole joint probability volume. Thus, it constitutes primarily a qualitative evaluation of the effect of including parameter uncertainties in the NTCP analysis, showing that the final result of the process is a dose-response curve within an interval. The inclusion of the uncertainties in the dose-response curve is important for the introduction of NTCP modeling in the clinical routine.

An important result of the present analysis is that age was found to be a factor associated with the expression of radiation pneumonitis. The impact of age on radiation-induced pulmonary complications has been previously considered in other studies, with varying results (9, 27). From the NTCP modeling point of view, the splitting of the study

Table 4. Clinical incidence and calculated probability of lung complication considering age

	Below 57 years (%)	Above 57 years (%)
	Clinical (95% CI) NTCP	Clinical (95% CI) NTCP
Group 4	13.2 (4–22) 13.0	30.6 (20–40) 29.0
Group 5	21.0 (7–35) 20.0	40.0 (23.5–56.4) 42.0

population into two groups according to the median age has produced two distinct sets of parameters. The clinical implications could be important; the size of our sample is, however, too limited to draw any further conclusion; other important risk factors, such as smoking and previous lung diseases, should be included in a more stringent analysis.

The NTCP predicted for the five patient groups (see Table 3) based on the optimum parameter set ($D_{50} = 30$ Gy, $\gamma = 0.97$, $s = 0.012$), show an agreement within the 95% CI between calculated and observed complication rate in three of the five cases. The main difference, which we have been unable to explain, was found for Group 2. However, due to the retrospective nature of the studies, the incidence figures can contain a bias. Age was a risk factor also for patients belonging to Group 4 (distributing the patient population in two groups above and below the age of 57 years, the O.R. was 2.9), but not for Group 3. In Groups 1 and 2, the incidence of radiation pneumonitis was too low to allow such an analysis. NTCPs were thus calculated also with the age-parameter sets for Groups 4 and 5 (see Table 4). The agreement between the observed clinical values and the predicted ones were very good in both cases.

The NTCP calculations used in the present paper are all based on lung DVHs, which were considered to be the most complete dosimetric information. The use of a scalar quantity, such as the mean dose, to quantify normal tissue response could, of course, simplify the calculation, but at the cost of losing much of the structure in the data (28, 29). The very inhomogeneous lung dose distribution in our dataset, due to the treatment technique and ultimately to the target definition, does not allow this kind of approximation which is valid in the hypothesis of small dose variation (30).

Our quantification of early lung response to irradiation was based on the hypothesis of a homogeneous radiosensitivity of the lung; this is an assumption that has been questioned in a set of prospective studies (31, 32), where data on mouse lung indicate that the lung is spatially heterogeneous in its sensitivity to irradiation. Irradiation seems to produce more severe injury in the base than in the apex of the lung, probably following the concentration of the alveoli (i.e., the structures dedicated to gas exchange). As a consequence of these results, not only dose and irradiated subvolume, but also the location of the subvolume, could become key factors in the NTCP modeling. On the basis of these observations, the dataset studied in the present analysis could be further analyzed also by using a model which takes into account the location of the different partial volumes irradiated; this will be deferred to future work, however.

We note that although the relative seriality model could describe our dataset, the present analysis cannot be considered as a validation of the model. It is also worthwhile to remember that the relative seriality model, as many other biophysical models used in NTCP calculation, is more phenomenological than mechanistic. In this sense, the dose-response curve obtained should not be considered as directly representative of lung radiobiology, but rather as a representation of a complex clinical situation, ultimately measured in terms of lung complication.

CONCLUSION

The present dataset, consisting of individual complication data and individual DVH for 68 patients irradiated for breast cancer, could be fitted by the relative seriality model. The dose-response curve obtained shows that the probability of inducing radiation pneumonitis after irradiation of the lung is largely volume dependent. The influence of the uncertainties in the parameter values on the dose-response curve, as quantified in a plane of the parameter space, was quite large. Age was found to be a risk factor; two separate dose-response curves were obtained by dividing the study population into two subgroups, below and above the median age of 57 years. The parameter set determined in the present analysis could be used predictively on three of five patient groups, of known radiation pneumonitis incidence, each group being associated to a specific treatment technique.

APPENDIX A

The relative seriality model

The model applied to the data was the relative seriality model (33). It assumes Poisson statistics to describe cell survival and the organization of the normal tissue in substructures responsible for the organ function. In this scheme, an organ where the substructures are organized in series (e.g., esophagus) becomes nonfunctional when one substructure is damaged, while for a parallel organ (e.g., lung), the probability of complication depends on the fraction of substructures damaged. The formal equations of the model are respectively

$$P(D) = 2^{-e^{e\gamma(1 - D/D_{50})}} \qquad \text{(Eq. 1)}$$

describing the response to a homogeneous dose distribution and

$$P = \left[1 - \prod_{1}^{n} [1 - P(D_i)^s]^{\Delta v_i} \right]^{1/s} \qquad \text{(Eq. 2)}$$

describing the tissue response to an arbitrary dose distribution.

The parameter D_{50} gives the 50% complication probability; the slope of the dose-response curve is given by the parameter γ. The functional architecture (relative seriality) of the organ is described by the parameter s, ranging between 0 and 1 (parallel and serial organization, respectively). The term n indicates the number of subvolumes in the calculation volume, as given by the DVH. Δv_i is defined as v_i/V; where v_i represents each subvolume in the DVH and V is the volume of the whole organ.

APPENDIX B

Dose-response curves were calculated using Eqs.1 and 2 with the optimum value of the parameters; it is assumed that a volume fraction V receives a homogeneous dose D, while the rest of the organ, 1-V, receives a dose equal to zero.

For this case, Eq. 2 yields:

$$NTCP(D) = \left(1 - (1 - P(0)^s)^{1 - dV} \cdot (1 - P(D)^s)^{dV}\right)^{1/s} \quad \text{(Eq. 3)}$$

with

$$P(D) = 2^{-exp(e\gamma(1 - D/D_{50}))} \quad \text{(Eq. 4)}$$

while P(0), obtained by Eq. 4 for D = 0, is:

$$P(0) = 2^{-e^{e\gamma}} \quad \text{(Eq. 5)}$$

Usually, the dose-response curve is calculated by assuming that the first term of the product in Eq. 3 is exactly equal to 1. This implies that $P(0)^s = 0$, which is an approximation for large values of γ and s (see Eq. 5). In the present study, however, due to the small values of γ and s, the full Eq. 3 was used to calculate the dose-response curves.

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