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Radiation Pneumonitis after Hypofractionated Radiotherapy: Evaluation of the LQ(L) model and different dose parameters

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Chapter 6

Abstract

**Purpose:** To evaluate the Linear Quadratic (LQ) model for hypofractionated radiotherapy (RT) within the context of predicting radiation pneumonitis (RP) and to investigate the effect if a linear model in the high region (LQL model) is used.

**Methods and Materials:** The radiation dose of 128 patients treated with hypofractionated RT was converted to the equivalent dose given in fractions of 2Gy for a range of $\alpha/\beta$ ratios (1Gy to infinity) according to the LQ(L) model. For the LQL model different cut off values between the LQ model and the linear component were used. The Lyman model parameters were fitted to the events of RP grade 2 or higher to derive the Normal Tissue Complication Probability (NTCP). The lung dose was calculated as the mean lung dose (MLD) and as percentages of lung volume receiving doses higher than a threshold dose $x$Gy ($V_x$).

**Results:** The best NTCP fit was found if the MLD or $V_x$ was calculated with an $\alpha/\beta$ ratio of 3 Gy. The NTCP fits of other $\alpha/\beta$ ratios and the LQL model were worse but within the 95%CI of the NTCP fit of the LQ model with an $\alpha/\beta$ ratio of 3 Gy. The $V_{50}$ NTCP fit was better compared to the NTCP fit of lower threshold doses.

**Conclusion:** For high fraction doses, the LQ model with an $\alpha/\beta$ ratio of 3 Gy was the best method for converting the physical lung dose to predict RP.
Radiation Pneumonitis after Hypofractionated RT: Evaluation of the LQ(L) model

Introduction

An increasing number of radiotherapy departments implement hypofractionated radiotherapy (RT) regimens for pulmonary malignant lesions, encouraged by reports of good tumor control and little toxicity. Consequently, clinical questions concerning the normal tissue tolerance dose, the possibility to include multiple targets or to irradiate larger lung volumes (e.g. applying multiple treatments or irradiation of larger tumors) are important.

For conventional fractionated radiotherapy the physical dose can be converted into a biological equivalent dose using the linear quadratic (LQ) model\[1,2\]. Historically, the strength of the LQ model for conventional fraction doses is twofold. First, it is a simple mathematical model fitting log cell survival data as function of the dose. Secondly, this model enables iso-effect calculations of fractionation schemes with different doses per fraction. However, already in 1954 Puck et al. observed that for the high dose regions the log cell survival was linear\[3\]. As a result, some modifications have been derived from NSCLC cell lines\[4\] and other tumor cell lines and animal iso-effect data\[5\]. In general, a non-linear part (LQ) in the low dose region and a linear (L) part for the high dose region differentiated by a transition dose ($d_t$) was proposed (i.e. LQL model)\[6\]. Since clinical data is lacking, the clinical iso-effect calculations by the LQ model at higher fraction doses remains uncertain as was comprehensively discussed previously\[7-11\]. Using the LQ model with an $\alpha/\beta$ ratio of 3Gy, it was observed that the normal tissue complication probability (NTCP) model predicting radiation pneumonitis (RP) after hypofractionated RT was not different compared to the NTCP model after conventional fractionated RT\[12\]. For conventional fractionated RT, the relation between lung dose and radiation pneumonitis (RP) is extensively evaluated (e.g.[13]). RP is a serious complication after irradiation, and also after hypofractionated schemes fatal RP toxicities are observed\[14\].

To evaluate the applicability of the LQ(L) model and normal tissue complication models for higher dose per fraction, we evaluated the prediction of RP after hypofractionated RT. Different $\alpha/\beta$ ratios and different $d_t$ values of the LQ(L) models were analyzed modeling the probability of RP after hypofractionated RT as function of the dose.

Material & Methods

Patients

Patients and treatment schedules were comprehensively described elsewhere\[12\]. In summary, 128 patients irradiated with hypofractionated RT at the Department of Radiation Medicine of the Hokkaido University School of Medicine, Sapporo, Japan, with 35 Gy in 4 fractions, 40 Gy in 4 fractions, 48 Gy in 8 fractions, 60 Gy
in 8 fractions and 48Gy in 4 fractions. Twenty patients had multiple targets in one treatment plan (18 patients had 2 targets, 2 patients had 3 targets). For 13 patients multiple treatment plans were made for different targets because of metastasis or recurrence (5 patients had 2 plans, 4 patients had 3 plans and 4 patients had 4 plans) (for time schedule, dose schedule and tolerated maximum dose for organs at risk see[12]).

Toxicity
Radiation pneumonitis (RP) was prospectively scored according to the NCI-CTC version 2, whereby grade 2 RP is scored after prescribing steroids for treatment related toxicity. Grade 3 RP is scored after requiring. None of the patients scored with RP grade 2 used steroids before. Radiation pneumonitis (RP) was prospectively scored according to the NCI-CTC version 2 whereby grade 2 RP is scored after prescribing steroids for treatment related toxicity, like progressive shortness of breath combined with typical RP changes on the X-thorax. Grade 3 RP is scored after requiring oxygen. None of the patients scored with RP grade 2 used steroids before radiotherapy. For all patients the diagnosis and grade of RP was determined by the radiation oncologist and a pulmonologist experienced in the diagnosis of RP. Patients whereby the diagnosis of RP was unlikely were not included (progressive cardiac problems, medical history of receiving oxygen before treatment, tumor progression).

Dose
Three dimensional (3-D) treatment plans were made using Focus (CMS, St Louis, MO), XiO (CMS) or Pinnacle. A convolution superposition algorithm for tissue density heterogeneity was used (plans initially planned with the Clarkson method were re-calculated). Normal lung tissue was defined in the CT scan by binary thresholding (thus excluding the gross tumor volume). Both lungs together were considered as one organ. Four to six non–coplanar beams were used. The beam energy was 4, 6 or 10MV. Plans were further analyzed with in-house developed software. The physical dose-distribution was converted into the Normalized Total Dose (NTD) distribution[15] using the linear quadratic (LQ) model. The NTD is defined as the equivalent total dose given in fractions of 2 Gy:

\[
\text{NTD} = \frac{D + \frac{\alpha}{\beta}}{2 + \frac{\alpha}{\beta}}
\]

whereby the total dose (D) is the number of fractions multiplied by the dose per fraction (d). The dose distributions were converted according to formula (1) for \( \frac{\alpha}{\beta} \) ratios of 1Gy, 2 Gy, 3 Gy, 4 Gy, 5 Gy, 7.5 Gy, 10 Gy and infinity (i.e. physical dose) to evaluate the effect of different \( \frac{\alpha}{\beta} \) ratios. After this conversion for the dose per fraction,
Radiation Pneumonitis after Hypofractionated RT: Evaluation of the LQ(L) model

we determined different dose-volume parameters from the dose volume histograms (DVHs): the mean lung dose (MLD) and the lung volume percentage receiving doses higher than 5 Gy(V_5), 13 Gy(V_{13}), 20 Gy(V_{20}), 40 Gy(V_{40}) and 50 Gy(V_{50}) or in general higher than x Gy(V_x). For the 33 patients irradiated on multiple lesions, individual plans were summed after NTD corrections and image registration had been performed. Time-related recovery of lung tissue was not taken into account for multiple treatments.

The dose response relation between RP and MLD was modelled by a sigmoid shaped dose effect relation according to Lyman\cite{16}. The normal tissue complication probability (NTCP) can be calculated from the MLD\cite{17} according to

\[ NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{\infty} e^{-\frac{x^2}{2}} \, dx \quad \text{with} \quad t = \frac{\text{MLD} - \text{TD}_{50}}{m \cdot \text{TD}_{50}} \quad (2) \]

whereby the TD_{50} represents the dose for a 50 % NTCP and m is the (inverse) steepness parameter in the standard formulation of the Lyman model. Similar for the V_x parameter, formula (2) was used with

\[ t = \frac{V_{x_{50}} - V_{50}}{m \cdot V_{50}} \quad \text{whereby} \quad V_{x_{50}} \text{represents the } V_x \text{ for a 50 % NTCP.} \]

Modification of the LQ model to the LQL model

We adapted the LQ model (LQL) by applying a two component model proposed by Park et al\cite{4} (Figure 1). For the low dose range, the total dose is corrected according to the LQ model using equation (1) according to the best \( \alpha/\beta \) ratio. For the high dose range, the log survival curve is assumed to be linear. The slope of the linear part is determined by the derivative of the LQ curve at the cut off value between the linear-quadratic part and the linear part (i.e. the transition dose \( d_T \)) (Figure 1 and Appendix) resulting in

\[ \text{NTD} = D \frac{\alpha/\beta + 2d_T - d_T^2}{2 + \alpha/\beta} \quad (3) \]

In contrast to the literature, we propose to use the denotation of a lower case letter (\( d_t \)) because this transition dose refers to the dose per fraction correction.
Chapter 6

We converted the dose distributions for \( d_T \) values of 0 Gy, 5 Gy, 7 Gy and 9 Gy and subsequently calculated the MLD (not the \( V_x \)) from these dose distributions (i.e. MLD\(_{LQL}\)).

Statistics

The TD\(_{50}\) and \( m \) were estimated by maximizing the logarithm of the likelihood function [17]

\[
\ln(L) = \ln \left( \prod_{i=1}^{N} L_i \right) = \sum_{i=1}^{N} \left[ e_p \ln(P_i) + (1-e_p) \ln(1-P_i) \right] \tag{4}
\]

where \( P_i \) (\( i = 1, \ldots, N \)) represents the predicted NTCP and \( e_p \) is the observed binary outcome (0=RP \( \leq \) grade 1, 1=RP \( \geq \) grade 2) for patient \( i \). The confidence intervals (CI) of the fitted parameters were calculated using the profile likelihood method [18]. These CI were calculated by finding the points in the parameter space where the \( \ln(L) \) values are \( \Delta \ln(L) \) lower than \( \ln(L_{\text{max}}) \) (e.g. for the 95%CI the value of \( \Delta \ln(L) \) is 1.92 corresponding to half of the 95% percentile of the cumulative chi-square value for one degree of freedom).

In order to evaluate which \( \alpha/\beta \) ratio would give the maximum likelihood estimation, a profile likelihood approach of the best NTCP fit was performed according to \( \alpha/\beta \) ratios in the range of 1 Gy up to infinity. This analysis was only performed for the MLD (i.e. the corrected mean lung dose (MLD\(_{LQL}\)).

Converting the dose according to the LQL model, we used an \( \alpha/\beta \) ratio of 3 Gy. The LQ and the LQL model are nested since the 3-parameter (TD\(_{50}\), \( m \) and \( d_T \)) MLD\(_{LQL}\) model reduces to the 2-parameter (TD\(_{50}\), \( m \)) MLD\(_{LQ}\) model when \( d_T \) goes to infinity (or at least becomes higher than the highest dose per fraction value in the data set) (see Figure 1). According to the LQL model, the doses were converted with \( d_T \) values of 0, 5, 7 and 9 Gy. The NTCP model fit using the MLD\(_{LQL}\) was compared to the NTCP model fit with the MLD\(_{LQ}\) using the maximum likelihood ratio test since the 2 models were nested [19]. For this analysis this requires that twice the difference of

![Figure 2](image-url)
Radiation Pneumonitis after Hypofractionated RT: Evaluation of the LQ(L) model

the log likelihoods between the two models should be larger than the quantile of a chi-square distribution with one degree of freedom (i.e. $3.84/2$) to be significantly different. For regression analysis, the slope of the linear regression ($s$) with a zero intercept was used to assess the relation between different parameters. A two-tailed p<0.05 was considered to be statistically significant.

Results

The crude incidence of RP was 10.9% (14 events in the group of 128 patients). One patient was observed with grade 3 RP, all other patients were diagnosed with grade 2 RP.

MLD corrected for different $\alpha/\beta$ ratios

The relationships between the MLD calculated with an $\alpha/\beta$ ratio of infinity (MLD$_{\text{phys}}$) and of 1Gy(MLD$_1$), 3Gy(MLD$_3$) and 10Gy(MLD$_{10}$) are illustrated in Figure 2. The MLD$_{\text{LQ}}$ calculated with a low $\alpha/\beta$ ratio is higher than the MLD$_{\text{LQ}}$ calculated with a higher $\alpha/\beta$ ratio, as expected. A linear fit of the data (with zero intercept) resulted in the following relations and correlations; MLD$_1$=1.83xMLD$_{\text{phys}}$ ($r^2 = 0.74$), MLD$_3$=1.50xMLD$_{\text{phys}}$ ($r^2 = 0.84$) and MLD$_{10}$=1.21xMLD$_{\text{phys}}$ ($r^2 = 0.95$), respectively. Two patients were located under the equality line. These two patients were also irradiated at a target in the mediastinum with a more fractionated scheme whereby the high dose region in the lung tissue received less than 2Gy.

To evaluate the effect of the dose per fraction, the MLD$_1$ and the MLD$_3$ were plotted as a function of the MLD$_{\text{phys}}$ (Figure 3) for each dose per fraction separately for patients irradiated on one single target. Because only 3 patients received 35 Gy/4fr,
these patients were excluded. As expected, the slopes of the linear regression of the higher dose per fraction schedules (10 Gy and 12 Gy per fraction) were higher than for the lower dose per fraction schedules (6 Gy and 7.5 Gy per fraction). In addition, the slope for the $\alpha/\beta = 1$ Gy was higher than the slope for the $\alpha/\beta = 3$ Gy for each dose per fraction. All correlations were significant with $p<0.001$.

The MLD calculated according to the LQL model (MLD$_{LQL}$) with a $d_T$ of 5 Gy is shown as a function of the MLD$_3$ in Figure 4. For patients with a high MLD$_3$ and irradiated with a high dose per fraction, larger differences between the MLD$_3$ and MLD$_{LQL}$ were observed than for other patients (Figure 4).

$NTCP$ for different $\alpha/\beta$ ratios and the $LQL$ and $V_x$ models

Optimizing the LQ NTCP model as a function of the $m$, $TD_{50}$ and $\alpha/\beta$ ratio, revealed that the highest maximum log likelihood was found at an $\alpha/\beta$ ratio of 3 Gy (with $TD_{50}=20.8$ Gy and $m=0.45$). All other evaluated $\alpha/\beta$ ratios had lower maximum log likelihoods (Figure 5) but were within the 95% CI of the NTCP fit with an $\alpha/\beta$ ratio of 3 Gy. The largest difference was found between the NTCP fit with an $\alpha/\beta$ ratio of 3 Gy and the NTCP fit with an $\alpha/\beta$ ratio of infinity (i.e. physical dose) (with $TD_{50}=14.6$ Gy and $m=0.48$) but this was not significant ($p=0.07$) (Figure 6).

Evaluating the NTCP model according to the LQL model with $d_T=5$ Gy, the maximum log likelihood was lower than the MLD$_3$ NTCP LQ model fit. The LQL model fit...
Radiation Pneumonitis after Hypofractionated RT: Evaluation of the LQ(L) model

NTCP fit parameters TD_50 of 19.5Gy and m=0.46 were not significantly different from the LQ fit parameters (p=0.28). The NTCP model according to the LQL model with d_T=7Gy and d_T=9Gy was approaching the MLD, NTCP LQ model fit as expected, because only a limited part of the distribution of doses per fraction was larger than these d_T values. The NTCP according to the LQL model with d_T=0Gy was as expected similar to the MLD_phys NTCP LQ model fit. For the V_x (calculated with the LQ model with an α/β ratio of 3Gy), the maximum likelihood profile approach revealed that the highest likelihood (i.e. best fit) is achieved with a threshold dose of 50Gy. The V_50 calculated with the LQL model had lower log likelihoods (worse fits) although these differences were not significant (p=0.16 for d_T=5Gy and p=0.21 for d_T=7Gy). For all other V_x values similar results were observed (data not shown). The V_5, V_13 and V_20 were outside the 95%CI of the V_50 (Table 1). Because one patient had 0% of the lung volume receiving doses higher than 60Gy (corrected for an α/β ratio of 3Gy) we did not evaluate V_x values higher than 50Gy.

Table 1.

<table>
<thead>
<tr>
<th>V_5</th>
<th>V_50 (%)</th>
<th>m</th>
<th>Maximum log likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>65.4</td>
<td>(49.0 - 121.0)</td>
<td>0.46</td>
<td>(0.34 - 0.66)</td>
</tr>
<tr>
<td>39.2</td>
<td>(30.0 - 77.0)</td>
<td>0.48</td>
<td>(0.36 - 0.67)</td>
</tr>
<tr>
<td>30.6</td>
<td>(23.0 - 57.0)</td>
<td>0.50</td>
<td>(0.37 - 0.68)</td>
</tr>
<tr>
<td>15.9</td>
<td>(13.0 - 27.0)</td>
<td>0.48</td>
<td>(0.37 - 0.65)</td>
</tr>
<tr>
<td>13.1</td>
<td>(11.0 - 21.0)</td>
<td>0.48</td>
<td>(0.37 - 0.65)</td>
</tr>
</tbody>
</table>

The TD50, V_5, and m optimized with the 95% confidence intervals for the general parallel model (with optimized D50 (i.e. D50 = ∞ Gy) and k (i.e. k = 1.3)), MLD, V_5, V_13, V_20, and V_40. Maximum log likelihood and the p-value of the NTCP models compared to the reference model are given. Note that the upper bound of 95% CI of the V_x exceeds the 100% lung volume due to the approximation in the statistical method applied whereas in mathematical and clinical terms the upper limit is 100%.

Discussion

Our results showed that the NTD corrected MLD_LQ, calculated with an α/β ratio of 3Gy was the best parameter to fit the NTCP model to the observed incidence of RP after hypofractionated RT. These data suggest that a correction for the dose per fraction after hypofractionated radiotherapy should be performed similar to conventional fractionated schemes (i.e. LQ model and an α/β ratio of 3Gy (e.g.[20])). Other tested α/β ratios, or a modification of the LQ model (by introducing a linear relation after a threshold dose d_T of 5 Gy or higher) deteriorated the predictive value of the lung dose but were within the 95% CI of the NTCP LQ model fit with an α/β ratio of 3Gy. The not significant differences in the NTCP fits might be explained by the strong correlations between the corrected dose parameters.

Since the dose per fraction in hypofractionated RT is considerably larger than 2 Gy, a substantial volume of lung tissue received more than 2 Gy per fraction. Because
the MLD\textsubscript{LQ} is expressed as 2 Gy equivalents, the MLD\textsubscript{LQ} is therefore expected to be larger than the MLD\textsubscript{phys}. Evaluating different $\alpha/\beta$ ratios resulted in different relations between the MLD\textsubscript{LQ} and the MLD\textsubscript{phys}. By nature of the LQ model, for lower $\alpha/\beta$ ratios and higher fraction doses the difference between the MLD\textsubscript{LQ} and MLD\textsubscript{phys} increased, and for higher $\alpha/\beta$ ratios the MLD\textsubscript{LQ} approached the MLD\textsubscript{phys}. Because of the strong correlation between the MLD\textsubscript{LQ} and the MLD\textsubscript{phys}, it might be questioned whether the physical dose can be used to estimate complication probabilities. However, our results confirm that also after hypofractionation the physical dose should not be used for calculation of toxicity probabilities. By calculating the MLD, the local dose in the lungs is weighted according to a linear local dose-effect relation. In contrast, for the $V_x$, the local dose-effect relation is considered as a binary effect whereby no damage is taken into account below the threshold dose of $x$Gy and a full damage above the threshold dose of $x$Gy. Different dose volume parameters and their mutual relations have not previously been evaluated for hypofractionated RT. Since the dose effect relation expressed by the MLD and $V_x$ are based on different parameters (i.e. models are not nested), a direct comparison of the NTCP fits via a log likelihood ratio approach is not possible. Including these parameters (MLD, $V_5$, $V_{13}$, $V_{20}$, and $V_{40}$) in a multivariate logistic regression analysis revealed that only the MLD was significantly associated.

Figure 6. a: The NTCP fit (solid line) as function of the MLD calculated according to the LQ model and an $\alpha/\beta$ ratio of 3 Gy with the 68% CI (dotted lines) (TD50=20.8Gy, m=0.45). The number of events and number of patients are indicated. b: The NTCP fit (solid line) as function of the physical MLD (i.e. LQ model and an $\alpha/\beta$ ratio of infinity) with the 68% CI (dotted lines) (TD50=14.6Gy, m=0.48). The number of events and number of patients are indicated.
Radiation Pneumonitis after Hypofractionated RT: Evaluation of the LQ(L) model

with RP (data not shown). However, these data should be interpreted with caution since it is known from studies with conventional fractionated RT evaluating clinical and dose factors predicting RP that there is a large heterogeneity of results[21-32] whereby no validation was performed. One collaborative study from the Duke University and the Netherlands Cancer Institute developed a prospective method to predict radiation pneumonitis from dose and clinical parameters in one group of patients but validation failed in another group of patients [33].

The validity of the LQ model for both clonogenic cell survival as clinical isodose calculations for higher dose per fraction was discussed previously; Hall and Brenner[11] estimated from the iso-effect data of van der Kogel[34] (late-responding damage to the rat spinal cord) and Douglas and Fowler[35] (acute damage to the mouse skin) that the LQ model would be valid for single doses up to 20Gy. According to this estimation, Fowler et al.[9] extrapolated the relation between RP and MLD, as determined for conventional treated patients, to hypofractionated schemes. Unfortunately, clinical data was lacking to validate such an extrapolation. Concerning RP (or other clinical toxicity endpoints), it might be questioned whether the applicability of the LQ model for these fraction doses can be answered by clinical studies. For example, the high number of (non-coplanar) beams results in an irradiation dose to healthy (lung) tissue that will be much smaller than the maximum dose. In addition, the relative volume of healthy tissue receiving such a high dose is limited by current advanced radiotherapy techniques (e.g. IMRT and IGRT). Moreover, the purpose of these techniques is to avoid high doses in normal tissues.

Guerrero et al[5] developed a modification of the LQ model by extending the LQ model with a protraction factor, based on the Lethal-Potentially Lethal (LPL) model which is supposed to be superior describing log cell survival data in the higher dose region[36]. This modification was based on cell survival and animal toxicity data. They observed a wide range of dose values where the LQ started to deviate from the LPL model (cell lines 0.6 Gy to 37.7 Gy, animal toxicity data 2.6 Gy to 100 Gy). It was shown that this modification results in a LQ model with a linear extension of the log cell survival as function of the dose for the high dose range by Carlone et al[6] and they proposed to name this model the linear-quadratic-linear (LQL) model.

Elaborating this discussion in the clinical setting, we evaluated the LQL model with clinical data using a more simple but similar method proposed by Park et al[4] using a linear extension of the log cell survival as function of the dose for doses higher than a threshold (i.e. transition dose \( d_T \)). For a \( d_T \) of 5 Gy we observed a (non-significant) worse NTCP fit. For higher \( d_T \) values the LQL NTCP fit approached to the LQ NTCP fit; the differences between the MLD_{LQL} and MLD_{LQ} are becoming smaller because less lung tissue dose will be recalculated according to the linear part of the LQL model (dose larger than the \( d_T \)). Lastly, if the \( d_T \) is larger than the largest fraction
Chapter 6

doses the LMDLQL equals the LMDLQ. Another mathematical model to describe the cellular response as a function of the irradiation dose is the Linear Quadratic Cubic (LQC)[37] model whereby the cubic term is negative. This LQC model has also a (more) linear response in the high dose region approximating the LPL model. As the LQL model, the LQC model is mathematically more simple compared to the LPL model with only one additional parameter (as in the LQL model).

At the NKI (and many other institutes) the hypofractionated schedule that is mainly given is 3 x 18 Gy. Unfortunately, the patients treated at the NKI could not be included in the current analysis. The first reason for this is the limited follow up of a substantial part of these patients. Secondly, the patients with sufficient follow up (>1 year) had only lung doses in the lower MLD range resulting in low incidences of RP. Consequently, these patients cannot be of additional value for this type of analysis. However, the relation between the LMDLQL as a function of the LMDLQ for higher transition doses than used in current analysis could be evaluated. As illustrated in Figure 7, only a dT of about 10 Gy or lower results in a difference between the LMDLQL and the LMDLQ. Introduction of a higher dT would lead to imperceptible differences between the LMDLQ and LMDLQL. Consequently, it might be questioned whether a higher dT can be clinically evaluated with respect to RP in the future due to limited amount of lung tissue receiving high doses. Irradiation of healthy lung tissue of animals with increasing fraction sizes, which could be possible in the future with advances in preclinical irradiation techniques, might facilitate resolving this issue.

We evaluated the LQL model, using an α/β ratio of 3 Gy which did not improve the NTCP fit to the data. Although the slope of the linear component is dependent of both the dT and the α/β ratio, we did not analyse the LQL model with other α/β values. The first reason for this is that evaluations of the LQL model with α/β ratios close to 3Gy would not affect the NTCP fit significantly according to current data. Secondly, for (much) higher α/β values the LQL model approaches the LQ model (for α/β equal to infinity the LQL and LQ model both are becoming the L (linear) model). Thirdly, for lung tissue an α/β value of 3-4 Gy is an accepted value converting doses in the lower dose range[38-42].

Predictive models based on clinical data are as good as the clinical data. Consequently, the limitations of this study should be stressed. We discussed the clinical limitations of our study comprehensible previously[12]. First, the study was a retrospective univariate analysis evaluating RP grade≥2. Secondly, although the assessment of RP was carefully performed, the prescription of steroids and oxygen is relying on the intention to treat of the physician. Thirdly, only one grade 3 RP was scored and the duration of the RP grade 2 treatment was not registered. Therefore, no dose response analysis could be performed regarding the severity of the radiation induced toxicity. Another discussion point is whether the time interval between the subsequent
Radiation Pneumonitis after Hypofractionated RT: Evaluation of the LQ(L) model

treatments should be taken into account. As discussed previously[12], we did not consider any repair between the treatments. A mouse study suggested that for higher doses per fraction less recovery might be expected[43]. Moreover, limited clinical data showed that patients are experiencing a high probability of RP after re-irradiation[44].

Besides the reliability of NTCP modeling on the robustness of the clinical data, some assumptions have to be made for (NTCP) modeling in general. First, a NTCP model based on one (dose) characteristic disregard all other factors influencing the probability to develop toxicity (e.g. genetic variability and/or comorbidity) for one individual patient. Secondly, to evaluate clinically applicable dose parameters, DVHs are reduced to simple parameters (e.g. MLD and Vx) whereby a (biological) background is assumed but questionable. Thirdly, the limited number of patients included in the current study might have caused that a real intrinsic difference between these parameters was not apparent with statistical significance.

In conclusion, with our study we provide clinical toxicity data for the discussion of the applicability of current radiobiological models for higher doses per fraction. We observed that the LQ model was valid (with an $\alpha/\beta$ ratio of 3 Gy for lung tissue) to recalculate the physical dose into biological equivalent dose and that the biological dose should be used for estimating toxicity probabilities. The LQL model did not improve the prediction of RP. This might be due to the limitations of our study and/or to (still) unknown fundamental mechanisms complicating the translation of mathematical models developed with cell survival data into clinical data. With currently used fraction doses of up to 18 Gy, substantially different results are not expected, but this should be confirmed in future evaluations.

Figure 7. For patients treated at the NKI-AVL, the $MLD_{LQL}$ is plotted as a function of $MLD_3$ for $dT$ of 5 Gy (closed diamonds), $dT$ of 10 Gy (open triangles) and $dT$ of 15 Gy (crosses). The straight line with a slope 1 represents the equivalent line where $MLD_{LQL}$ equals $MLD_3$. 
Chapter 6

References


Radiation Pneumonitis after Hypofractionated RT: Evaluation of the LQ(L) model

Chapter 6


