Radiotherapy for lung cancer
Borst, G.R.

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Radiation pneumonitis for patients treated for malignant pulmonary lesions with stereotactic body radiation therapy

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Radiotherapy & Oncology
Abstract

Purpose: We evaluated the relationship between the mean lung dose (MLD) and the incidence of radiation pneumonitis (RP) after SBRT and compared this with conventional fractionated radiation therapy (CFRT).

Material and Methods: For both SBRT (n=128) and CFRT (n=142) patients, RP grade ≥ 2 was scored. Toxicity models predicting the probability of RP as a function of the MLD were fitted using maximum log likelihood analysis. The MLD was NTD (Normalized Total Dose) corrected using an α/β ratio of 3 Gy.

Results: SBRT patients were treated with 6 Gy to 12Gy per fraction with a median MLD of 6.4 Gy (range:1.5 Gy to 26.5 Gy). CFRT patients were treated with 2 Gy or 2.25Gy per fraction, the median MLD was 13.2Gy (range:3.0Gy to 23.0 Gy). The crude incidence rates of RP were 10.9% and 17.6% for the SBRT and CFRT patients, respectively. A significant dose-response relationship for RP was found after SBRT that was not significantly different from the dose-response relationship for CFRT (p=0.18).

Conclusion: We derived from clinical data a significant dose-response relationship between the risk of RP and the MLD for SBRT. This relation was not significantly different from the dose-response relation for CFRT although statistical analysis was hampered by the low number of patients in the high dose range.
Introduction
Stereotactic body radiation therapy (SBRT) for pulmonary lesions is becoming more widely used following the first clinical experiences described by Blomgren et al. in 1995 [1]. Collaboration of Japanese radiation departments resulted in the publication of encouraging outcomes among stage I lung cancer patients after SBRT [2,3]. In addition, SBRT proved to be an effective treatment for metastases in lung and liver with high tumour control rates being achieved [4,5]. With respect to healthy tissue injury, Timmerman et al. [6] observed a significantly higher toxicity for centrally located tumours compared to peripherally located tumours using similar irradiation schedules. In an analysis of Lagerwaard et al. [7], lowering the fraction dose for centrally located tumours resulted in similar toxicity for central and peripheral tumours. A recent review of Brock et al. [8] evaluating SBRT studies showed limited toxicity whereas between these studies a large heterogeneity of treatment techniques, dose parameters and clinical endpoints is observed. To extend the applicability of SBRT, knowledge of the dose-toxicity relationship is necessary. However, dose response evaluations are hampered by the restricted dose range and (consequently) the low number of toxicity events following SBRT. Moreover, the influence of larger fraction dose, shorter overall treatment time and differences in dose distribution on existing radiobiological models is rather unknown. In addition, patients receiving pulmonary SBRT are a select group of patients with a high comorbidity.
Radiation pneumonitis (RP) is a serious complication which was fatal after SBRT in 3 of the 25 patients in a recent study of Yamashita et al [9] after 48Gy in 4 fractions. The incidence of RP requiring clinical intervention ranges from 0% to 29% after SBRT [9-14]. Unfortunately, no predictive model to assess the probability of RP is available for SBRT.
The goal of our study was to evaluate the relation between the radiation dose and the occurrence of RP after SBRT. In addition, since for CFRT the relation between lung dose and radiation pneumonitis (RP) is extensively evaluated (e.g. [15]), we compared the dose relationship of SBRT and CFRT patients.

Material & Methods
Patients
SBRT patients were irradiated with hypofractionated schedules at the Department of Radiation Medicine of the Hokkaido University School of Medicine, Sapporo, Japan. Clinical data and treatment plans were retrievable for 128 patients, treated between April 1998 and December 2005. Follow up was performed at the outpatient clinic of the Department of Radiation Medicine. Irradiation regimens were 35 Gy in 4 fractions, 40 Gy in 4 fractions, 48 Gy in 8 fractions, 60 Gy in 8 fractions and 48 Gy in 4 fractions. A subgroup of these patients with a schedule of 40 Gy and 48 Gy in
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4 fractions (n = 41) was previously described in a tumour dose-response study [16]. The approach to define appropriate doses and margins for the SBRT patients can be described as a continuous reassessment approach which was dependent on tumour control and toxicity. This has been accurately described previously [16]. Patients with a schedule of 35 Gy in 4 fractions, 48 Gy and 60 Gy in 8 fractions (irradiated before 2000) and patients treated for multiple targets were treated in a similar manner. Ninety-five SBRT patients were irradiated on one single target. The treatment schedule, diagnosis of RP and the MLD of these patients are given in Table 1. Thirty-three patients received irradiations on multiple targets. For 20 patients, the initial radiation treatment consisted of multiple targets that were successively treated (Table 2). For 13 patients a new treatment plan was made some time after the initial treatment because of additional pulmonary lesions (Table 3). No time-related recovery of lung tissue was taken into account for these 13 patients. These 33 patients received an individually adapted (i.e. restricted) dose schedule. For all plans (and summed plans in case of re-irradiations) a maximum dose of 46 Gy and 60 Gy (recalculated into 2 Gy per fraction with an $\alpha/\beta$ ratio of 2 Gy) for the spinal cord and oesophagus, respectively was allowed. A total dose of 60 Gy/8 fr or equivalent dose calculated using LQ model with an $\alpha/\beta$ ratio = 2 Gy was allowed as maximum dose in the lung.

Patients with a conventional dose per fraction (CFRT) schedule were treated at the Department of Radiation Oncology of the Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital (NKI-AVL), Amsterdam, The Netherlands. We updated our previous analysis (with 106 patients) by Seppenwoolde [17] to a total of 142
Radiation pneumonitis for Patients Treated for Malignant Pulmonary Lesions with SBRT

Table 2. Treatment schedule, number of irradiated targets, diagnosis of RP and the MLD of SBRT patients with multiple targets incorporated in one single treatment plan.

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Table 3. Treatment schedule, time between subsequent treatments, diagnosis of RP and the MLD of SBRT patients with multiple targets incorporated in different treatment plans.

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patients. Our update included 86 patients of the dose escalation (DE) study of Belderbos et al [17] (with 88 patients). For 2 patients included in this study dose data were lost. Of the 58 non-DE patients included in the Seppenwoolde study, we excluded 2 patients, of which the treatment was interrupted and not finished. Therefore, we were able to include 86 patients of the DE study (who were irradiated to a dose of 60.8 and 94.5 Gy with 2.25 Gy per fraction) and 56 patients who were irradiated with a dose of 70 Gy in 2 Gy per fraction.)
For both SBRT and CFRT patients, three dimensional (3-D) treatment plans were made. To correct for the effect of dose per fraction, the local dose was converted to the 2 Gy equivalent Normalized Total Dose (NTD) [18] using the linear quadratic (LQ) model [19] with an $\alpha/\beta$ ratio of 3 Gy. The $\alpha/\beta$ ratio of 3 Gy was used because a detailed analysis (see companion paper [20]) revealed that for SBRT this was the best value to correct for the dose per fraction evaluating RP. For the 33 SBRT patients irradiated on multiple lesions, individual plans were summed after NTD corrections and image registration had been performed. From the 3-D dose data, the MLD was calculated as the average corrected dose over the total lung volume (based on CT) excluding the gross tumour volume.

For the SBRT plans, a convolution superposition algorithm for tissue density heterogeneity was used. For the CFRT patients the inhomogeneity correction was performed using the equivalent-path length inhomogeneity-correction (EPL). The MLD$_{EPL}$ was converted to the MLD according to convolution superposition algorithm using the conversion factor determined by De Jaeger et al. (MLD = 0.64(MLD$_{EPL}$)$^{1.10}$) [21].

The dose response relationship in the lungs between RP and MLD was modelled by a sigmoid-shaped relation according to Lyman [22] using the TD$_{50}$ representing the dose for a 50 % complication probability. The slope of the dose response relationship is proportional to the reciprocal value of m·TD$_{50}$. Using this model and parameter values, the normal tissue complication probability (NTCP) (i.e. RP) can be calculated from the MLD [23].

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

Radiation pneumonitis (RP) was prospectively scored for both SBRT and CFRT patients and classified according to the NCI-CTC (CTC 2.0) or SWOG criteria. Grade 2 RP was scored for both SBRT and CFRT after steroids had been prescribed for RP symptoms. Grade 3 RP was scored after oxygen was required and grade 4 for assisted ventilation. Grade 5 was scored after death due to RP.

None of the included SBRT patients that were scored with RP grade 2 used steroids for other pulmonary morbidities than RP before or after the irradiation. For the CFRT patients, information on pre-treatment use of steroids was not available. For all patients the diagnosis and grade of RP was determined by the radiation oncologist and a pulmonologist experienced in the diagnosis of RP.

Statistics

By maximizing the logarithm of the likelihood function of a dataset containing N patients where $P_i$ (i=1, ..., N) represents the NTCP of a patient i, and ep$_i$ is the binary outcome (0=no RP, 1=RP), the parameters TD$_{50}$ and m of the NTCP model
Radiation pneumonitis for Patients Treated for Malignant Pulmonary Lesions with SBRT were estimated.

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

95% confidence intervals around m and TD$_{50}$ were calculated using a profile likelihood approach [22]. For each parameter, the confidence interval includes a certain value if twice the difference of the log likelihood evaluated at the maximum likelihood estimate and at the value of interest do not exceed the quantile of a chi-square ($X^2$) distribution with one degree of freedom [24]. To determine the confidence interval of the NTCP curve, a similar approach was performed, however, this test was performed with two degrees of freedom.

To test the difference between the fitted NTCP model of SBRT and CFRT the data of both models was pooled. The NTCP model based on the pooled data (i.e. one TD$_{50}$ and one m) was compared to the NTCP model whereby the data set-specific optimized parameters of SBRT and CFRT were included in a 2 degree of freedom likelihood ratio test [22]. We also compared the empirical incidence of RP across data sets for several non-overlapping dose intervals using Fisher’s exact test.

The Hosmer-Lemeshow Goodness-of-Fit Test [25] was used to estimate the goodness of the fit of the fitted NTCP model. Patients were divided into 10 equal bins in increasing order of the estimated NTCP. The chi square test statistic was calculated by

\[
\chi^2_{RT} = \sum_{i=1}^{10} \frac{(O_i - N_i \cdot NTCP_i)^2}{N_i \cdot NTCP_i \cdot (1 - NTCP_i)}
\]

where $N_i$ is the total number of patients in the $i^{th}$ group, $O_i$ is the total number of events in the $i^{th}$ group, and NTCP$_i$ is the mean calculated NTCP in the $i^{th}$ group. The test statistic is compared to chi square distribution with 8 degrees of freedom (by definition of the Hosmer-Lemeshow goodness of the fit test). The null hypothesis is that there is no difference between the observed and expected values of RP. (i.e. large values of chi square( and small p values) indicate a lack of fit by the model). A two-tailed $p < 0.05$ was considered to be statistically significant.

Results

Radiation Pneumonitis

Median follow up was 16.1 months for the SBRT patients and 13.0 months for the CFRT patients. All 39 events occurred within 6.2 months following treatment for both SBRT and CFRT within a similar time frame. Within this period 4 SBRT and 18 CFRT patients were censored (Figure 1).

For the SBRT the crude incidence of RP grade 2 or higher was 10.9% (14 events in the group of 128 patients). Only 1 SBRT patient was diagnosed with grade
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3 RP. Three SBRT patients included in the analysis, received oxygen within the first year after irradiation and were not scored as having RP because of the uncertainty of diagnosis (one patient had cardiac problems, one patient had a medical history of receiving oxygen before treatment and one patient had fibrosis and tumour progression). For CFRT the crude incidence of RP was 17.6 % (25 events in the group of 142 patients). Four CFRT patients experienced a grade 3 RP and one patient died due to pulmonary toxicity (grade 5 RP).

Tumour volume and Mean Lung Dose
The median MLD for SBRT was 6.4 Gy (range: 1.5 Gy to 26.5 Gy). The median tumour volume of the SBRT patients was 9.6 cm³ (range: 0.2 cm³ to 106.9 cm³). For CFRT patients, the median MLD was 13.2 Gy (range: 3.0 Gy to 23.0 Gy) and the median tumour volume was 61.2 cm³ (range: 3.8 cm³ to 789.9 cm³).

Normal Tissue Complication Probability
SBRT
For SBRT the observed incidence of RP as a function of the MLD is plotted in Figure 2a. The error bars represent the 68% confidence interval (CI) of the observed incidence in 4 Gy dose bins. The observed number of RP and the total number of patients within each dose bin are indicated. The solid line represents the best fit of the NTCP model based on the MLD. The best parameter values of the NTCP model were TD$_{50}$ = 19.6 Gy (95%CI: 16.0 Gy to 30.0 Gy) and m=0.43 (95%CI: 0.33 to 0.59). The dashed lines represent the 68% CI of the fitted curve.

CFRT
For the CFRT the observed incidence of RP as a function of the MLD is plotted in Figure 2b. The optimal fit of the NTCP model using MLD resulted in a TD$_{50}$ of 28.6 Gy (95%CI: 21.5 Gy to 125.0 Gy) and an m value of 0.56 (95%CI: 0.39 to 0.99).
Radiation pneumonitis for Patients Treated for Malignant Pulmonary Lesions with SBRT

SBRT versus CFRT
Both the SBRT model and the CFRT model fitted the clinical data well ($X^2_{HL}$=8.27, $p=0.41$ and $X^2_{HL}$=4.36, $p=0.82$, respectively).
A comparison of the dose-specific observed RP incidence between SBRT and CFRT revealed that there was no significant difference for any of the 6 dose ranges covering 4 Gy each. However, RP occurred more frequently in the 2 highest dose ranges for SBRT compared to CFRT but this difference was not significant (Table 4). Importantly, lower numbers of patients were included in the higher dose ranges for both SBRT and CFRT limiting the power of statistical comparison of these particular high dose groups.
Evaluating the whole dose range, the NTCP curve of SBRT is steeper for the high dose range suggesting an increased risk for RP after SBRT compared to CFRT for patients with a higher MLD. However, there was no statistical evidence that the fitted NTCP model (with the parameters

Table 4. Incidence of RP by MLD range and treatment type (SBRT, CFRT).

<table>
<thead>
<tr>
<th>Dose bin (Gy)</th>
<th>SBRT Number of RP events / total number of patients</th>
<th>CFRT Number of RP events / total number of patients</th>
<th>$p$-value Fisher’s exact test</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 4</td>
<td>0/23 (0%)</td>
<td>0/3 (0%)</td>
<td>0.99</td>
</tr>
<tr>
<td>4 - 8</td>
<td>4/60 (7%)</td>
<td>3/22 (14%)</td>
<td>0.38</td>
</tr>
<tr>
<td>8 - 12</td>
<td>4/28 (14%)</td>
<td>3/32 (9%)</td>
<td>0.70</td>
</tr>
<tr>
<td>12 - 16</td>
<td>1/8 (13%)</td>
<td>4/46 (9%)</td>
<td>0.99</td>
</tr>
<tr>
<td>16 - 20</td>
<td>4/7 (57%)</td>
<td>9/31 (29%)</td>
<td>0.20</td>
</tr>
<tr>
<td>20 - 28</td>
<td>1/2 (50%)</td>
<td>2/8 (25%)</td>
<td>0.46</td>
</tr>
</tbody>
</table>
m and TD$_{50}$ differed between SBRT and CFRT (p=0.37, likelihood ratio test). Again, we would like to stress that the statistical power was limited due to lower number of patients in the high dose range.

The optimal fit of the SBRT and CFRT together resulted in a TD$_{50}$ of 24.4 Gy (95%CI: 21.0Gy to 32.0Gy) and m of 0.49 (95%CI: 0.42 to 0.61) (Figure 3).

**Discussion**

A significant relationship between the MLD and the incidence of RP following SBRT was observed. Moreover, the NTCP model fitted the SBRT data well. We observed no significant difference between the NTCP models predicting RP in SBRT and CFRT patients. Furthermore, no significant difference between SBRT and CFRT was observed in the incidence of RP in any dose range. Nevertheless, an increased risk for SBRT in higher dose ranges was suggested by both the NTCP model fit and the observed RP incidences. However, because fewer patients were available in the high dose range no firm conclusions can be made concerning these differences.

At the Department of Radiation Medicine of the Hokkaido University School of Medicine, different SBRT dose schedules have been used since 1998. The first applied schedule was 35 Gy in 4 fractions that was escalated to 48 Gy in 4 fractions. Between these schedules, interim doses of 40 Gy in 4 fractions and 48 Gy and 60 Gy in 8 fractions were given. In addition, tumours located near to critical structures were more fractionated than peripheral tumours. The absence of severe toxicity strengthened the approach of re-treating patients with tumour recurrence or irradiating multiple lesions sequentially. Consequently, a dose-response analysis could be performed with a dose range similar to the dose range of the CFRT. The comparison of SBRT with CFRT was performed with an update of previously evaluated NKI-AVL CFRT patients. As expected, the m and TD$_{50}$ for these CFRT patients were similar to a previous publication [18] and the meta-analysis of Semenenko et al. [15].

Previous SBRT studies reported a 0 % to 29 % incidence of RP grade 2 or higher [3,9-14,26]. Unfortunately, only a limited number of studies reported...
dose parameters to describe the lung dose. Yamashita et al [9] reported a high incidence of RP grade 2 or higher in 7 of the 25 patients treated with 48 Gy in 4 fractions. The mean MLD was only 4.3 Gy (ranging from 1.72 Gy to 5.85 Gy). However, for the calculation of the lung dose, which was not NTD corrected, not only the tumour volume was subtracted from the total lung volume but also an extra margin surrounding the tumour, resulting in an underestimation of the lung dose. Nagata et al [13] reported a 4 % incidence of RP grade 2 in patients treated with 48 Gy in 4 fractions with a mean V20 (percentage volume of the whole lung receiving more than 20 Gy) in this patient group of only 4.5 %. In the study by Ng et al. [26], no RP grade 2 or higher was observed. However, this study included only 20 patients with 80 % of the patients having a V20 < 20 % (GTV ranged from 4.27 cm³ to 74 cm³).

The clinical applicability of our results in relation to other SBRT schedules may be questionable as many institutions in Europe and the USA use fraction doses of 18 Gy or 20 Gy. In our study, 48 Gy in 4 fractions was the most commonly used fractionation schedule having 8 different beam angles (i.e. 1.5 Gy per beam). For fraction doses of 18 Gy, at least 12 different beam angles are used [6], which results also 1.5 Gy per beam. Therefore, the major part of the lung tissue will receive equivalent doses per fraction. Moreover, in the 18 Gy or 20 Gy per fraction schedule, the percentage of lung tissue receiving the highest proportion of the dose is small because smaller dose planning margins of 5 mm to 10 mm around the tumour are used [6] (most of our patients had 11 mm to 13 mm margins [16]). Therefore, large deviations in the lung tissue response of these hypofractionated schedules are not expected.

Because the collaboration encompassed two different radiotherapy departments, a lot of effort was invested in standardizing methods for dose planning and dose calculation between the patient groups. A recent study by Gershkevish [27] showed that deviations between different treatment planning systems decrease with the use of more advanced calculation algorithms. For all patients included in this analysis, the superposition or collapsed cone algorithm was used for treatment planning. The clinical variability in the prescribing of steroids between the two institutes was limited as only patients who were diagnosed by both radiotherapists and pulmonologists experienced with the diagnosis of radiation pneumonitis were included. Patients were excluded if the diagnosis of RP was hampered or accompanied by pulmonary comorbidity (e.g. infection, tumour progression, previous use of oxygen). Nevertheless, the uncertainties of including patients from 2 different institutes should be taken into account, and a similar one single-institute validation would be of interest.

We observed a similar time frame for RP occurrences in both SBRT and CFRT; RP occurred several weeks to 6 months after irradiation as both Guckenberger et
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al. [10] and Yamshita et al. [9] reported for SBRT and Graham et al. [28] reported for CFRT. Further toxicity may be observed with a longer follow up. In the study by Timmerman [6] et al. four of the six treatment related deaths occurred after 12 months. Four of the patients suffered from a bacterial pneumonia and 1 patient experienced tumour recurrence adjacent to the carina. Evidently, both short and long term toxicity may conceivably be obscured by pulmonary comorbidity or tumour progression. Therefore, these patients, who are often suffering from pulmonary comorbidities, should be intensively followed by both radiation oncologists and pulmonologists.

For lung cancer patients or patients with pulmonary metastases, the critical prognostic importance of controlling RP risks must be balanced against not only the patient's physical condition, but also against tumour control. A strong consequential component between acute and long term pulmonary toxicity after lung irradiation is observed in animal studies [29,30]. Consequently, even though grade 2 RP might not be life-threatening, it may substantially contribute to a cascade of pulmonary deterioration in patients with pulmonary comorbidity. Moreover, a long-term dose dependent progressive decline of pulmonary function is observed in patients treated with CFRT [31] with MLD up to 21.9 Gy (mean MLD 13.9 Gy). In a recently published SBRT phase II study [32] no relationship was observed between toxicity and lung dose. In this study a mean MLD of 7 Gy for 60 patients was found. Our retrospective study encompassed a larger dose range for a larger number of patients but no pulmonary function data or follow up CT's were evaluated. A prospective study with a large dose range with long term follow up should reveal the predictability of any radiation induced toxicity after hypofractionated schedules.

To date, there is no clinical data available which compares the prognosis (survival) of lung cancer patients experiencing clinical relevant radiation induced toxicity versus non-symptomatic patients. With regards to the optimal treatment, the clinical evaluation of the risk of tumour recurrence and the probability of toxicity is a matter of concern in a patient group with a poor tumour related prognosis and a high incidence of co-morbidity. Our retrospective evaluation can serve as a guideline estimating the probability of RP for the clinical decision making (i.e. staying on the safe side for pulmonary compromised or palliative patients and accepting a higher risk of toxicity for curable patients without pulmonary comorbidities). Nevertheless, prospective studies are needed to reveal the relation of short and long term toxicity and tumour control.

Time related recovery of lung tissue was not taken into account in our patients who had received multiple treatment schemes. A mouse study by Terry et al. [33] showed that irradiation induced lung injury tissue could (partly) recover, suggesting an early target cell depletion and regeneration which was dependent on the size of the initial injury (i.e. dose). For a single dose of 10 Gy, less recovery was observed than for 6 Gy.
Clinical studies, evaluating toxicity after re-irradiations for lung cancer patients are limited due to poor prognosis. Okamoto et al. [34] studied 34 lung cancer patients re-irradiated because of a local recurrence. The large number of patients (19 patients, i.e. 56%) experiencing grade 2 or higher RP suggest limited (or no) time related recovery. Moreover, from the long term survivors (20 to 58 months after re-irradiation) 71% of the patients experienced a grade 2 RP. However, no lung dose characteristics were reported and RP risk estimating could therefore not be performed.

To predict normal tissue complication probabilities (NTCP) after radiotherapy treatment, the delivered dose has to be re-calculated into a biological-effective dose using a mathematical model (Linear Quadratic model) [35,36] derived from in-vitro and animal studies [37]. The clinical applicability of this model is a historical cornerstone in assessing tumour doses and dose tolerance of normal tissues. Although the use of SBRT is increasing, no study validated the clinical applicability of the LQ model for SBRT. We evaluated the applicability of the LQ model in this patient group in the accompanying paper [20].

Although there were numerous limitations in our study we were able to show a relationship between the lung dose and the incidence of RP for SBRT that was not significantly different from CFRT.
Chapter 4

References
15. Semenenko VA, Li XA. Lyman-Kutcher-Burman NTCP model parameters for radiation
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Chapter 4
