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ORIGINAL ARTICLE

Variation in radiation sensitivity and repair kinetics in different parts of the spinal cord

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Abstract

Background. The spinal cord, known for its strongly serial character and high sensitivity to radiation even when a small segment is irradiated, is one of the most critical organs at risk to be spared during radiation therapy. To compare the sensitivity of different parts of the spinal cord, data for radiation myelopathy have been used. *Material and methods.* In the present study, the relative seriality model was fitted to two different datasets of clinical radiation myelitis concerning cervical spinal cord after treating 248 patients for head and neck cancer and thoracic spinal cord after treating 43 patients with lung carcinoma. The maximum likelihood method was applied to fit the clinical data. The model parameters and their 68% confidence intervals were calculated for each dataset. The α/β ratio for the thoracic cord was also found to be 0.9 (0–3.0) Gy. *Results.* The dose-response curve for the more sensitive cervical myelopathy is well described by the parameters $D_{50}=55.9$ (54.8–57.1) Gy, $\gamma=6.9$ (5.0–9.2), $s=0.13$ (0.07–0.24), whereas the thoracic myelopathy is described by the parameters $D_{50}=75.5$ (70.5–80.8) Gy, $\gamma=1.1$ (0.6–1.6), $s=36$ (3.3–∞). *Discussion and conclusions.* Large differences in radiation response between the cervical and thoracic region of spinal cord are thus observed: cervical myelopathy seems to be characterized by medium seriality, while thoracic spinal cord is characterized by a highly serial dose-response. The much steeper dose-response curve for cervical spinal cord myelopathy can be interpreted as a higher number of functional subunits consistent with a higher amount of white matter close to the brain.

Curative radiation therapy in the head and neck and thoracic region is associated with a risk of having injury to spinal cord and other involved normal tissues. In certain irradiation techniques, part of spinal cord may be located within the irradiated volume and therefore it may receive a significant dose. Consequently, there is a certain risk of developing radiation myelopathy after curative radiotherapy and its avoidance is especially important. Radiation myelopathy is usually diagnosed based on clinical symptoms including myelography. Different radiotherapy scoring protocols can be used to estimate the severity of radiation injury such as the RTOG criteria [1], or the LENT SOMA scale [2].

The risk of severe acute and late damage to normal tissues increases with dose [3]. Among the different radiation-induced spinal cord endpoints that may develop are: white matter necrosis, vascular damage and radiation myelopathy. Especially the latter develops slowly over a period of several months to years, generally making spinal cord a late responding tissue. Apart from the fact that human spinal cord is considered to be one of the most critical organs, there is not so much knowledge about whether it only becomes dose limiting when large volumes are irradiated or if the radiation sensitivity varies along its length. This is expected to depend on the distribution and structural organization of its functional subunits (FSU) since there are structural differences between the different parts of spinal cord especially as far as the proportions of white and gray matter is concerned (Figure 1). The main factors that appear to affect radiation injury in spinal cord are total dose, fractionation scheme, irradiated volume and inter-patient variability of radiation sensitivity.

The objective of cancer radiation therapy is to design treatments that result in maximum tumor control probability and minimum normal tissue

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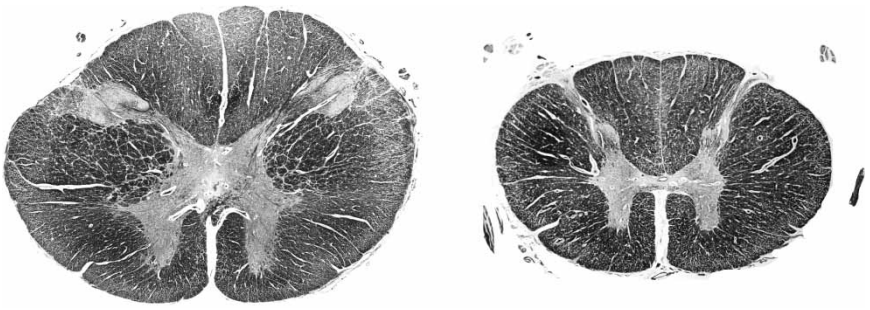

Figure 1. Images presenting upper cervical (left) and upper thoracic (right) cross sections of spinal cord. White matter has a tendency to decrease with increasing the distance from the brain. These differences may influence the observed radiosensitivity of the different parts of spinal cord. (Images courtesy of DK Morest)

morbidity. The radiobiological parameters of the models are useful to quantify the clinical improvements in dose distributions delivered by IMRT and particularly biologically optimized IMRT instead of conventional conformal radiation therapy. Since the pioneering work of Rubin [3] and Emami et al. [4], newer and more accurate dose-response relations of tumors and normal tissues have been reported by many investigators [5–9]. To improve the reliability of biological treatment planning a continued evaluation is needed through local clinical verification and update of these data. In order to use and collect more information about local normal tissue radiation responses for clinical applications, patient datasets should be continuously analyzed [6,10–12]. For the evaluation and comparison of treatment plans, different radiobiological models have been developed to describe normal tissue complication probability (NTCP) [13–16]. In the case of lung and head & neck radiation therapy, radiobiologically optimized treatment planning can be performed using relevant dose-response parameters, which can be estimated from well organized studies of treated patients with long follow-up. Usually prospective studies are performed to verify the validity of published parameter sets, whereas the kind of studies carried out to determine these parameter sets are often retrospective since the prevalence of late complications is usually low [8,10]. Regarding the characterization of the dose-response relation for spinal cord, most models seem to work well and are rather accurate in predicting its response to radiation therapy [17].

The aim of the present study is to determine the parameters that describe the dose-response curves for myelopathy of the cervical and thoracic parts of spinal cord. The relative seriality model [16] has been tested for the estimation of the radiation myelopathy incidence in two relatively large groups of patients trying to draw some conclusion about whether response modeling can be safely used. Spinal cord is generally considered to have a strongly serial character and it is rather sensitive to radiation even in small sections of the cord. However, its sensitivity appears to differ in different parts along its length. In order to estimate the differences in radiosensitivity of different parts of spinal cord, published clinical data for radiation myelopathy have been used. There exists evidence of spinal cord recovery after radiotherapy, where the repair capacity seems to depend on the α/β ratio of the LQ-model, when trying to account for fractionation effects [18]. The importance of having a reliable α/β ratio is due to the possibility to optimize the fractionation and the use of a second radiation course in some patients [19]. For normal tissues, whose dose distribution can vary significantly between different irradiation techniques, these kinds of studies can be sensitive to the treatment method applied. Finally, the clinical probabilities should be compared and associated with other known spinal cord radiation responses of these patient groups.

Material and methods

Clinical data from spinal cord irradiation

Following our previous experience, the relative seriality model [16] was fitted to two different sets of clinical data for spinal cord radiation myelitis as the clinical endpoint. The first dataset is based on cervical spinal cord irradiation after treating 248 patients for malignant disease of head and neck [20]. Of these patients 12 developed myelitis, whereas 236 patients showed no neurological signs. The second dataset is rather small but concerns the manifestation of radiation myelitis in the thoracic spinal cord after radiation treatment of 43 patients with lung carcinoma [21] of whom 19 patients developed complications. In all cases, clinical diagnosis of radiation myelitis was invariably made by experienced neurologists based on clinical symptoms, including myelography for the majority of the cases. In Figure 2, the distribution of the patients (responders and non-responders) is demonstrated as a

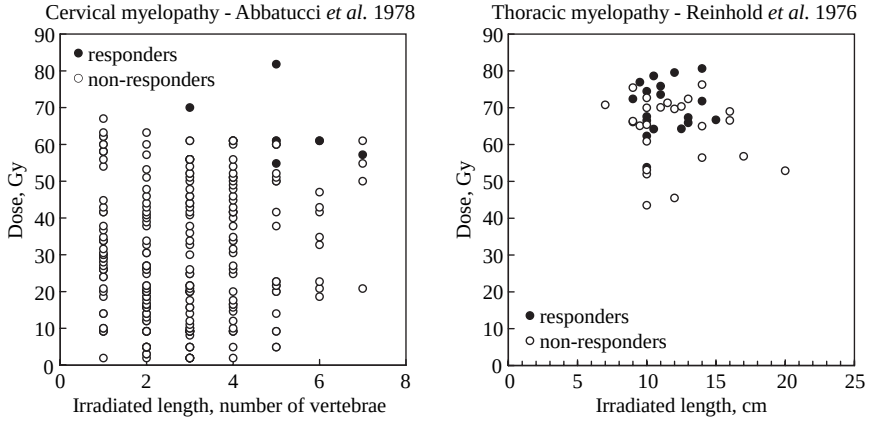

Figure 2. Diagrams representing the relations between the length or vertebrae and the delivered dose for the responders and non-responders regarding the study materials of Abbatucci et al. [20] and Reinhold et al. [21], respectively. It is shown that in the cervical myelopathy case, the responders are concentrated in the region of high doses and large number of vertebrae being irradiated, whereas there is a spread of the patients that developed thoracic myelopathy over a large range of doses and lengths. This observation indicates that there is a more clear relation between the manifestation of cervical myelopathy with a dose cutoff and volume effect compared to the thoracic myelopathy case.

relation of the dose that was delivered to spinal cord and the length of spinal cord that was irradiated. For each patient all the required data were available to participate in the study. Regarding the clinical end-point of radiation myelitis, for both the cervical and thoracic parts of spinal cord the mean latent period was 1.5–2.0 years after the end of radiotherapy. The maximum likelihood method was applied for the determination of the model parameters such as D_{50}, γ and s together with their 68% confidence intervals for each of the datasets, respectively. In case of the thoracic dataset we had access to fractionation information, therefore the α/β ratio for radiation myelopathy in the thoracic part was also obtained.

The Relative Seriality model

The normal tissue complications observed after the therapeutic use of radiation can be viewed as the inactivation of functional subunits (FSU). However, the calculation of the response probability becomes complex because of the dependence of normal tissue injury on the organization of the functional subunits and internal structure of the irradiated organ. For this reason, it is important to understand and identify the volume effect, which is determined by the pattern of functional organization in parallel and serial subunits. Due to its high flexibility [15] the relative seriality model is used in this work, to handle the concept of the volume effect [5,22,23]:

$$P_I(\vec{D}) = \left[1 - \prod_{i=1}^{M}(1 - \exp(-e^{e\gamma-(D_i/D_{50})(e\gamma-\ln\ln 2)})^s)^{\Delta v_i}\right]^{1/s} \quad (1)$$

where $P_I(\vec{D})$ (I denotes injury) is the mathematical expression of the response probability for a normal tissue being irradiated with a heterogeneous dose distribution, $\vec{D}$ [15,16,24,25] where $\vec{D}$ is a vector denoting the discrete dose points $\{D_1, D_2, \ldots, D_M\}$. In this model the basic radiobiological parameters are the following: D_{50} is the dose corresponding to the 50% complication rate and γ is the maximum normalized gradient of the dose-response curve. $\Delta v_i = \Delta V_i / V_{\text{ref}}$ is the fractional subvolume of the irradiated organ, where V_{ref} is the reference volume for which the values of D_{50} and γ were calculated. In this study, the length of 7 vertebrae or 20 cm was used as reference for the cervical and thoracic parts of spinal cord, respectively. The relative seriality parameter, s characterizes the internal organization of the functional subunits in the organ. A high relative seriality is related to a tissue with serially organized FSUs and high doses to small volumes of the organ determine the risk for complications. An s value close to 0 characterizes a tissue of more parallel structure where the mean dose to large volumes of the organ is best associated to the radiation injury. For the case of the thoracic part of spinal cord, each dose distribution was converted to a fractionation scheme of 2 Gy per fraction by using the linear-quadratic model, which accounts for the fractionation effects [26]. Furthermore, the α/β ratio was estimated during the fitting process. Hence, each dose in the dose volume histograms was corrected, separately. The radiation sensitivity was assumed to be homogeneous throughout each of the two spinal cord regions examined.

Using the maximum likelihood method to fit response models to clinical data

By fitting the predictions of the relative seriality model to the clinical follow-up results, the best

estimates of the model dose-response parameters were determined together with their confidence intervals. The sampling method that was followed considered a number of consecutive patients with known treatment and follow-up information. The maximum likelihood method determines the best estimates of the parameters by maximizing the likelihood to reproduce the given pattern of observations [6,22]. The parameters describing the radiosensitivity of a normal tissue are model dependent and for the relative seriality model they are D_{50}, γ, s. Similarly, the parameters expressing the characteristics of the treatment applied to each patient are the dose distribution and the corresponding subvolumes of the organ $(\vec{D}, \vec{V})$. For computational simplicity the logarithm of the maximum likelihood function, $\ln L$ is usually used.

To estimate the goodness of the fit, three independent statistical methods were applied. In the first method, the log-likelihood function was assumed to follow a Gaussian distribution. By comparing the expected mean and maximum values of the $\ln L$ function to consider the magnitude of the variance, the goodness of fit was determined [6,27]. The fit can be considered as optimal for high probabilities (close to 1 or 100%), which corresponds to a very good agreement between the two distributions (predictions, clinical results). An estimate of the goodness of fit can be obtained by comparing the theoretical predictions based on the best estimates of the parameters with the observed responses and follow-up results. Calculating the mean value of $\ln L$ and its variance σ^2 over the whole group of patients and assuming that the value of $\ln L$ is normally distributed, the goodness of fit was determined.

The second method that was applied to investigate the goodness of fit is the Pearson's chi-squared (χ^2) test, which characterizes the dispersion of the observed frequencies from the expected frequencies. The goodness of fit is investigated by comparing the observed and expected response results. The patient data was divided into subgroups, which were sorted in order of ascending dose. Thus, the probability $P(\chi^2, v)$ that a random sample of data points drawn from the assumed probability distribution, which is calculated by the models for radiation myelopathy, would yield a value of χ^2 as large as or larger than the observed clinical outcome with v degrees of freedom, is calculated. A probability close to unity means that the spread of the data points is well described by the assumed distribution.

The third method for estimating the goodness-of-fit was through Monte Carlo simulations. This method was based on the assumption that the NTCP model is a good representation of the average outcome of a statistical distribution and the clinical data is one realization from the statistical distribution. In this case the response predictions (NTCP values) can be simulated multiple times and the result will be a set of alternative experimental outcomes with a realistic statistical spread. In the present analysis, the primary theoretical NTCP values of the patient group were calculated by using the best estimate of the parameters [28]. Subsequently, a large number of alternate experimental outcomes were sampled from the distribution given by the best fit parameters. For each simulation, the number of complications was counted and stored. So, the NTCP model could be fitted to all secondary experimental outcomes, yielding a large number of NTCP sets from which the probability distribution of the NTCP values can be found. As it is shown in the diagrams of Figure 5, a probability distribution of the number of complications was built by using the stored data obtaining a confidence interval of the NTCP values.

Results

The mean dose delivered to the patients was 31.0 ± 18.7 Gy for the cervical part and 62.6 ± 7.0 Gy for the thoracic part, whereas the length of spinal cord irradiated, ranged up to 7 vertebrae for the cervical part and up to 20 cm for the thoracic part. For the thoracic part of spinal cord the dose values mentioned refer to doses that have been converted to a fractionation scheme of 2 Gy per fraction.

The best estimates of the model parameters together with their 68% confidence intervals were obtained for cervical and thoracic part of spinal cord. These parameters were used to produce the corresponding dose-response curves shown in Figures 3 and 4, where the curves are plotted for different lengths of irradiated volume of spinal cord. The values of the parameters are presented within their respective figures. The spread among the dose-response curves corresponding to whole and partial spinal cord irradiation indicates that the induction of cervical myelopathy varies substantially with the irradiated volume. This is not observed in the case of the thoracic myelopathy. From the viewpoint of functional organization, spinal cord shows a weak serial architecture in the cervical part and a strong serial architecture in the thoracic part, respectively, as expressed in the relative seriality model by their respective s values.

The expected value and standard deviation of the maximum likelihood function was used to determine the goodness of the fit. Using the best estimates of the model parameters, the individual complication probabilities of the patients were calculated. The expected value of the log-likelihood function was

Myelopathy of cervical spinal cord (Abbatucci *et al.* 1978)

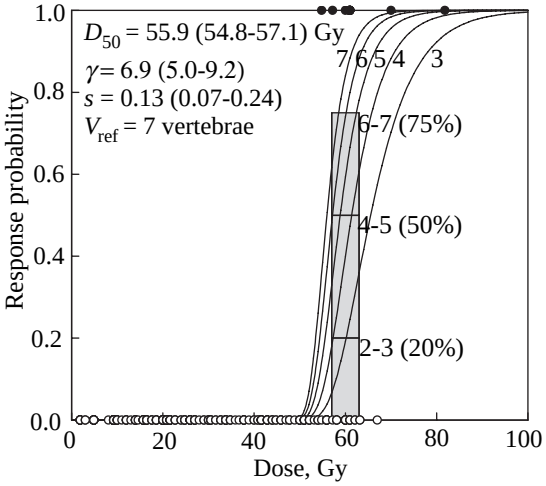

Figure 3. In the diagram, the dose-response curves of spinal cord, which were produced using the relative seriality model and the estimated radiobiological parameters, are presented for the clinical endpoint of cervical myelopathy. In this diagram, the solid lines represent the model fitting of the clinical data for 3–7 irradiated vertebrae. The black dots correspond to the patients with complications, whereas the white dots to the complication-free patients. In the dose region 57–63 Gy, the shaded bars corresponding to the observed response rates of 20% for the 2–3 vertebrae being irradiated, 50% for the 4–5 vertebrae and 75% for the 6–7 vertebrae appear to be closely associated with the predictions of the relative seriality model.

Myelopathy of thoracic spinal cord (Reinhold *et al.* 1976)

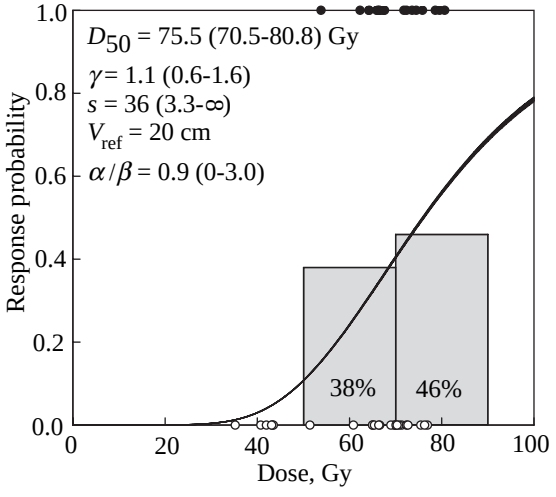

Figure 4. The dose-response curves of spinal cord, which were produced using the relative seriality model and the estimated radiobiological parameters, are presented for the clinical endpoint of radiation myelitis. The volume of irradiated spinal cord ranges from 9 to 15 cm in this diagram. The black dots correspond to the patients with complications, whereas the white dots to the complication-free patients. In the dose ranges 50–70 Gy and 70–90 Gy (shaded regions), the observed responses of all the lengths are compared with the model predictions. In the first dose interval, 38% of the patients developed radiation myelitis compared to the predicted complication rate of 43%, whereas in the second interval, the observed incidence rate was 46% compared to the predicted rate of 57%.

-14.0 with a variance, σ^2 of 8.7 for cervical myelopathy (Table I). For thoracic myelopathy, the expected value of ln$L$ was -28.6 with a variance σ^2 of 2.2. The corresponding observed values of the log-likelihood function for the fit were -14.54 and -26.52, respectively. Under the assumption that ln$L$ follows a Gaussian distribution, these results correspond to a probability of finding a worse fit of 60.7% and 85% for the two clinical endpoints, respectively. To apply the Pearson's χ^2 test, the patient populations were divided in 7 and 6 subgroups for the cervical and thoracic myelopathy, respectively. The values of reduced χ^2_v that were calculated were 0.031 for cervical myelopathy and 0.371 for thoracic myelopathy (Table I). The probabilities for having a perfect agreement between the expected and the observed complication results are 0.98 and 0.54, respectively, corresponding to the above values of χ^2_v (2 degrees of freedom). These values indicate that the pattern of the clinically recorded complications is reproduced very well by the relative seriality model and the estimated parameters, especially for the endpoint of cervical myelopathy. Another set of results that confirms the validity of the estimated parameters is the agreement between the fitted and observed complication rates, which are 4.7% and 4.8% as well as 44.2% and 44.2%, respectively, for the two complication endpoints.

The dose-response curves for the two parts of spinal cord are calculated for a range of uniform doses using the relative seriality model and the estimated radiobiological parameters (Figures 3 and 4). Using again these parameters and the individual dose distributions for spinal cord for every patient, the individual response probabilities were calculated. To examine whether the fitted curve reproduces the observed complication rates, the patients confined in the dose region 57–63 Gy were selected for the cervical part of spinal cord. In Figure 3, the observed responses of all the irradiated lengths are compared with the model predictions in the grey regions. For the case of cervical myelopathy, the 20% response rate corresponds to 2–3 vertebrae being irradiated, the 50% to 4–5 and the 75% to 6–7 vertebrae being irradiated. In Figure 4, the grey regions represent the patients confined to two dose ranges: 50–70 Gy and 70–90 Gy. In the first dose interval, 38% of the patients developed radiation myelitis and in the second interval, the observed incidence rate was 46%. The corresponding average expected response probabilities of the patients in these dose intervals were 43% and 57%, respectively. From the position of the theoretical dose-response curves, it is apparent that there is a close association between the clinical observations and the prediction of the relative seriality model. In these diagrams, statistically valid

Table I. Statistical evaluation of the biological model fitting on the patient data. The goodness of fit was determined for the patient populations by two different methods (Normal error distribution, χ^2-test).

Statistical method	Association of theoretical and clinical results			
Normal error distribution	Observed ln$L$	Expected ln$L$	Variance ln$L$	$P_{\text{Worse-fit}}$ (%)
Cervical myelopathy [20]	−14.5	−14.0	8.7	60.7
Thoracic myelopathy [21]	−26.5	−28.6	2.2	85.0
Pearson's χ^2 test	Predicted P_{I} (%)	Observed P_{I} (%)	$1\chi^2_v$	$P_\chi(\chi^2_v, v)$
Cervical myelopathy [20]	4.7	4.8	0.031	0.98
Thoracic myelopathy [21]	44.2	44.2	0.37	0.54

[1]Degrees of freedom = number of patients subgroups − number of fitted parameters − 1.

comparisons between average predicted and true follow-up rates can be made only for dose ranges where there is a considerable number of patients with and without complications. Towards the low and high doses, the low number of patients tends to make such comparisons statistically biased and consequently strongly inaccurate. Taking into account the fact that the complete 3-dimensional dose distribution was not available, the agreement between respective sets of probability values is quite good.

In the diagrams of Figure 5, where a Monte Carlo goodness of fit method was applied, it is shown that the most probable numbers of complications predicted by the relative seriality model and the two estimated parameter sets are very close to the mean of the corresponding distributions. More specifically, for the cervical part of spinal cord, the most probable number of complications is 12 while the mean of the distribution is 11.8 with a standard deviation (SD) of 2.2 and a 95% confidence interval (CI) of 8–16. Similarly, the most probable number of complications for the thoracic part is 18 with a mean of 18.3, SD of 3.0 and CI of 13–24. In both cases, the most probable values are very close to the true number of responders, namely 12 and 19, respectively.

Discussion

One of the most important objectives of treatment planning is to deliver a curative dose to the tumor with minimum dose to the surrounding tissues. Diminishing the dose given to spinal cord as well as reducing the length of spinal cord being irradiated may reduce the risk of radiation myelitis. There exists evidence for differences in sensitivity within the rat spinal cord irradiated with experimental proton beams [29]. The authors observed large regional differences within the rat cervical spinal cord and conclude that lateral white matter is more sensitive to radiation than the central one. Their other conclusion is that the gray matter is highly radioresistant, as no lesions were observed even after a single dose of 80 Gy. Burman *et al.* [30] showed that application of a larger field size on human spinal cord leads to a slight increase in complications, which suggests existence of volume effect within that

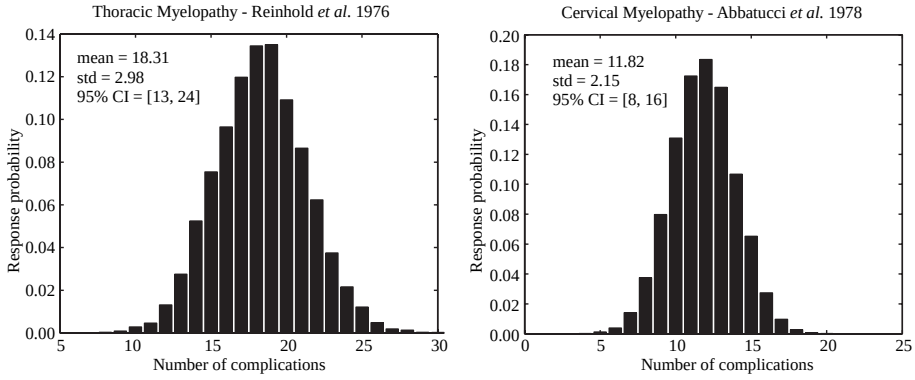

Figure 5. The most probable number of complications predicted by the theoretical NTCP values of the different model parameter sets, using the Monte Carlo goodness-of-fit method considering the dose distribution in the treated part of spinal cord. For the thoracic myelopathy, the most probable number of complications is 18 with a standard deviation (SD) of 2.98 and a 95% confidence interval (CI) of 13–24, whereas for cervical myelopathy the most probable number of complications is 12 with a SD of 2.15 and CI of 8–16. In both cases, the most probable values are very close to the true number of responders, namely 19 and 12, respectively.

organ. Only a few research groups have investigated radiation-induced human spinal cord complications because of the difficulty in collecting uniform data. The comparison of data from different sources is sensitive to many factors like endpoint definition, follow-up, dosimetric data and possibly the radiobiological model used.

A very interesting point of this study is the high relative seriality, value s of the thoracic part and the quite low value of the cervical part. Such observations had not been reported in the past. One of the reasons is that most of the older studies applied simpler statistical methods to perform the data analysis since the computational speed of personal computers did not generally allow complex calculations. It is important to state that more patients showed cervical myelopathy when a larger portion of cervical spinal cord was irradiated. More specifically, when 1 or 2 vertebrae were irradiated 0% of radiation myelitis was observed, for 3 vertebrae the response was 3.3%, for 4 vertebrae it was 4.7%, for 5 vertebrae 13.6% and for irradiation of 6–7 vertebrae, the response rate was 20%. This is evidence that cervical spinal cord is characterized by high volume dependence like a relatively parallel organ. The observed relative seriality can be influenced by the size of the reference volume. If the selected reference volume is small, the observed relative seriality will be low indicating a more parallel behavior. For the thoracic part of spinal cord, the relative seriality parameter is almost as high and serial as it can be. In the diagrams of Figure 2, it is shown that there is a spread of the patients that developed radiation myelitis over a large range of doses and lengths of irradiated thoracic spinal cord, whereas for the cervical part of spinal cord the responders are concentrated in the region of high doses and large number of vertebrae being irradiated. This observation indicates that in the cervical case there is a more clear relation between the manifestation of radiation myelitis with a dose threshold and volume effect. Radiation myelopathy is usually considered a strongly serial endpoint, but the cervical data indicate that this is not always the case. It appears that there are differences in radiation sensitivity between the cervical and thoracic regions of the spinal cord as these are expressed by quite different dose-response parameters.

Of the 12 patients that showed cervical spinal cord complications, 10 had received a uniform dose in the whole circumference of the irradiated vertebrae (83%). Furthermore, of the 248 patients, only 18 had received a uniform dose in the anterior and posterior parts of the irradiated vertebrae out of which 56% (10/18) patients showed complications. Of the patients that had been treated so the posterior part of the irradiated vertebrae had been spared, only 2 of 230 (0.9%) showed radiation myelitis. According to this analysis, it seems that the number of vertebrae being irradiated and the shape of the dose distribution delivered play a major role in the risk of having cervical spinal cord complications after radiotherapy. Unfortunately, there were not data available to perform a similar analysis for the thoracic part.

Gray matter contains mostly entire cells, while white matter contains mostly axons with myelin sheaths. The myelin sheaths work as insulators and one could speculate that their function in that respect might be damaged (short-circuited) by radiation, making the white matter a more sensitive structure of the spinal cord. It is known that the amount of the white matter decreases with increasing distance from the brain along the spinal cord [31], as there are less axons going to or from the entire body. The higher sensitivity of white matter would then be connected to the presence of more Schwann cells building up the myelin, which may comprise the tissue FSUs. The rough conclusion would then be: the more sensitive region is the one containing more white matter. The structural differences between different regions along the spinal cord can be seen in Figure 1. The different values of the relative seriality parameter, s, could also be caused by the different structure of white and gray matter regions along the spinal cord in the sense that there might be a functional redundancy in the upper (cervical) part causing a lower s value. Our results, giving $D_{50} =$ 55.9 Gy for the cervical region of the spinal cord and $D_{50} = 75.5$ Gy for the thoracic region seem to agree with this approach as they indicate cervical region to be more sensitive. It is also confirmed if we compare the intrinsic radiation sensitivity of both regions using the dose representing the 37% survival probability for a single FSU ($D_0 = 2.9$ Gy for the cervical and $D_0 = 21.9$ Gy for the thoracic spinal cord). For the cervical part of spinal cord, Ågren and colleagues [32] used the same patient material and they estimated the parameter values of $D_{50} = 57.0$ Gy, $\gamma = 6.7$, $s = 1.0$ for radiation myelopathy. The values of D_{50} and γ are very close to the parameter values estimated by the present study. However, the s parameter, which was estimated here (0.13) is significantly lower than the value of 1.0. This stems from the fact that the maximum likelihood method, which was used in this study to estimate the different model parameters is more sensitive than the least square curve fitting process applied in the past. This is also indicated by the statistical methods, which were employed to verify the estimations. Studying the endpoint of white matter necrosis from spinal cord irradiation of Rhesus Monkey, the parameter

values of $D_{50} = 72 \pm 3$ Gy, $\gamma = 6.3 \pm 1$, $s = 1.2 \pm 0.4$, $V_{ref} = 16$ cm were estimated. Similarly, from irradiation of rat spinal cord, they determined the parameter values of $D_{50} = 20.2$ Gy, $\gamma = 7.9$, $s = 0.1$ for vascular damage and $D_{50} = 18.7$ Gy, $\gamma = 2.3$, $s = 1.0$ for white matter necrosis, respectively [32].

The dose-response curve is much steeper in the case of myelopathy of cervical spinal cord, due to the much higher γ value. The γ value may be linked to the heterogeneity of the white and gray matter regions along spinal cord. It can be speculated that the higher heterogeneity of the white and gray matter in the thoracic spinal cord could be the reason for the lower γ value in this region ($\gamma = 1.1$), while for cervical spinal cord $\gamma = 6.9$. The high γ value indicates smaller variability in tissue composition within this specific part of spinal cord. A second possible reason for a low thoracic γ value could be the quality of the basic data. In the case of the thoracic group, the small number of patients and larger variability in response may have resulted in a lower γ value. Another possible source of error is the dosimetry in the two datasets. The confidence interval of 68% roughly corresponded to 7% uncertainty in the dosimetry, for the thoracic spinal cord. For the cervical part, the same confidence interval corresponded to 1% dosimetric uncertainty, due to a very high γ value for that region. The main finding that the D_{50}s of the upper and lower part differ by more than 20 Gy is unlikely to change due to any dosimetric errors. For the thoracic part of the spinal cord the fractionation data were available, which allowed an estimate of the α/β ratio for radiation myelopathy. The calculated value ($\alpha/\beta = 0.9$) is lower than the value of 3.0 Gy, which is usually assumed for spinal cord. However, this observation is accompanied by a rather large confidence interval.

The statistics shown in Table I indicate that for both of the spinal cord regions, the radiobiological model used and its estimated parameters predict complication probabilities, which closely agree with the observed incidences for the populations studied. Apart from the purpose of verifying the estimated parameters, the presented statistical methods also serve as a means for checking if other patient populations' irradiation techniques or treatment methods are compatible with the derived model parameters. Before using parameters from the literature or other sources in the clinic, such verification should always be done with the aim that locally derived data will support and update the historically used parameters. The confidence intervals of the dose-response curves were quantified from the individual uncertainties of the model parameters. The supporting role of the confidence intervals accompanying the dose-response curves is important for a secure introduction of radiobiological modeling in the clinical routine.

For better understanding of the mechanisms behind radiation-induced spinal cord injury, further studies should be carried out in the future based on better imaging data. In this way the percentage contribution of white/gray matter in spinal cord as a function of its length could be better estimated. Furthermore, the variation of the amount of white and gray matter along the spinal cord and their impact on the dose-response parameters could be investigated and modeled more accurately. In studies such as the present one, the complete dosimetric information may be used in the form of 3-dimensional dose distributions or DVHs or preferably the entire dose distribution. Because of the fact that this information was not available in the examined clinical materials, the calculations for the quantification of normal tissue response were simplified by using the mean dose, at the cost of losing important information in the data structure. In this case, the mean dose approximation is not applicable since it is only valid under the hypothesis of having small dose variations. Factors like doses, irradiated subvolumes but also location of these subvolumes can be significant in NTCP modeling. In the light of these observations, the estimation of the parameter sets and associated confidence intervals could be improved.

The biological optimization of a treatment plan should be based on biological objectives such as high probability of tumor cure and minimal risk of side effects. Consequently, dose distributions are optimized by trying to satisfy these objectives as close as possible. Biologically Optimized Treatment Planning requires knowledge about the dose-response relations of the different tumors and normal tissues. Having more accurate information about the dose-response parameters characterizing the radiosensitivity of tumors and sensitive organs at risk will thus allow a more accurate and reliable biologically based optimization of the delivered dose distribution.

Conclusions

The estimated radiobiological parameters of the model indicate that the probability of inducing radiation myelitis after radiation therapy is volume dependent for the cervical part of spinal cord, whereas for the thoracic part almost no volume effect could be observed. Different values of D_0 calculated with the present model may be interpreted as different intrinsic radiosensitivity that might be caused by different amount of white matter in different regions of the spinal cord. The

three different statistical methods applied to the patient material showed that the radiobiological model and the estimated parameters can be used to closely predict the clinically observed complication rates.

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