Improved dose response modeling for normal tissue damage and therapy optimization

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Bartoszowi, Adasiowi i ...
Abstract

The present thesis is focused on the development and application of dose response models for radiation therapy. Radiobiological models of tissue response to radiation are an integral part of the radiotherapeutic process and a powerful tool to optimize tumor control and minimize damage to healthy tissues for use in clinical trials. Ideally, the models could work as a historical control arm of a clinical trial eliminating the need to randomize patients to suboptimal therapies. In the thesis overview part, some of the basic properties of the dose response relation are reviewed and the most common radiobiological dose-response models are compared with regard to their ability to describe experimental dose response data for rat spinal cord using the maximum likelihood method. For vascular damage the relative seriality model was clearly superior to the other models, whereas for white matter necrosis all models were quite good except possibly the inverse tumor and critical element models. The radiation sensitivity, seriality and steepness of the dose-response relation of the spinal cord is found to vary considerably along its length. The cervical region is more radiation sensitive, more parallel, expressing much steeper dose-response relation and more volume dependent probability of inducing radiation myelitis than the thoracic part. The higher number of functional subunits (FSUs) consistent with a higher amount of white matter close to the brain may be responsible for these phenomena. With strongly heterogeneous dose delivery and due to the random location of FSUs, the effective size of the FSU and the mean dose deposited in it are of key importance and the radiation sensitivity distribution of the FSU may be an even better descriptor for the response of the organ. An individual optimization of a radiation treatment has the potential to increase the therapeutic window and improve cure for a subgroup of patients.

Keywords:
Normal tissue complications, radiobiological models, dose-response, volume effect, spinal cord, effective FSU size
List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.


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List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>BIO-ART</td>
<td>Biologically optimized 3-dimensional <em>in vivo</em> predictive assay-based radiation therapy</td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
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<tr>
<td>CT</td>
<td>Computed tomography</td>
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<tr>
<td>DMH</td>
<td>Dose-mass histogram</td>
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<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
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<tr>
<td>DSB</td>
<td>Double-strand break</td>
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<tr>
<td>DVH</td>
<td>Dose-volume histogram</td>
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<tr>
<td>EUD</td>
<td>Equivalent uniform dose</td>
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<tr>
<td>FSU</td>
<td>Functional subunit</td>
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<tr>
<td>IGRT</td>
<td>Image-guided radiation therapy</td>
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<tr>
<td>IMRT</td>
<td>Intensity-modulated radiation therapy</td>
</tr>
<tr>
<td>LQ</td>
<td>Linear-quadratic model</td>
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<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<tr>
<td>NTCP</td>
<td>Normal tissue complication probability</td>
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<tr>
<td>PET</td>
<td>Positron emission tomography</td>
</tr>
<tr>
<td>PET-CT</td>
<td>Positron emission tomography – Computed tomography</td>
</tr>
<tr>
<td>RCR</td>
<td>Repairable-conditionally repairable model</td>
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<td>RNA</td>
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1. Introduction

The total number of cancer patients in Sweden, both those who are receiving their treatment as well as those who are already successfully treated, exceeds at present 300,000. Every year almost 50,000 new cancer cases are reported to the National Cancer Registry throughout the whole country with a population of 9 million. Worldwide, there are ten million new cancer cases diagnosed every year. Projecting the present trends, one can expect every third individual in Sweden, and of the young generation about every second will develop cancer at some point during their lifetime, usually at late age (Cancerfonden, 2005; SBU, 2003). Up to the age of 65-70 years the most common cause of death is cancer, only after that age vascular and heart diseases become more common. The high incidence is a really global problem, therefore prevention strategies that could decrease the cancer incidence, together with improvements in early detection through screening programs and accurate molecular diagnostics should be followed by innovative treatments and medical care and regular follow up programs (Ringborg, 2008).

The main goal of radiation therapy is to eradicate the tumor, while at the same time sparing the surrounding healthy tissue as much as possible. Starting with the discovery of X-rays and radioactivity in the mid 1890s and the following rapid progress of improved treatment techniques this goal has increasingly been achieved throughout the years. The treatment techniques have evolved, driven by discoveries that are considered to be the milestones in radiation therapy development. Intensity-modulated radiotherapy (IMRT) is widely considered the most important and exciting advance in radiation oncology, since the introduction of computed tomography-based treatment planning in 1970s (Bentzen, 2005; Bortfeld, 2006; Webb, 2003). The first paper on the conceptual basis of IMRT was published by Brahme et al. (1982) and was followed by a landmark work in inverse planning six years later (Brahme, 1988). Two decades after its invention, IMRT is a widely accepted treatment technique, clinically proven to reduce the side effects in normal tissues while achieving excellent long-term tumor control outcomes (Zelefsky et al., 2006). Due to the necessity of delivering very precise dose distributions to an exact localization of the target volume, as well as close checking of the treatment dose delivery, reliable imaging techniques for both diagnostics and treatment
verification had to be developed. Initiated with computed tomography to delineate gross tumor growth as well as organs at risk using diagnostic X-rays and followed by magnetic resonance imaging (MRI) with even more accuracy to distinguish between tumor and normal tissues, cancer imaging experienced revolutionary developments. Image-guided radiation therapy (IGRT) became a tool that aids to control the tumor location, both before and during the treatment (Verellen et al., 2008). The new approaches in this area include the concept of biologically optimized 3-dimensional in vivo predictive assay-based radiation therapy (BIO-ART) where the fusion of images from positron emission and X-ray computed tomography within one diagnostic unit allows to achieve significant improvements in distinguishing between the tumor and normal tissue (Brahme, 2003). In the near future, the combined PET-CT into a treatment unit will be possible to monitor the metabolic response of the target, together with dose deposition during the treatment (Janek et al., 2006).

In parallel to the rapid development in radiation therapy techniques, further progress in providing the best possible tumor control while sparing the healthy tissue is driven by better knowledge and the utilization of biological basis for radiation oncology (Fowler, 2006). In clinical practice, the meaning of all the improvements in radiation therapy planning and delivery translates into improvements in the treatment outcome. With availability of clinical and experimental data facilitating "the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients" (according to the definition of evidence-based medicine by Sackett et al. (1996)) there are opinions that radiation oncology is becoming increasingly an evidence-based science (Bentzen, 2004). Further improvements in the therapy of cancer depend however on constant incorporation of the newly-available biological knowledge into clinical practice. This aim is being realized using the chain of translational research that consists of several steps including in vitro studies, animal experiments, mathematical modeling or, finally, clinical trials. Simultaneous development in all the areas constituting the translational research chain is a prerequisite for that multidirectional process to work successfully (Baumann et al., 2001). Mathematical modeling of the tissue response to radiation, as an integral part of that chain, constitutes a significant improvement to the dogma of evidence-based medicine and is a prerequisite for the effectiveness of the whole treatment optimization system, bringing a clear cut scientific approach to the historical trial and error process of medical care.

The principal aim of this thesis is to improve the modeling of the dose response used for normal tissue complications and optimization of radiation therapy. In order to achieve this goal, the thesis provides a thorough
analysis of the normal tissue complication probability (NTCP) models that are nowadays most commonly used and demonstrates the models ability to predict the experimentally or clinically observed complication rates. The thesis is based on four papers, where the requirements for a good and reliable NTCP model are defined and their use in a wide range of applications is demonstrated.

In Paper I the model describing normal tissue complication probability is fitted to two different sets of clinical data for radiation myelopathy to compare the sensitivity between the cervical and thoracic regions of the human spinal cord. There is a large difference in radiation response between the two regions. Thoracic spinal cord is characterized by a highly serial dose-response, while cervical myelopathy seems to be of medium seriality. The possible reason for much steeper dose-response curve for cervical spinal cord myelopathy can be a higher number of functional subunits consistent with a higher amount of white matter close to the brain.

In Paper II one of the NTCP models is used to explain the induction of white matter necrosis observed in rat spinal cord irradiated with proton beams, both with homogeneous and bath and shower dose distributions. Two new concepts are introduced: the effective size of the functional subunit (FSU) as well as the effective FSU dose and thereby describing the observed volume effect quite well.

In Paper III radiobiological measures are employed to compare the two concepts: dose-volume histogram (DVH) and dose-mass histogram (DMH). Arguments for a better description of effectiveness of the dose distribution delivered to the patient and its associated radiation effects using the DMH concept are discussed in some detail.

Paper IV indicates the necessity and advantages of truly individualized biological optimization of radiation treatment and highlights the possible benefits obtained by increasing the therapeutic window and switching from generalized into individualized radiation therapy. The significance of collecting the increasingly available information relating radiation dose to tissue response is discussed and development of methods to categorize the individual patient's sensitivity is described.

Together these papers indicate improvements in dose response modeling, particularly with strongly heterogeneous dose delivery such as IMRT, and its use when describing the efficacy of a treatment and biologically optimizing its outcome.
2. Cellular response to radiation

2.1 Intrinsic radiation sensitivity
In 1906, following their experiments on rat testis, Bergonie and Tribondeau formulated a law that relates radiation sensitivity to the reproductive capacity of cells. Their law can be expressed as follows: The ionizing radiation is more effective on cells and tissues that have a higher reproductive activity. In practice this means that radiation will rather destroy cells that have a less specified morphology and functions and, due to the high reproductive activity with more cell cycle division during their lifetime. The law explains one of the reasons why radiation therapy treatments are expected to destroy tumor cells more efficiently than healthy tissue (Perez and Brady, 1992). The other and more important reason has been understood better during the last decade, since the genetic instability of all tumor is really challenged by inducing large amounts of DNA damage during fractionated radiation therapy. The normal tissues are well organized and repair most of the damage from treatment to treatment, whereas the tumors most often have an impaired cell cycle regulation and therefore accumulate more DNA damage from fraction to fraction.

2.2 Normal and malignant cells
There is no major difference between the radiation response of normal and malignant cells if it was not for the differences in the cell cycle regulation, cell population kinetics and the functional organization of malignant cell populations. The same radiation sensitivity of normal and malignant cell populations in vitro is often obtained. Cells, however, do not exist in such artificial state, but instead they are part of living tissues and they do express different histopathological features and cell population kinetics. The factors responsible for the difference in radiation response between normal and malignant tissues are actually the same properties that constitute the nature of their normality and malignancy (Nias, 1998). For tumor cells, the essence of malignancy may be manifested through alterations in the following six functional capabilities (Hanahan and Weinberg, 2000), even if the processes and strategies for acquiring them may vary:

1. independence of growth signals,
2.3 Time scale of radiation effects

The consequence of irradiation in mammalian cell system is manifested by a cascade of successive physical, chemical and biological events extending from picoseconds when ionizations and excitations caused by a traversing high-speed particle take place up to even many years, with the occurrence of late radiation effects. The absorbed dose of 1 Gy causes $10^5$ ionizations within a diameter of 10 $\mu$m which corresponds roughly to the volume of a cell. The physical radiation effects such as ionizations and excitations in turn give rise to DNA strand breaks and rapid chemical reactions including interactions of free radicals causing radiation chemical damage. The following phase of biological effects is the response of the biological system to the damage. Most of the direct DNA breaks and chemical damage gets quickly and efficiently repaired, but not always with high fidelity. However, unrepair radiation damage and misrepair may lead to cell death and if there are fast proliferating cells that cannot be renewed due to damage to their stem cells, an early radiation response may occur. Skin and mucosa are examples of the early reacting tissues. Late effects in normal tissues take place after longer time following irradiation and they include fibrosis or telangiectasia, as well as damage to spinal cord or blood vessels. They occur when the slowly proliferating cells and vasculature cannot be renewed. The time scale of radiation effects could be extended up to many years, when radiation-induced carcinogenesis may occur (Steel, 2002).

2.4 Cellular targets of radiation

The correlation between the radiosensitivity of the cells and their DNA content in a wide range of cellular species (from viruses to mammals) suggests that the DNA is the radiation target in the cell (Tubiana et al.,...
For single-stranded DNA and RNA viruses the correlation is observed between the radiosensitivity and the amount of DNA or RNA, suggesting that breakage of strands leads to inactivation of the virus. The DNA or RNA molecule is then the cellular target for radiation and the larger amount of the target in the cell, the more radiosensitive the cell is. Experiments with viruses with double-stranded DNA show 10 times greater radiosensitivity than for the single-stranded nucleic acids. These results show that a double-strand break (DSB) is required for inactivation of the virus, while a single-strand break (SSB) can be repaired based on the other strand as a template (Kaplan and Moses, 1964). Other experiments suggest that there might be other targets responsible for cellular radiosensitivity (Schmidt-Ullrich, 2003).

2.5 Modeling of cell survival

Many cell survival models have been used through the years (Zimmer, 1961; Hug and Kellerer, 1966; Tobias, 1985; Curtis, 1986; Sontag, 1997), most of which have one shortcoming or another. To really describe the low, intermediate and high dose region well neither the simple exponential:

\[ S = e^{-D/D_0} \]

(2.1)

nor the linear-quadratic (LQ) model (Sinclair, 1966):

\[ S = e^{-\alpha D - \beta D^2} \]

(2.2)

is sufficient. A recent development is the repairable-conditionally repairable (RCR) damage model:

\[ S = e^{-aD} + bDe^{-cD}, \]

(2.3)

cf. Figure 2.1, which fulfills most classical needs over the entire dose range (Lind et al., 2003). It handles the low dose hypersensitivity well, the sublethal damage repair and the shoulder of the survival curve is handled well by the second term and the closely exponential shape at very high doses is defined by the last term. Interestingly this model is based on the two main repair systems in mammalian cells: non-homologous end joining (NHEJ) and homologous recombination (HR). The NHEJ is fast repairing most double strand breaks (DSBs). However, it is not doing it with a high degree of fidelity so the HR process is often needed in the G2-M phase to proof read all the repair done by NHEJ. In the RCR model it is assumed that most of the potentially lethal damage is rapidly repaired and if this happens also the conditionally repairable damage may be correctly repaired. Thus the first term describes the exponentially surviving cells due to unhit cells,
whereas the last linear exponential term describes the correct repair \((e^{-cD})\) of sublethal damage to the first approximation induced linear to the dose \((bD)\).

Figure 2.1: Different types of cellular events associated with sublethal, potentially and conditionally repairable damage, as shown by the Venn diagrams and the associated survival curves. Interestingly the RCR model can be interpreted in terms of the two major repair systems for double-strand breaks: NHEJ and HR for potentially and conditionally repaired damage, respectively. Adapted from Brahme and Lind (2008).

Interestingly, the second term can be derived from the experimental data in Figure 2.1 (gray dots) since it pertains to two cell lines M059K and M059J, of which the latter is mutated in DNA PK and thus not capable of repairing DSBs by the NHEJ process. The repair proficient cell line has a nice normal shoulder with a small amount of low dose hypersensitivity for \(^{60}\)Co whereas the DNA PK mutant line has a purely linear and exponential survival curve without repair of sublethal damage. The difference expresses thus the sublethal repair and is well described by the second term in equation (2.3), as seen in the Figure 2.1. Also seen in the figure is that \(^{60}\)Co and nitrogen ions have almost identical survival curves for the mutant cells, whereas the repair proficient cell line has no possibility to repair any of the damage produced by the nitrogen ions. This experiment thus also illustrates the small difference between the cellular response of different cell lines with high LET ions, but not between the same cell lines with low LET radiation where the difference can be very large. At low doses without low dose
hypersensitivity the LQ model agrees very well with the new expression and it is possible to derive $a$, $b$ and $c$ from known $\alpha$ and $\beta$ values (Lind et al., 2003). The new expression is also shown to handle the interaction of low, intermediate and high LET damage and hypoxia quite well (Persson, 2002; Lind et al., 2003).
3. Tissue response to radiation

Radiation response of a tissue is investigated using sigmoidal dose-response curves where position on the dose scale shows the sensitivity to radiation and the steepness of the curve gives an estimate of change in the response that will be a consequence of change in dose. Examples of dose-response curves are shown in Figures 3.3 and 4.1.

3.1 Radiation tolerance

In clinical radiotherapy it is easy to notice that the dose distribution that can be tolerated is dependent on the volume irradiated and structural organization of the irradiated tissue. The definition of the tolerance dose is based on the acceptable probability of a mild type treatment complication that it may produce. However, there is no such thing as a single tolerance dose for any tissue or patient. A better approach is to determine the normal tissue dose response which requires a good understanding of its biology and dose response relationship (Hall and Giaccia, 2006; Withers, 1992). For this reason a serious therapy optimization approach needs to take the gradual increase with dose, both of normal tissue side effects and the probability of tumor cure.

3.2 Volume effect

The risk of acute or late normal tissue reactions increases with increasing dose (Rubin and Casarett, 1972) and avoidance of severe radiation injuries is particularly important. To be able to effectively spare the healthy normal tissue during radiation therapy it is essential to understand the underlying phenomena which are responsible for the response of those tissues and whether a high local dose or the mean dose is most deleterious.

The volume effect is defined as the dependence of radiation damage to normal tissues on the volume of the tissue irradiated (Hall and Giaccia, 2006; Steel, 2002) or as the relationship between the radiation doses causing the same probability of normal tissue complication and the irradiated volume of the investigated tissue (Hopewell and Trott, 2000). The volume effect phenomenon has been widely studied to improve the understanding
of doses that can be delivered to normal issues during radiation therapy and particularly the understanding of partial organ irradiation (Ten Haken, 2001).

The concept of this phenomenon was based on skin reactions of patients observed in clinical practice. It has been demonstrated in many experimental settings, abundance of which concentrate on the spinal cord as an organ that is especially important to be spared during radiation therapy of patients. Experimental results on irradiating rat spinal cord have been published by Hopewell et al. (1987), Hopewell and Trott (2000) and a group from the Netherlands (Bijl et al., 2002, 2003, 2006; Philippens et al., 2004, 2007; van der Kogel, 1993). Experiments performed on cervical spinal cord of pigs do not show significant field size-related difference in response to single doses of clinically relevant level (Schultheiss et al., 1994), but results from rhesus monkies which is the animal model most similar to that of humans regarding radiation myelopathy, indicate the existence of volume effects (van den Aardweg et al., 1995). Reports of clinical data are also available, describing the existence of dose-volume dependence in human spinal cord (cf. Schultheiss et al. (1995) and references therein) as well as in other organs, e.g. brain (Levegrün, 2001), heart (Gagliardi et al., 2001), liver (Dawson et al., 2001), lung (Seppenwoolde and Lebesque, 2001), parotid gland (Eisbruch et al., 2001) and rectum (Jackson, 2001).

According to Withers (1992) there are several types of volume effects existing in clinical practice, depending on the type of tissue and the endpoint under consideration. The factors contributing to the effect are the following: reduced tolerance to equally severe injury with increasing volume irradiated, increased probability of a complication from the same severity of injury, increased heterogeneity of the dose distribution in the tissue and reduction of organ progenitor cell "reserve".

### 3.2.1 Reduced tolerance due to more intense complications

A patient can tolerate injury in a small volume better than the same damage in a larger volume, where consequences are more dangerous and healing is slower. Therefore, increasing the volume is a reason of making the injury more incapacitating to the host, even if the radiosensitivity of the target cells or FSUs is unchanged and so is the severity of radiation response per unit volume, being independent on the treated volume.

### 3.2.2 Increased probability of complications

In a normal tissue where FSUs are arranged in series (for example spinal cord, cf. Figures 3.3 and 4.2), the loss of one subunit results in organ injury.
regardless on the state of the other subunits in the series. This way, the probability of complication increases with increase in the number of exposed FSUs.

The relationship between number of irradiated functional subunits \( (n) \) and probability of complications \( (P) \) can be described by the formula:

\[
P = 1 - (1 - p)^n
\]  

(3.1)

where \( p \) is the probability of losing one FSU, see also equation (3.2).

3.2.3 Increased heterogeneity of dose

When a large volume is treated there are large gradients in dose distribution. Such a situation may lead to serious consequences including producing a marked change in incidence of complication when the dose-response curve is steep. The so called double trouble effect implies that an increased dose in part of the volume will receive an increased total dose and an increased dose per fraction and also often an increased dose rate.

3.2.4 Reduction in organ "reserve"

A volume effect relates to decreasing of the organ’s functional reserve in direct proportion to the irradiated volume. In such a tissue (for example lung) the total dose required to cure most local tumors would be sufficient to eliminate the functional integrity in the treatment volume (Withers, 1992).

3.3 Functional organization of normal tissues

The fundamental effect of ionizing radiation on a tissue is caused by the slowing down secondary electrons that induce DNA damage responsible for the associated cell kill. But the tolerance of a tissue to radiation is dependent on the clonogenic cells’ ability to maintain organ functions. The function of an organ depends upon the way the cells are organized into functional subunits (FSUs). Concerning the tolerance doses, there are two types of functional subunits:

1. Structurally defined FSU, where survival of an organ depends upon the survival of at least one clonogenic cell within it. An example of such an organ is kidney, consisting of a large number of relatively small nephrons. Each of the FSUs is generally assumed to be independent of its neighbors. Since the FSU is relatively small, it can be easily damaged by relatively low doses, which explains the low radiation tolerance of the kidney.
2. Structurally undefined FSU, where cells are not aggregated into a structurally defined FSUs, like the skin in which the cells are organized in wide sheets. The maximum area or volume that can be repopulated by one clonogenic stem cell to maintain organ function, defines the size of structurally-undefined FSU (Källman et al., 1992; Withers, 1992).

For the radiation response of tissue the functional organization of its FSUs is critical. There are two extreme cases of tissue organization: serial and parallel. A number of intermediate, mixed or cross-linked tissues with combined serial-parallel organization are more common (cf. Figure 3.3). The probability of the tissue response depends on its respective organization, cf. Källman et al. (1992), according to the following equations:

\[ P_{\text{serial}} = 1 - \prod_{i=1}^{m} (1 - P_i), \]  
\[ P_{\text{parallel}} = \prod_{j=1}^{n} P_j, \]  
\[ P_{\text{mixed}} = \prod_{j=1}^{n} \left[ 1 - \prod_{i=1}^{m} (1 - P_{ij}) \right], \]  
\[ P_{\text{crosslinked}} = 1 - \prod_{i=1}^{m} \left( 1 - \prod_{j=i}^{n} P_{ij} \right). \]

These four different FSU arrangements are schematically visualized in the upper part of the Figure 3.3.

### 3.3.1 Serially arranged FSUs
In serial organs FSUs are arranged like links of the chain (for example in spinal cord). In such a case each of the FSUs is critical to the functions of the organ and its elimination results in a measurable complication probability. In the spinal cord specific functions are controlled by different units that are linearly arranged, such as the myelin sheaths and associated oligodendrocyte progenitor cells. Death of critical cells in any of the organ’s units will result in the failure of the whole organ.

### 3.3.2 FSUs arranged in parallel
The opposite cases are tissues where the FSUs are organized in parallel, like for example liver. This means that there is a redundancy so that many
of the FSs have to be destroyed in order to damage the function of the organ and thus creating a pronounced volume effect.

### 3.4 Probability of tissue damage

Since the response of an irradiated organ depends on the organization of its internal structures, i.e. the way the functional subunits constituting the organ are arranged, two opposite cases of tissue arrangement are considered: parallel and serial organization of functional subunits. The organ presented schematically in Figure 3.1 is irradiated with the doses \( D_1 = D - \delta \) and \( D_2 = D + \delta \) in the left and right half, respectively. This results in the probabilities \( P_1 \) and \( P_2 \) for damage of the left and right part, respectively. The relation between the small dose difference, \( \delta \), and corresponding change in the probability of injury, \( \varepsilon \), can be estimated using the \( \gamma \)-value (Brahme, 1984):

\[
\varepsilon = \Delta P \approx \gamma \frac{\Delta D}{D} = \gamma \frac{\delta}{D}.
\]  

\((3.6)\)

![Diagram](image)

\( D_1 = D - \delta \quad D_2 = D + \delta \)

\( P_1 = P - \varepsilon \quad P_2 = P + \varepsilon \)

**Figure 3.1:** Schematic drawing showing an organ irradiated with different doses \( D_1 \) and \( D_2 \), resulting in the probability of damage \( P_1 \) and \( P_2 \), respectively.

The probability of damage to the whole organ, assuming parallel organization of its functional subunits, can be calculated as:

\[
P_{\text{parallel}} = (P - \varepsilon)(P + \varepsilon) = P^2 - \varepsilon^2,
\]

\((3.7)\)

where \( P \) is the probability of injuring of half the organ when irradiated with dose \( D \). For a serial organ the probability of damage is given by the following expression:
\[ P_{\text{serial}} = 1 - (1 - (P - \varepsilon))(1 - (P + \varepsilon)) = 1 - (1 - P)^2 + \varepsilon^2 \]  

(3.8)

cf. Equations 3.1 and 3.2. When \( P \) is small, Equation 3.8 shows that the probability of response is almost doubled in the serial case:
\[ P_{\text{serial}} = P(2 - P) + \varepsilon^2. \]  

(3.9)

The different behavior due to the tissue architecture is here clearly seen for nonuniform dose delivery. The probability of injury of the parallel organ will decrease, whereas the probability of injury will increase if the organ is of a serial type with increasing non-uniform dose delivery. This implies that if a certain amount of mean energy imparted (integral dose) has to be delivered in an organ at risk which is of serial type then the dose should be distributed as uniformly as possible in order to minimize the complication probability. For parallel organs it is better to concentrate the high dose region as much as possible into small volumes.

The biologically effective uniform dose, \( \bar{D} \), is the uniform dose that causes exactly the same tumor control or normal tissue complication probability as a given nonuniform dose distribution, as calculated with a given model. The way of denoting this dose indicates that it has been averaged over both dosimetric (dose distribution) and biological (dose response relationship) information about the patient. The dose \( \bar{D} \) has been calculated with the Poisson model (cf. 4.1.2) for the two extreme cases of organ structure, parallel and serial, and is shown in the left panel of the Figure 3.2. It is clearly seen, especially for large \( \gamma \)-values, that \( \bar{D} \) for parallel structures is close to the minimum dose since tumors have parallel structure and the coldest spot determines the level of tumor eradication.

The right panel of the Figure 3.2 is illustrating the same as the left panel, but for the relative seriality model (Källman et al., 1992). The dose \( \bar{D} \) is minimal for organs with parallel structure (like tumors, for example) at large dose variations. For serially organized organs (that is more relevant to normal tissue) the dose is more close to the maximum one (Mavroidis et al., 2000, 2001). It is interesting to note that for \( \bar{D} \) to approach \( D_{\text{max}} \), the \( s \) value (cf. Figure 3.3) has to be \( \gg 1 \), implying the ”super-seriality”. 

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Magdalena Adamus-Górka
Figure 3.2: The variation of $\bar{D}$ as a function of the nonuniformity of the dose for different tissue architectures. The dose in the left panel has been calculated with Poisson model for parallel and serial organ structure. The right panel is a demonstration of the relative seriality model, adapted from Mavroidis et al. (2001).
Figure 3.3: The functional organization of the most simple tissues have a strong influence on the observed dose response relation. The relative seriality

is expressed by the parameter

\[ s = \frac{m_1}{m_2} \]

Adapted from Brahme (1999).

**Influence of Functional Organization of Tissues on Dose Response Relation**

- **Serial**
- **Mixed**
- **Crosslinked**
- **Parallel**
4. Dose response models

Modeling of normal tissue response to radiation has become an important domain of modern radiation therapy. Numerous models have been developed during the years to help in determining the optimal treatment. The process of creating such models usually involves many simplifying assumptions. The damage induction is considered stochastic, so the survival of cells is following basically either binomial or Poisson statistics. The organ response is either assumed to depend on the response of individual cells and/or the response of the FSU. All cells as well as all FSUs are assumed to respond identically. The isoeffect relationships do not depend on the level of response and equal dose fractions are assumed to cause equal effects, provided the time separation is sufficient. Two connected levels of radiation response are generally modelled, namely survival of cells and response of an organ. Many models originate from an expression for cell survival and they incorporate this expression in the formula for the organ function. However, other models are purely phenomenological, where no explicit formula for cell survival is included. A radiobiological model, to be considered reliable, has to fulfill certain requirements. It should appropriately predict the shape of the dose-response curve, it should duely handle the volume and fractionation effect and it should accurately describe the probability of a specified response for arbitrary non-uniform dose delivery as accurately as possible.

Numerical quantitative comparisons of existing dose-response models have been done by many authors, for example van der Kogel (1993); Baltas and Grassman (1997); Philippens et al. (2004); Tucker et al. (2004); van Luijk et al. (2005) and references therein. However, despite the great interest in this subject an important issue has not been taken into account in these studies, namely the separation of the volume effect from the dose-response of the whole organ. Being able to separate these two different phenomena should not only allow estimation of the accuracy and clinical validity of the models, but also make it possible to investigate the diversity of the models and emphasize the differences between them. A model combining accurate dose response description together with precise volume effect handling is required for accurate optimization of the treatment outcome.
4.1 Distributions describing the shape of dose response

The study of the dose response relations in radiation therapy is important for improving quantification and knowledge about mechanisms influencing the response of organs and tissues to radiation therapy. It is important to know the expected response level in normal tissues when irradiating a patient, since the aim of radiation therapy is to eradicate the tumor while sparing healthy normal tissues as far as possible. This is particularly important when using radiobiologically optimized radiation therapy where both the therapeutic effect and adverse normal tissue damage need to be accurately quantified to maximize the treatment outcome. Most often the dose to the tumor is limited by the tolerance of surrounding normal tissues. Understanding the underlying biological processes is essential for selecting the model for describing the normal tissue response and determining tissue tolerance in different situations. Even more important is to be able to quantify the quality of life after the treatment, that is to estimate the probability of a truly successful treatment such as having a high probability of tumor cure or local control and negligible risk of treatment related morbidity.

There exist several types of volume effects, defined by the decrease in tissue function or the probability of a specific endpoint with increasing irradiated volume, as described in Section 3.2. The FSUs can for example be functionally arranged in series, paralell or have a mixed serial-parallel or crosslinked organisation. Serially arranged FSUs are organized like links of a chain, such as the insulating myelin cells of the axons in the spinal cord. In such a case the function of each FSU is critical for the function of the organ and elimination of any one of them may result in a measurable loss of function or an increased complication endpoint. Therefore in serial tissues the maximum dose is largely determining the therapeutic response. However, when the FSUs are organized functionally in parallel, there is a redundancy where neighbouring FSU can take over function. In such tissues the volume dependence of the dose-response relation is very significant since the response in a small high-dose volume can be almost fully compensated by surrounding FSUs. For parallel tissues the mean dose is therefore the most important factor determining the clinical effect. Mixed serial-parallel tissue organizations are the most common and the most general way of tissue organization, combining the structure and function of the two basic arrangements (Källman et al., 1992). The relative seriality model is designed to describe the gradual change in response from a closely serial tissue to one which is largely parallel.

Spinal cord is a critical normal tissue that almost at all cost should be spared during radiation therapy. It is an example of an organ with a highly
serial arrangement of its functional subunits. It is built of nerve cells - neurons, the axons of which are arranged in bundles along the organ. The characteristic H-shaped pattern on the spinal column cross section is a result of the arrangement of the nerve cell bodies and axons within the cord. The inner part, creating the H-letter shape consists of gray matter, while the white matter creates a more lipid-rich, pale surrounding. It is well known that the material building the gray matter is mainly nerve cell bodies, while axons and the associated myelin cells are the ones constituting the white matter. In mammalian nerve tissue, the axons (e.g. motor neurons or sensory neurons) are equipped with a special layer of insulation, namely the myelin sheath. The myelin sheath is created by oligodendrocytes surrounding the axons of a neuron, increasing the integrity, speed and information content of the transmitted signal (Bunge, 1968; Baumann and Pham-Dinh, 2001).

There are often very serious consequences of exceeding the tolerance dose of normal tissues. As far as the latency period is concerned, the radiation response can be divided into an early and a late occurring damage. There is a close correlation between the time of appearance of radiation-induced damage and the normal proliferative activity of the considered tissue. The higher the rate of normal cell turnover, the faster the onset of the damage. In slowly proliferating tissues, such as spinal cord, the induction of radiation damage is considerably delayed in time. The late types of radiation-induced damage, in case of spinal cord myelopathy and paralysis, consist of two main endpoints: white matter necrosis and demyelination, occurring usually between six to eighteen months after irradiation, followed by vascular damage with the onset of between one to four years.

Dose-response models can be categorized into several groups based on the statistical distribution they use for describing the sigmoid shape of the dose-response curve (see Figure 4.1). The five distributions used in the models investigated in the present study are: binomial, Poisson, probit, logit and Weibull distributions. They constitute a basis for the following seven radiobiological models for normal tissue complication probability: the critical volume model (Niemierko and Goitein, 1992) based on the binomial distribution for the dose-response curve shape, the relative seriality (Källman et al., 1992), the inverse tumor (Källman et al., 1992) and the critical element (Schultheiss et al., 1983) models, all of which are based on Poisson statistics, the Gaussian model (Lyman, 1985) based on the normal distribution or probit function, the parallel architecture model (Jackson et al., 1995) using logit expression and the Weibull distribution model (Klepper, 2001) based on Weibull distribution. The four first models are using cell-survival-based response (Poisson and binomial distribution for the shape of the dose-response curve), while the other three are more phenomenological. To rationalize the comparison in this work, the expressions for the normal...
tissue complication probability (NTCP) of all the models have been rewritten in terms of $D_{50}$ and $\gamma_{50}$ (see Table 4.1), explanation of symbols will follow.

*Figure 4.1: Comparison of the shape of the dose-response curve for different statistical distributions used to describe the cell kill. The two figures differ only in $\gamma$ value and the different horizontal scales.*
4.1 Distributions describing the shape of dose response

Figure 4.2: Volume and dose-response curves for white matter necrosis of different lengths of rat cervical spinal cord, data from Hopewell et al. (1987). The dashed lines give the combined best fitting. The solid lines have been fitted for each of the irradiated spinal cord segment lengths separately, i.e. without any volume effect.
Table 4.1: Overview of the dose response models.

<table>
<thead>
<tr>
<th>Model</th>
<th>Statistics</th>
<th>dose response, $P(D)$</th>
<th>critical volume $P(D, V)$</th>
<th>4D dose-volume response $P(D, V)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>binomial</td>
<td>binomial</td>
<td>$1 - e^{-D/D_0}$</td>
<td>$1 - \sum_{N=0}^{M} \binom{N}{M} P_M + 1 - e^{-D/D_0} \ln \left( \frac{1}{1 - \frac{1}{N_0}} \right)$</td>
<td>$P(D, V) = P(D) \frac{1}{V}$</td>
</tr>
<tr>
<td>implicit</td>
<td>Poisson</td>
<td>$e^{-N_0} e^{-D/D_0}$</td>
<td>$e^{-N_0} e^{-\left(\frac{D}{D_0}\right)^a} + \frac{k \ln \left( \frac{V}{V_{ref}} \right)}{D_{FSU}}$</td>
<td>$P(D, V) = \frac{1}{V} \ln \left( \frac{N_0}{\ln 2} \right)$</td>
</tr>
<tr>
<td>implicit</td>
<td>Gaussian</td>
<td>$\int_{D_0}^{D} e^{-\frac{1}{\pi} \left( \frac{x - D_0}{\gamma} \right)^2} dx = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} e^{-\frac{1}{2} \tau^2} d\tau$</td>
<td>$\int_{D_0}^{D} \frac{1}{\sqrt{2\pi}} \left( \frac{x - D_0}{\sigma} \right) e^{-\frac{1}{2} \left( \frac{v - v_{50}}{\sigma} \right)^2} dv = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} e^{-\frac{1}{2} \tau^2} d\tau$</td>
<td>$P(D, V) = \frac{1}{V} \int_{D_0}^{D} e^{-\frac{1}{\pi} \left( \frac{x - D_0}{\gamma} \right)^2} dx$</td>
</tr>
<tr>
<td>implicit</td>
<td>logit</td>
<td>$\frac{1}{1 + \left( \frac{D_{FSU}}{D_0} \right)^a}$</td>
<td>$\frac{1}{1 + \left( \frac{D_{FSU}}{D_0} \right)^a}$</td>
<td>$P(D, V) = \frac{1}{V} \int_{D_0}^{D} e^{-\frac{1}{\pi} \left( \frac{x - D_0}{\gamma} \right)^2} dx$</td>
</tr>
<tr>
<td>implicit</td>
<td>probit</td>
<td>$\int_{D_0}^{D} e^{-\frac{1}{\pi} \left( \frac{x - D_0}{\gamma} \right)^2} dx = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} e^{-\frac{1}{2} \tau^2} d\tau$</td>
<td>$\int_{D_0}^{D} \frac{1}{\sqrt{2\pi}} \left( \frac{x - D_0}{\sigma} \right) e^{-\frac{1}{2} \left( \frac{v - v_{50}}{\sigma} \right)^2} dv = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} e^{-\frac{1}{2} \tau^2} d\tau$</td>
<td>$P(D, V) = \frac{1}{V} \int_{D_0}^{D} e^{-\frac{1}{\pi} \left( \frac{x - D_0}{\gamma} \right)^2} dx$</td>
</tr>
</tbody>
</table>

The upper limit, $t$, of the normal distribution probability function is given by equation (4.20): $t = \frac{\mu}{\sigma} \Phi^{-1}(1 - \alpha)$.
4.1 Distributions describing the shape of dose response

4.1.1 The binomial distribution,

The binomial distribution, assuming \( N_0 \) functional subunits and a probability of FSU survival, \( S(D) \), at a dose \( D \), gives the following probability of response:

\[
P(D) = (1 - S(D))^{N_0}.
\]

(4.1)

The following simple equation for exponential cell survival is used, cf. Brahme et al. (2001):

\[
S(D) = e^{-nd/D_0},
\]

(4.2)

where \( D = nd \) is the total dose, \( d \) is the dose per fraction, \( n \) is the number of fractions and \( D_0 \) is the dose giving on the average one lethal hit per FSU. Together with the binomial model, equation (4.1), for response, the dose giving 50\% response probability, \( D_{50} \), and the maximum value of the normalized dose-response gradient, \( \tilde{\gamma} \) (Lind et al., 2001), become:

\[
D_{50} = -D_0 \ln \left( 1 - \frac{1}{2^{1/N_0}} \right)
\]

(4.3)

and

\[
\tilde{\gamma} = \ln N_0 \left( 1 - \frac{1}{N_0} \right)^{N_0 - 1}
\]

(4.4)

respectively. \( \tilde{\gamma} \) is defined by

\[
\tilde{\gamma} \equiv \tilde{D}P'(\tilde{D})
\]

(4.5)

where

\[
P'(\tilde{D}) = \max_D \left( \frac{\partial P(D)}{\partial D} \right)
\]

(4.6)

(Lind et al., 2001). For large \( N_0 \), the expressions for \( D_{50} \) and \( \tilde{\gamma} \) for the binomial model become identical to the expressions for the Poisson model (see Figure 4.1).

The critical volume model

This model has been developed by Niemierko and Goitein (1992). The probability \( P \) that more than \( M \) of the \( N \) FSUs are killed is given by the cumulative binomial probability:

\[
P = \sum_{t=M+1}^{N} P_t = \sum_{t=M+1}^{N} \binom{N}{t} P_{FSU}^t (1 - P_{FSU})^{N-t}
\]

(4.7)

where \( P_t \) is the probability that \( t \) of the \( N \) FSUs are killed, \( \binom{N}{t} \) is the binomial coefficient, \( P_{FSU} \) is the complication probability for \( t \) functional subunits, while \( P_{FSU} \) is the complication probability for one FSU. The NTCP
for the entire inhomogeneously irradiated organ can be calculated using equation (4.7) with the \( P_{FSU} \) being replaced by the effective complication probability for one FSU:

\[
P_{FSU}^{eff} = \frac{1}{N_p} \sum_{i=1}^{N_p} P_{FSU}^i(D_i) \quad (4.8)
\]

where \( N_p \) is the number of calculational points inside the organ of interest, \( P_{FSU}^i \) is the complication probability for the \( i^{th} \) FSU and \( D_i \) is the corresponding dose received. Due to the difficulties in calculating the cumulative binomial distribution a normal distribution approximation suitable for numerical calculations is often used.

\[
P = \sum_{t=M+1}^{N} \binom{N}{t} P_{FSU}^t (1-P_{FSU})^{N-t} \approx \frac{1}{\sigma_{FSU} \sqrt{2\pi}} \int_{-\infty}^{M} \exp \left( -\frac{(x-NP_{FSU})^2}{2\sigma_{FSU}^2} \right) dx \quad (4.9)
\]

where:

\[
\sigma_{FSU} = \sqrt{NP_{FSU} (1-P_{FSU})}. \quad (4.10)
\]

Such an approximation is more accurate for large \( NP_{FSU} (1-P_{FSU}) \) values.

### 4.1.2 The Poisson distribution

This distribution is the limiting case of the binomial distribution when \( N_0 \) is large and presents the probability of complications in normal tissue by:

\[
P(D) = e^{-N_0 S(D)} \quad (4.11)
\]

where \( N_0 S(D) \) becomes the average number of FSUs surviving a dose \( D \). Using the exponential cell survival equation (4.2) for clonogenic cell survival, together with the Poisson model, equation (4.11), for response, \( D_{50} \), and \( \tilde{\gamma} \), become:

\[
D_{50} = D_0 (\ln N_0 - \ln \ln 2) \quad (4.12)
\]

and

\[
\tilde{\gamma} = \frac{\ln N_0}{e} \quad (4.13)
\]

respectively, where \( e \) is the base of the natural logarithm. For models based on Poisson statistics the maximum slope of the dose response relation is at the dose giving 37% probability of response. For that reason \( \tilde{\gamma} \) is sometimes denoted \( \gamma_{37} \). In order to facilitate comparison between different models, also those using \( \gamma_{50} \) the following transformation can be used:

\[
\gamma_{50} = \frac{\ln 2}{2} (e\tilde{\gamma} - \ln \ln 2). \quad (4.14)
\]
4.1 Distributions describing the shape of dose response

The relative seriality model
This model was developed to better account for the functional organization of FSUs, cf. Källman et al. (1992). An arbitrary combination of serial and parallel organized of FSUs can be considered. For this model, normal tissue complication probability $P_i$ is mathematically expressed by:

$$ P(D,V) = \left[ 1 - (1 - P(D)^s)^{V/V_{\text{ref}}} \right]^{1/s} $$  \hspace{1cm} (4.15)

where $P(D)$ is given e.g. by the Binomial or Poisson expression (4.11), $s$ is the parameter which expresses the degree of seriality (the value varies from $s$ close to zero for nearly parallel organs and upwards for increasing seriality) and $V/V_{\text{ref}}$ is the volume fraction being irradiated to dose $D$.

The critical element model
This model was proposed by Schultheiss et al. (1983) and it is a simplified case of the relative seriality model, obtained by putting $s=1$ into equation (4.15). The expression for NTCP is given by:

$$ P(D,V) = 1 - (1 - P(D))^{V/V_{\text{ref}}} $$  \hspace{1cm} (4.16)

where $P(D)$ is given by equation (4.11).

The inverse tumor model
This model was developed by Källman et al. (1992) based on a simplistic inverse tumor response. It has been derived for uniform tumors and then adapted to model the volume dependence of normal tissues by introducing a constant $k$ which for uniform tumors equals to unity, but for normal tissues generally has a negative value. The NTCP may then be approximated in the following way:

$$ P(D,V) = e^{-N_0 e^{-(D/D_0)}} + k \ln(V/V_{\text{ref}}) $$  \hspace{1cm} (4.17)

where the free parameter $k$ takes into account the importance of the volume effect in the tissue.

4.1.3 The normal probability (probit) distribution
This distribution for the response results in the following expression:

$$ P(D) = \frac{1}{2} \left( 1 - \text{Erf} \left[ \gamma_{50} \sqrt{\pi} \left( 1 - \frac{D}{D_{50}} \right) \right] \right). $$  \hspace{1cm} (4.18)

The Gaussian model
This model was developed by Lyman (1985) based on the error or probit function form. In this case, the normal tissue complication probability is given by the following expression:

$$ P(D,V) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} \exp(-\tau^2/2) \text{d}\tau $$  \hspace{1cm} (4.19)
where the upper limit, $t$, of the normal distribution probability function is defined as follows:

$$t(D, V) = \frac{D - D_{50}(V/V_{\text{ref}})}{mD_{50}(V/V_{\text{ref}})}$$

(4.20)

and

$$D_{50}(V/V_{\text{ref}}) = D_{50}(1) \left( \frac{V}{V_{\text{ref}}} \right)^{-n}.$$  

(4.21)

The model contains four free parameters: $D_{50}$, $n$, $m$ and $V_{\text{ref}}$. $D_{50}$ and $V_{\text{ref}}$ were defined above, while $D_{50}(1)$ is the tolerance dose for 50% complications for uniform whole organ irradiation, $D_{50}(V/V_{\text{ref}})$ is the 50% tolerance dose for uniform partial organ irradiation. The volume dependence of the complication probability is determined by the parameter $n$, which quantifies the sensitivity of $P$ to the irradiated volume of the organ. The slope of the dose response curve is governed by the value of the parameter $m$. The slope parameter $m$ is inversely proportional to $\gamma_{50}$ through the relation $m = \frac{1}{\gamma_{50} \sqrt{\pi}}$.

### 4.1.4 The logit distribution

This distribution is an analytical sigmoidal shaped curve commonly used in biology defined the following way:

$$P(D) = \frac{1}{1 + \left( \frac{D_{\text{FSU}}}{D_{50}} \right)^{k}}.$$  

(4.22)

The parallel architecture model

This model (Schultheiss et al., 1983; Yorke et al., 1993; Jackson et al., 1995) presents NTCP as an increasing function of the number of FSUs inactivated by radiation. The probability $p$ that a dose $D$ inactivates an FSU is given by the logit expression (4.22) where the slope parameter $k = 4\gamma_{50}$. The above sigmoid dose response function, $P(D)$, is assumed to describe the probability of damaging a subunit at a given biologically equivalent dose. Apart from the assumption that biologically equivalent doses can be calculated from the linear quadratic formula no connections of this probability with any underlying vascular mechanism of radiation injury or identification of the subunits involved has been attempted. Instead it has been chosen to describe the subunit response phenomenologically, using a logistic function of dose parametrized in terms of the dose $D_{\text{FSU}}$ at which 50% of the subunits are damaged, and the slope parameter $k$, that determines the rate at which the probability of damaging a subunit increases with dose. For a given dose matrix the total fraction of FSUs, being inactivated is given by the sum over all the individual contributions:

$$f = \sum v_i \cdot P(D_i)$$

(4.23)
where $D_i$ and $v_i$ are the dose and the volume fraction of the $i^{th}$ voxel and $f$ is the fractional damage. To fit the parallel architecture model to clinical data, expressions for both $P(D)$ and the statistical distribution of functional reserves over the patient population are required. Normal tissue complication probability $P_I$ for a general DVH is calculated from the equation:

$$P_I = \frac{1}{\sqrt{2\pi\sigma^2}} \int_0^f \exp \left[ -\frac{(v - v_{50})^2}{2\sigma^2} \right] dv$$  \hspace{1cm} (4.24)

in which it is assumed that the cumulative functional reserve distribution can be described as a displaced error function and quantified by the mean value of the functional reserve $v_{50}$, and the width of the functional reserve distribution $\sigma$. In this equation $v$ is the partial organ volume being irradiated (Jackson et al., 1993, 1995; Yorke et al., 1999).

### 4.1.5 The Weibull distribution

**The Weibull distribution model**

In this model the mathematical expression for the NTCP $P_I$ is based on a modified Weibull function (Johnson et al., 1994):

$$P_I = 1 - \exp \left[ - \left( \frac{DV^b}{A_1} \right)^{A_2} \right]$$  \hspace{1cm} (4.25)

where $A_1$, $b$ and $A_2$ are three model parameters, which are determined from the clinical data (Klepper, 2001). This can be rewritten in terms of $D_{50}$ and $\gamma_{50}$ as:

$$P(D) = 1 - \exp \left[ - \ln 2 \left( \frac{D}{D_{50}} \right)^{\frac{2}{\ln \gamma_{50}}} \right].$$  \hspace{1cm} (4.26)

### 4.2 Example of models fitting to experimental data

The models were fitted to experimental data for paralysis after irradiation of spinal cord of rats (Hopewell et al., 1987). They show development of two different endpoints: white matter related spinal cord paralysis (white matter necrosis) within 30 weeks and paralysis or histological evidence of vascular lesions (vascular damage) after a latent interval of 30 weeks following single dose irradiation of rat spinal cord. Three different lengths of irradiated spinal cord were used, 4, 8 and 16 mm.

For all the models the reference volume $V_{ref}$ was defined by the reference spinal cord length of $L_0=16$ mm corresponding to a relative volume $v = 1$, cf. Baltas and Grassman (1997); Cronqvist et al. (1995). Even if the size of the dataset is limited, it was sufficient to apply the statistical method...
we have chosen. Using these data, different parameters of the models were calculated for each of the endpoints using all the irradiated spinal cord lengths. The results were used to make an intercomparison between the predictions of the different models.

Two aspects of this study should be emphasized: the shape of the dose-response curve and the volume effect. To be able to judge each of the above phenomena individually we tried to separate them by removing the volume effect. The removal of the volume effect was achieved through making a separate fit of the models for each of the irradiated volumes or lengths of spinal cord separately, assuming that each partially irradiated length is a separate unity. Each of the models had a total of six free parameters due to the canceling of the parameters describing the volume dependence. The model intercomparison was made for fitting both with and without the volume effect.

We used the maximum likelihood method in our study to both compare the overall (i.e. including the volume effect) fitting results of all investigated models as well as to compare the fitting results of the models where the volume effect has been removed, as described above.

After fitting the models to the clinical data, the goodness of fit of the models and their parameters was evaluated by Pearson’s $\chi^2$-test, which was applied as suggested by (Baltas and Grassman, 1997). The $\chi^2$ value, although referred to as a measure of goodness of fit, actually represents a measure of lack of fit and it should thus be as low as possible. This means that the smaller the $\chi^2$ or the reduced $\chi^2$ values (taking into account the number of degrees of freedom, DF, that is the number of datapoints in the particular dataset reduced by the number of parameters in the respective model), the better the overall fit of the model or the better the dose-response curve agrees with the experimental data, when the volume effect has been removed.

An intercomparison of the fitting of the models to the experimental data was done using the F-test method. The main principle of this method is to perform a comparison between a given model and a reference model by comparing their fitted results to the experimental data. The $P_\chi$ value is a probability distribution calculated for the $\chi^2$ value for the reference model divided by the $\chi^2$ value for the model it is being compared to. The smaller the $P_\chi$ value, the better the compared model is in comparison to the reference model. The value of $P_\chi = 0.5$ means that the compared model and the reference one are identical; for $P_\chi < 0.5$ the compared model is better than the reference one, while for $P_\chi > 0.5$ the reference model is better. For intercomparison of the overall fits of the models, the commonly used Gaussian distribution model was chosen as reference. In order to compare fits of the models without volume effect, their overall fits were compared with the corresponding fits
without the volume effect for each individual model separately. For a more thorough discussion of the mentioned methods, see Collett (1991).

4.2.1 Results of comparison using the likelihood function

The best estimates as well as the 68\% confidence intervals (corresponding to one standard deviation for standard distribution) for the parameters ($D_{50}$, $\gamma_{50}$ and the respective volume parameters) of all models are given in Table 4.2. In this Table a comparison of the maximum likelihood results can be made for the respective endpoint. The values for the logarithm of the likelihood function (Log-likelihood) as well as the $\chi^2$, the number of degrees of freedom (DF) and reduced $\chi^2$ values are given. Based on parameters from this table the associated dose-response curves were plotted in Figure 4.2 for each of the models, respectively.

4.2.2 Results of comparison using the F test

Table 4.2 presents also results of the model comparison when the F test method was used. The values of $P_{\chi^2}$ are given in the last column, i.e. the distribution function for the $\chi^2$ ratio, where DF for separate fits are the numerator and DF for the overall fit is the denominator degrees of freedom.

4.2.3 Conclusions from the model comparison

From the presented results one can clearly see that the differences in fitting the experimental data by the different models are rather small with a few exceptions. One should also remember that the confidence intervals are rather large. The reason for this is their experimental uncertainty with such a small number of data points. There may also be fine differences in the results caused by small errors within the experimental dataset. Based on the results in Table 4.2 and Figure 4.2 the following general conclusions can be drawn:

1. The Gaussian model is a symmetric sigmoid, which may be suboptimal for describing the response of some normal tissues (cf. 4 below).

2. The relative seriality model, having "fine-tuning" ability with the relative seriality parameter $s$ may be most suitable for fitting mixed parallel and serial to mainly serial tissues.

3. For white matter necrosis most of the models gave a good fit, with the following exceptions:
the fitting results of the inverse tumor and the critical element models were considerably worse (showing much lower Log-likelihood values) than the other models, taking the volume effect into account,

- when making a fit without the volume effect the Gaussian model gave inferior results with the lowest Log-likelihood,
- the Weibull distribution model was the only one giving better overall fit than the Gaussian distribution model (we chose the Gaussian model as the reference model in the F test and although this model is most commonly used, our results show it is not always the best),
- the Gaussian distribution, the parallel architecture and the Weibull distribution models were best handling the volume effect, giving best F test results.

4. Testing the dose-response curve shape without considering the volume dependence the Gaussian model gave the worst fit.

In clinical radiotherapy there is an increasing need of accurate models capable of describing the normal tissue response as a function of the dose and the irradiated volume. The present study gives an overview of the main existing models that are most frequently used. However, still more effort has to be given to radiobiological studies that can develop improved models suitable for biologically optimized radiotherapy planning.

Most modern radiobiological models have the potential to be used in radiobiologically optimized radiation therapy if they accurately describe the volume dependence and result in a good sigmoid dose-response curve. The models used here are good enough for both these aspects.

The separation of the volume effect from the sigmoid shape generating part in the models also opens up the possibility of novel combinations of them like e.g. relative seriality together with a binomial sigmoid.

Today all organs are assumed to be totally homogeneous and amorphous, without internal structure, even if we know that some organ regions are more sensitive and others more tolerant to irradiation. In the future such variations need to be considered, eg. by splitting the hilus region from the rest of the organ in most organs of mixed serial-parallel organization. Fortunately this problem has not been a major problem in this study. However, if the dataset had information where white and gray matter were separately irradiated, this would have changed the situation since they have different sensitivity as shown in Paper I.
Table 4.2: Model parameter values for white matter necrosis. Parameters are given with their 68% confidence intervals. LL stands for the logarithm of the likelihood function.

<table>
<thead>
<tr>
<th>name of the model</th>
<th>$D_{50}$, Gy</th>
<th>$\gamma_{50}$</th>
<th>volume parameters</th>
<th>LL</th>
<th>$\chi^2$</th>
<th>DF</th>
<th>red. $\chi^2$</th>
<th>$P_\chi$</th>
</tr>
</thead>
<tbody>
<tr>
<td>critical volume</td>
<td>20.70 (20.25–21.18)</td>
<td>3.20 (2.57–3.29)</td>
<td>$M=20$ (18–21), $N=397$ (320–431)</td>
<td>-35.57</td>
<td>12.75</td>
<td>10</td>
<td>1.28</td>
<td>0.57</td>
</tr>
<tr>
<td>no volume effect</td>
<td></td>
<td></td>
<td></td>
<td>-31.99</td>
<td>4.57</td>
<td>8</td>
<td>0.57</td>
<td>0.92</td>
</tr>
<tr>
<td>relative seriality</td>
<td>21.30 (21.14–21.54)</td>
<td>3.99 (3.64–4.41)</td>
<td>$s=0.01$ (0.01–0.01)</td>
<td>-35.25</td>
<td>14.09</td>
<td>11</td>
<td>1.28</td>
<td>0.63</td>
</tr>
<tr>
<td>no volume effect</td>
<td></td>
<td></td>
<td></td>
<td>-31.92</td>
<td>4.84</td>
<td>8</td>
<td>0.61</td>
<td>0.93</td>
</tr>
<tr>
<td>critical element</td>
<td>24.20 (23.14–26.03)</td>
<td>0.99 (0.73–1.27)</td>
<td>—</td>
<td>-47.26</td>
<td>25.76</td>
<td>12</td>
<td>2.15</td>
<td>0.90</td>
</tr>
<tr>
<td>no volume effect</td>
<td></td>
<td></td>
<td></td>
<td>-31.92</td>
<td>4.84</td>
<td>8</td>
<td>0.61</td>
<td>0.99</td>
</tr>
<tr>
<td>inverse tumor</td>
<td>19.47 (17.51–21.48)</td>
<td>0.99 (0.80–1.17)</td>
<td>$k=-3.05$ (-3.59– -2.53)</td>
<td>-40.17</td>
<td>16.89</td>
<td>11</td>
<td>1.54</td>
<td>0.73</td>
</tr>
<tr>
<td>no volume effect</td>
<td></td>
<td></td>
<td></td>
<td>-31.92</td>
<td>4.84</td>
<td>8</td>
<td>0.61</td>
<td>0.96</td>
</tr>
<tr>
<td>Gaussian distribution</td>
<td>20.96 (20.46–21.71)</td>
<td>4.03 (3.31–4.70)</td>
<td>$n=0.62$ (0.58–0.66)</td>
<td>-35.98</td>
<td>11.46</td>
<td>11</td>
<td>1.04</td>
<td>0.50</td>
</tr>
<tr>
<td>no volume effect</td>
<td></td>
<td></td>
<td></td>
<td>-33.41</td>
<td>5.56</td>
<td>8</td>
<td>0.70</td>
<td>0.84</td>
</tr>
<tr>
<td>parallel architecture</td>
<td>21.17 (17.97–30.38)</td>
<td>3.89 (3.15–5.10)</td>
<td>$\nu_{50}=0.14$ (0.13–0.16), $\sigma_v=0.03$ (0.02–0.03)</td>
<td>-34.29</td>
<td>11.52</td>
<td>10</td>
<td>1.15</td>
<td>0.51</td>
</tr>
<tr>
<td>no volume effect</td>
<td></td>
<td></td>
<td></td>
<td>-32.10</td>
<td>5.02</td>
<td>8</td>
<td>0.63</td>
<td>0.87</td>
</tr>
<tr>
<td>Weibull distribution</td>
<td>22.77 (22.59–23.35)</td>
<td>3.20 (2.49–3.95)</td>
<td>$B=0.63$ (0.59–0.66)</td>
<td>-35.44</td>
<td>10.33</td>
<td>11</td>
<td>0.94</td>
<td>0.43</td>
</tr>
<tr>
<td>no volume effect</td>
<td></td>
<td></td>
<td></td>
<td>-31.62</td>
<td>4.26</td>
<td>8</td>
<td>0.53</td>
<td>0.89</td>
</tr>
</tbody>
</table>
4.3 Possible future extensions

For historical reasons organs are outlined without internal structures which is obviously suboptimal as the vascular hilus region with large vessels is generally more resistant than the periferal regions with more microcapilaries. In the future sub-volumes of an organ will be identified to make the models more realistic. Work of Källman et al. (1992) as well as Papers I and III might indicate the need for such improvement.
5. Maximum likelihood method

To perform the fitting of the models to experimental data, statistical methods were used. The maximum likelihood method is perhaps the most powerful estimation. By likelihood we understand the likelihood of unknown parameters in the model on the basis of observed clinical data. The weight of evidence in favour of a given set of parameters is greater, the larger the likelihood value. The logarithm of the likelihood function is often used for computational convenience. The logarithm of the likelihood function is the logarithm of probability that the experiment ends in the way it actually did. The bigger the Log-likelihood value, the better the respective fit.

5.1 The Likelihood Function

Assume that we have a real stochastic variable (or a set of $N$ stochastic variables) $\vec{X}$, with p.d.f. (probability density function) $f(\vec{X}|\vec{\theta})$, where $\vec{\theta}$ is a real parameter (or a set of $k$ real parameters). The set of allowed values of $\vec{X}$ (the range of $\vec{X}$) will be denoted by $\Omega_{\vec{\theta}}$, where the subscript denotes the possible dependence of $\Omega$ on $\vec{\theta}$.

Consider a set of $N$ independent observations of $X$, say $X_1, \ldots, X_N$. These could be $N$ events found in an experiment, an event being the measurement of $p$ quantities. The joint p.d.f. of the $X$'s is, by independence,

$$L(\vec{X}|\vec{\theta}) = L(X_1, \ldots X_N|\vec{\theta}) = \prod_{i=1}^{N} f(X_i|\vec{\theta}). \quad (5.1)$$

$L(\vec{X}|\vec{\theta})$ is usually called the likelihood function when considering it as a function of $\vec{\theta}$ only, the $\vec{X}$'s having fixed values observed in the experiment.

5.2 The Maximum Likelihood Estimate

The maximum likelihood estimate of the parameters $\vec{\theta}$ is that value $\hat{\theta}$ for which $L(\vec{X}, \vec{\theta})$ has its maximum, given the particular observations $\vec{X}$. The maximum likelihood method is usually performed by maximizing the logarithm
of the likelihood function:

\[ \hat{\theta} \equiv \max_{\theta} \ln L(\bar{X}|\bar{\theta}). \]  

(5.2)

### 5.2.1 Example: Throwing a coin

Assume that a coin has an unknown probability \( \theta \) of landing with the head up. The range \( \Omega_{\theta} \) is thus \( 0 \leq \theta \leq 1 \). The number of coins with head up when repeatedly throwing the coin \( n \) times can be considered as an observation of the stochastic variable \( X \in \text{Bin}(n, \theta) \). The likelihood function becomes:

\[ L(\theta) = \binom{n}{x} \theta^x (1-\theta)^{n-x}. \]  

(5.3)

Taking the logarithm gives:

\[ \ln L(\theta) = \ln \binom{n}{x} + x \ln \theta + (n-x) \ln(1-\theta). \]  

(5.4)

Taking the derivative with respect to \( \theta \) gives:

\[ \frac{d\ln L(\theta)}{d\theta} = \frac{x}{\theta} - \frac{n-x}{1-\theta}. \]

Putting the derivative equal to zero and solving for \( \theta \) gives the ML-estimate \( \hat{\theta} = x/n \), which is the relative frequency of coins with tail up.

### 5.2.2 Example: Fitting of response data

Assume that \( n \) patients have been treated and that \( x \) of them responded (e.g. tumor control or normal tissue complications). The number of responders can then be considered as an observation of the stochastic variable \( X \in \text{Bin}(n, p) \), where \( p \) is the unknown probability of response. In the general case when a response model with several parameters is used \( X \in \text{Bin}(n, p(\bar{\theta})) \) where e.g. \( \bar{\theta} = (D_0 N_0) \) for the standard Poisson model for radiation response is used. The log-likelihood function then becomes:

\[ \ln L(p(\bar{\theta})) = \ln \binom{n}{x} + x \ln p(\bar{\theta}) + (n-x) \ln(1-p(\bar{\theta})). \]  

(5.5)

Since the first term does not depend on \( p(\bar{\theta}) \) it can be disregarded in the maximization procedure, and the ML-estimate of \( \bar{\theta} \) can be found by:

\[ \hat{\bar{\theta}} = \max_{\bar{\theta}} \left\{ x \ln p(\bar{\theta}) + (n-x) \ln(1-p(\bar{\theta})) \right\}. \]  

(5.6)
6. Treatment optimization with biological objectives

6.1 $P_+$ and $P_{++}$

Generally, the aim of radiation therapy is to eradicate the malignant disease, while at the same time sparing the surrounding healthy tissue as much as possible. Optimization of radiation therapy aims at achieving those two goals in an optimal way. Modern radiobiologically optimized intensity-modulated radiation therapy is rapidly becoming a clinical tool of great importance. It improves the treatment outcome through increasing the dose to the tumor, as well as the dose per fraction, while at the same time decreasing or at least keeping constant the dose and dose per fraction to the healthy tissue (organs at risk) and perhaps even reducing the number of fractions together with the overall treatment time (Brahme, 2000).

Throughout the years, various efforts have been directed towards developing a measure to quantify the treatment risks vs. benefits. One of the first objective functions with radiogiological basis (as distinct from the previously used physical objective functions) was the complication probability factor (CPF) described in the early 1980s by Wolbarst and coauthors (Wolbarst, 1984; Wolbarst et al., 1982, 1980) and measuring the likelihood of a given dose distribution leading to damage of healthy tissue and resulting in serious complications for the patient. More recently, a similar concept expressing the probability of uncomplicated tumor control ($P_+$) has been introduced (Ågren et al., 1990). It can generally be described as the probability of tumor control reduced by the probability of tumor control associated with severe normal tissue damage at the same time. $P_+$ can be presented by the following equation:

$$P_+ = P_B - P_{B \cap I}$$  \hspace{1cm} (6.1)

where $P_B$ is the probability of achieving tumor control and $P_{B \cap I}$ is the probability of having both tumor control (B=benefit) and severe normal tissue complications (I=injury) at the same time.

From a statistical point of view it is important that both effects (i.e. benefit=tumor cure and injury=normal tissue complications) should be of similar character or importance to be able to compare them with each other. Since all malignant diseases are of life-threatening nature, the risk of death from recurrences in case of suboptimal treatment should preferably be weighted.
against the risk of death from severe or fatal radiation-induced normal tissue complications.

Figure 6.1: Schematic drawing showing possible configurations of the mutual relations between treatment benefit (B) and normal tissue injury (I). In the left column, benefit and injury are disjunct events, in the middle column the events are statistically independent, provided that their intersection is described by \( P_{B \cap I} \), in panel (7.) normal tissue injury always results in treatment benefit, for (8.) benefit and injury are totally correlated and for panel (9.) treatment benefit always results in normal tissue injury.

Let us consider the following five typical cases (cf. Figure 6.1), where:

a) both events, benefit and injury are disjunct so they do not intersect each other and are thus are mutually exclusive (the whole left column in the Figure 6.1), the probability of complication free tumor cure is then by definition given by:

\[
P_+ = P_B - 0 = P_B.
\]  

This case is not really clinically relevant, since it is not very likely that the two end points do not intersect each other.

b) Both events, benefit and injury are statistically independent and accordingly uncorrelated (the whole middle column in the Figure 6.1), the probability of complication free tumor cure is given by the following equation:

\[
P_+ = P_B - P_B \cdot P_I = P_B (1 - P_I).
\]
c) Both events are correlated in such a way that the normal tissue injury always results in treatment benefit \((I \Rightarrow B, \text{panel (7.) in the Figure 6.1})\), the complication free tumor cure will be the following:

\[ P_+ = P_B - P_l. \]  

(6.4)

This is quite common since a radiation sensitive tissue will often generate a more sensitive tumor.

d) Both events are totally correlated \((B \equiv I, \text{panel (8.) in the Figure 6.1})\), may describe the clinical case of parallel opposed beams) when tumor and healthy tissue receive roughly the same dose, the complication free tumor cure is:

\[ P_+ = P_B - P_B = 0, \]  

(6.5)

e) Both events are dependent in such a way that the treatment benefit always results in normal tissue injury \((B \Rightarrow I, \text{panel (9.) in the Figure 6.1})\), the complication free tumor cure can be presented as:

\[ P_+ = P_B - P_B = 0. \]  

(6.6)

The disjunct case (left column in the Figure 6.1) shows clearly that the traditional definition of \(P_+\) in terms of intersection and a conditional probability is not perfect. It would be more desirable to define \(P_+\) by maximizing \(P_B\) and simultaneously minimizing injury. In principle, this is to some extent done by using \(P_B(1 - P_l)\) and \(P_B - P_l\) or even \(P_B/P_l\) objective functions. The \(P_{++}\) strategy is really the ideal combination since first \(P_+\) is maximized and then \(P_l\) is conditionally minimized, keeping the reduction of \(P_+\) below 0.5 to 1% \((\text{cf. Figure 6.2})\).

The clinically optimal dose using the \(P_{++}\) strategy is located just in front of the \(P_+\) maximum to reduce injury without significant loss of complication free cure. Figure 6.2 presents dose response curves for tumor cure, normal tissue damage and complication free tumor cure based on the \(P_{++}\) optimized three field treatment of prostate. By definition, the local \(\gamma\) value at the maximum of the complication free cure is the same for both tumor cure and normal tissue injury. This means that since the difference between the two sigmoids is bell-shaped, the complication free cure near its maximum is well described by a Gaussian function and varies slowly both at slightly lower and slightly higher doses (Brahme, 1996). It is thus possible to significantly reduce the delivered dose to reduce complications while the complication free cure will remain almost unchanged. This way a dose reduction of less than 1% will result in clinically unnoticeable loss in tumor cure and at the same time in 5% reduction in probability of normal tissue complications and it is also possible to show that, \(\text{cf. Löf (2000); Brahme and Lind (2008):}\)

\[ \Delta P_1^2 \approx \frac{1}{\pi} \frac{\Delta P_+}{P_+} \]  

(6.7)
6.2 Predictive assays

There is an increasing need for as much knowledge as possible on the response of tissue to radiation. The aim of Paper IV was to improve the accuracy of the existing dose-response parameters and to show the potential benefit that would be triggered by availability of individual radiosensitivity data for each treated patient. Being able to identify the radiosensitive or radioresistant subgroups of patients could already allow for increasing the therapeutic window for the identified patients. Therefore, the *in vivo* human data containing information relating radiation dose to tissue response is absolutely necessary to be systematically collected. Such information is increasingly available and keeping clinical follow-up record would provide the *in-vivo* data to support or verify radiobiological models of tissue and tumor response. Intensive efforts should be dedicated to methods that could categorize patients according to their radiation sensitivity that could lead to estimation or quantification of radiosensitivity of the individual patients.

The optimal predictive assay should be made on the patient *in vivo* during the first week of therapy resulting in the ultimate possibility of biologically...
6.2 Predictive assays

optimized therapy (Brahme, 2003, 2005). However, no predictive essays are in clinical routine use yet and however many studies have been published that develop methods aiming to quantify the radiation response of patients, both in terms of normal tissue complications as well as tumor control.

6.2.1 Predictive assays for normal tissues

Searching for a possibility to predict individual radiosensitivity of normal tissues is motivated by minimizing the suffering from possible severe side effects as well as improving the quality of life of radiosensitive patients. Results from Tucker et al. (1996) as well as from Paper IV support the concept of a significant therapeutic gain that could be achieved for a subgroup of patients, provided the availability of a predictive assay estimating the sensitivity of normal tissue. Various research groups have investigated the possibility of prospective assessing the tolerance of normal tissue from different factors. Below, some examples of such studies are highlighted:

- Late reaction to radiation therapy was correlated to in vitro radiosensitivity of fibroblasts from skin biopsies (Geara et al., 1993);
- excretion of a common DNA base damage (7,8-dihydro-8-oxo-2'-deoxyguanosine) was found to be a possible marker for acute radiosensitivity of breast cancer patients receiving adjuvant radiotherapy after surgery (Haghdoost et al., 2001);
- extracellular levels of the same base damage of DNA (8-oxo-dG) after in vitro irradiation were found to have a potential as a sensitive marker for oxidative stress (Haghdoost et al., 2005);
- increased level of prostate-specific antigen sentinel rise (PSA-SR) above 0.5 ng/mL in patients undergoing androgen deprivation therapy (ADT) and radiation therapy for prostate cancer was identified as early predictor of biochemical failure (D’Ambrosio et al., 2007).

6.2.2 Predictive assays for tumors

For prediction of tumor response to radiation therapy the combination of inherent sensitivity, oxygenation status, proliferative capacity and number of clonogenic cells would be enabled in practical way by a combination of cell-based and imaging assays (Peters and McKay, 2001; Hall and Giaccia, 2006). Below, some examples of predictive assays proposed for assessing the tumor response are presented:
• Higher hemoglobin levels as well as higher vascularity were favorable prognostic factors for cervical cancer patients treated with radiotherapy (Gasinska et al., 2002); 
• age over 50 years and high grade tumors were significantly unfavorable prognostic factors in survival of patients with astrocytic gliomas treated with radiotherapy (Gasinska et al., 2005); 
• age over 51 years and high tumor proliferation rate were significant unfavorable prognostic factors in survival of patients with high-grade glioma treated with surgery and radiotherapy (Gasinska et al., 2006); 
• pretreatment Bromodeoxyuridine labeling index (BrdUrdLI) was not predictive for early clinical and pathologic response of rectal cancer to preoperative radiotherapy (RT), while the ratio of BrdUrdLI after to BrdUrdLI before RT was correlated to inhibition of proliferation in responsive tumors (Gasinska et al., 2007). 

6.2.3 Future perspective

In the future, quantification of DNA double-strand breaks or other types of DNA damage could allow creating a rapid and accurate indication of both normal tissue and tumor radiosensitivity (McMillan et al., 2001). However, until the ability of molecular biology to create rapid and inexpensive genetic tests for radiosensitivity the truly optimal way of prospective assessing the probability of late effects and tumor control may remain only an attractive speculation (Peters and McKay, 2001; Brahme, 2003; Hall and Giaccia, 2006).
7. Conclusions

The main observations made from this thesis are the following:

- For vascular damage the relative seriality model is clearly superior to the other models, whereas for white matter necrosis all models are quite good except possibly the inverse tumor and critical element models.

- The radiation sensitivity, seriality and steepness of the dose-response relation of the spinal cord vary considerably along its length, as shown by comparing cervical and thoracic spinal cord regions.

- The cervical region of the spinal cord is more sensitive to radiation than the thoracic part.

- The dose-response relation for the cervical spinal cord is much steeper than the thoracic one.

- The cervical spinal cord is characterized by a more parallel structural organization than the thoracic region.

- The probability of inducing radiation myelitis is therefore more volume dependent for the cervical part of spinal cord.

- All the above phenomena are most likely caused by higher number of functional subunits in the cervical region consistent with a higher amount of white matter close to the brain.

- With strongly heterogeneous dose delivery the effective size of the functional subunit is of importance.

- Due to the random location of FSUs, the mean dose deposited in the FSU will be of importance for the response.

- The mean dose to the FSU can be determined by convolution of the FSU size with the delivered dose distribution.
7 Conclusions

- The radiation sensitivity distribution of the FSU may be an even better descriptor characterizing the response of the organ with heterogeneous dose delivery.

- To characterize the effectiveness of a dose distribution, the concept of dose-mass histogram (DMH) is a better descriptor than the presently used dose-volume histogram (DVH) concept.

- For normal tissue with heterogeneous response and non-uniform dose delivery, the whole dose distribution needs to be known and not just the DMH are DVH.

- With non-uniform sensitivity and heterogeneous dose delivery, $P_1$ is the quantity to use rather than the DMH or DVH, provided that the biological response model is rather well known.

- To categorize the radiation sensitivity of individual patients, detailed information relating radiation dose to tissue response are needed to accurately optimize the treatment.

- An individual optimization of a radiation treatment has the potential to increase the therapeutic window and improve cure for an identified subgroup of patients.

- Improved radiobiological description of radiation responses can contribute to increase the efficacy of a radiation treatment and will allow an improved biological optimization of the outcome.
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Gratitude is the memory of the heart.
French Proverb

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Gratitude is merely the secret hope of further favors. 
FRANCOIS DE LA ROCHEFOUCAULD
Outside of a dog, a book is man’s best friend.
Inside of a dog it’s too dark to read.
Groucho Marx


Improved dose response modeling for normal tissue damage 47


