Modeling the risk of toxicity in brain tumor patients treated with protons

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Abstract
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Introduction

Radiotherapy for treating tumors is spread nowadays all around the world. About 50% of the cancer treatments rely on radiotherapy, but this is one of the possible therapies of the larger family of the cancer treatments, to which also chemotherapy and surgery belong. They are often used also in combination in order to improve the effect of the treatment (e.g. chemotherapy and radiotherapy). The idea of radiotherapy is to exploit the damage that ionizing radiations can induce at the molecular level in order to induce cell damage and death. Beams of radiation are generated to release dose to tumor masses and different technologies are exploited in order to achieve the best tumor (target) covering and the best healthy tissue sparing.

In particular, the proton therapy (PT) is the most diffused alternative to the more conventional and widespread radiotherapy with photons. The use of protons for radiotherapy started to spread in the 90’ and it is now diffused all over the world with over 50 operating proton therapy centers [1] and over 150000 patients treated [2].

In Trento (I), a proton therapy center is operating since 2014 and has so far treated more than 300 patients. Patients generally benefit from protons compared to photons for what concerns healthy tissue sparing and target covering. In fact dose deposited by charged particles within a medium, is described by a sharped peaked curve compared to photons (Fig. 1.1), which can be exploited to focus the dose released, making protons suitable for radiotherapy. Nevertheless some potential drawbacks have to be considered; for instance, dose deposited to the skin is generally higher in a proton therapy treatment, due to the contribution of several single energy beams that are added together to build the spread out Bragg peak (SOBP) when treating extended regions. This may induce toxicity events during and after the treatment concerning skin, such as alopecia, dermatitis, necrosis.

Furthermore, charged particles, in addition to a physical gain, take advan-
tage of an enhanced biological effect compared to photons, quantified by the relative biological effectiveness (RBE) parameter which is generally maximized when particles are near to stop. This effect, which is significant for heavy ions, is slighter for protons, but, if not considered in a proper way, may underestimate the dose released on different structures, generally the more inner organs located in the distal part of the beam. Therefore, even though in clinics a constant value of RBE is assumed, more accurate models describing the RBE parameter are required to take into account variation in the biological response to radiation.

Toxicities induced by radiation may affect the quality of life of patients (QoL) undergoing radiotherapy, in particular when the disease is permanent. Therefore, models able to describe the risk of developing certain toxicities after radiotherapy treatment are needed. About this, normal tissue complication probability (NTCP) models have been derived for several organs and endpoints. However, as a relatively recent cancer treatment approach, proton therapy still lacks NTCP models describing the risk of developing certain radiation induced toxicities.

Aim of this work is thus to find dosimetric variables, able to predict the onset of radiation induced alopecia (RIA) and radiation induced fatigue (RIF), assessing a database of patients treated at the proton therapy facility of Trento with proton therapy for brain tumors (BT). For this purpose, NTCP models based on multivariate logistic regression are developed.

Therefore the thesis is organized as follows:

1. A general introduction on the proton therapy, concerning the physics of protons and the radiobiology.
2. A detailed chapter on the data set and method used in the study
3. A chapter presenting the results and discussion of the work
4. A final part with conclusions about the work and possible outlook
Chapter 1

Physics and radiobiology of proton therapy

Figure 1.1: Comparison of depth-dose curves for various particles (photon, proton, carbon ion). The peculiar Bragg peak for both ion types and their differences are clearly visible. Image taken from [3].

This chapter is intended to give basic principles of proton therapy and in particular the tools to comprehend the work. Therefore, a first section will be dedicated to the physics of protons interacting with matter, moving from the microscopic nature of the interaction, to the macroscopic effect when looking on the dose deposited within the medium, which gives the
typical peaked depth dose curve for charged particles (Fig. 1.1). Moreover a section will be dedicated to the radiobiology, i.e. the biological response to radiation, starting from the damage induced by radiation to cells, and then introducing the concept of RBE to describe the response of cells and tissues to different radiation types, and how this parameter is considered in clinic. Furthermore a paragraph will highlight features of tumor control probability (TCP) models and normal tissue complication probability (NTCP) model adopted in order to have a clinical significant predictive quantity for a given irradiation schedule (treatment plan). Finally an introduction to the Monte Carlo methods for simulations which have been exploited in this work will be given at the end of this chapter.

1.1 Proton interaction with matter

While protons travel through the absorbing medium, they can experience three distinct types of interactions (Fig.1.2): they can slow down (stopping) by multiple collisions with atomic and molecular electrons, leading to excitation and ionization of the medium, they can be deflected (scattering) by multiple Coulomb collisions with the atomic nuclei, and finally can have an head-on collision with nuclei (nuclear interactions) that can result in the production of $\gamma$-rays, neutrons $n$ or ions ([4]). To a first-order approximation, protons continuously lose kinetic energy via frequent inelastic collision with atomic electrons. They travel nearly straight since their mass is $10^3$ times the mass of the electrons. Differently, when a proton passes near the nucleus it experiences a repulsive force that deflects its trajectory due to the large mass of the nucleus. Inelastic nuclear reactions between proton and the nucleus are less frequent, but may lead to target fragmentation via emission of protons or heavier ions. Eventually Bremsstrahlung is also a theoretically possible process, but at the energies used for therapeutic application, it is unlikely to happen [5].

1.1.1 Stopping power and Bethe-Block equation

The energy transfer from an ion to matter in each individual atomic interaction is generally small, so that the particle undergoes a large number of interactions before its kinetic energy is spent. Stopping power is the parameter used to describe the gradual loss of energy of the charged particle as it
Figure 1.2: Three different types of collisions of a proton with an atom. Inelastic collision via electromagnetic interaction with an orbital electron (a); elastic collision via electromagnetic interaction with the atomic nucleus (b); and inelastic collision via nuclear interaction with production of gamma rays $\gamma$, neutrons $n$ or alpha particles (c) [5].
penetrates into an absorbing medium. Two classes of stopping powers are known: the *collision* stopping power \( S_{\text{col}} \) which can be electronic, due to the Coulomb interaction of the incident ions with the electrons of the traversed material, or nuclear, due to the Coulomb interactions with the nuclei, and the *radiative* stopping power, related to the emission of radiation in the electric field of atomic nuclei or atomic electrons.

The rate of energy loss by the charged particle per unit length \((-dE/dx)\) in the medium is called linear stopping power and it is dependent on both particle and absorbing medium properties. Generally the stopping power is best expressed in MeV cm\(^2\)/g because it is divided by the density \( \rho = g/cm^3 \) of the absorber in order to remove its dependence (Mass stopping power). The energy loss is given by both collision loss and radiative loss contributions, so that the total stopping power is \( S_{\text{tot}} = S_{\text{rad}} + S_{\text{col}} \).

The formulation of the mass stopping power was developed by Bethe and Block in 1933 and has its relativistic expression in the formula:

\[
S_\rho = -\frac{dE}{dx} = 4\pi N_A r_e^2 m_e c^2 Z z^2 \frac{Z}{A} \frac{2Z}{\beta^2} \left[ \ln \frac{2m_e c^2 \gamma^2 \beta^2}{<I>} - \frac{\beta^2 - \delta}{2} - \frac{C}{Z} \right] \tag{1.1}
\]

where \( N_A \) is Avogadro’s number, \( r_e \) is the classical electron radius, \( m_e \) is the mass of an electron, \( Z \) and \( A \) are the atomic number and atomic mass of the absorber medium, \( z \) is the atomic number of the charged particle and \( <I> \) is the mean excitation energy of the target material, namely the mean minimum energy \( \Delta E_{\text{exc}} \) that can be transferred from the incoming particle to an absorber atom via Coulomb interaction with an orbital electron. \( <I> \) is a monotonic increasing function of \( Z \) and ranges from 19 eV for hydrogen to 820 eV for lead. The last two terms in the equation 1.1, \( \delta \) and \( C \), are two correction terms which involve relativistic theory and quantum mechanics and need to be considered when protons with high or very low energy are used in calculations.

Concerning the dependence of the stopping power from the incoming charged particle, we notice that \( S_\rho \) is proportional to \( z^2 \), so that in general, heavier nuclei suffer more energy loss for the same \( \beta \); in addition it is also proportional to \( \beta^{-2} \), meaning that the stopping power increases as the particle slows down in the medium (Fig. 1.3). This gives the typical Bragg peak profile along the penetration direction for a charged particle shown in Fig.1.1. On the other hand the dependence on the medium is expressed by the factor \( Z/A \) and by the logarithm of \( I^{-1} \).

Once the stopping power is known one can calculate the range of a charged
particle with a certain initial kinetic energy inside a medium. This is a fundamental task in hadron therapy, in order to select the energy of a particle that has to reach the target (tumor). The range for heavy particles can be calculated with CSDA (continuous slowing down approximation) as suggested by Berger and Seltzer in 1983:

\[
R_{\text{CSDA}}(E_k) = \int_{E_{\text{kin}}}^{0} - \frac{dE}{S_{\text{tot}}(E_k)}
\]

In the case of heavy charged particles the CSDA is a good approximation of the average range \( \bar{R} \) of the particle in the medium, because of their essentially straight path through the medium compared to that of lightest particles (e.g. electron, positrons) as shown in Fig.(1.4). Fig.(1.5) shows the range for a proton beam as a function of the energy calculated with CSDA and compared to the range obtained by projecting the path along the beam direction. We notice that the approximation is reliable in the energy range required to cover the human body size \((10^1-10^2 \text{ MeV})\). Another quantity used in dosimetry is the LET (Linear Energy Transfer) expressed in keV/µm which is defined as the energy released by the ionizing particle per unit length.
to the electrons in the medium \( \frac{dE}{dx} \). LET differs from linear stopping power as the former considers only the electronic collision stopping power, while the latter takes into account also radiative losses and nuclear collision losses by electromagnetic interaction. Moreover, LET is normally referring to energy deposited locally and loses the energy transported by secondaries at distant locations. In fact, LET is generally calculated considering energy released by primary particles to the secondaries up to a certain threshold. This is defined as the restricted LET \( LET_\Delta \):\[ LET_\Delta = \frac{dE_\Delta}{dx} \quad (1.3) \]

Which excludes all the secondary particles with energy larger than \( \Delta \). When we do not consider restriction in energy of the secondaries, we deal with the unrestricted LET \( LET_\infty \) which is equal to minus the electronic collision stopping power. Nevertheless, at energies considered for therapeutic application (e.g. protons up to 250 MeV), the LET and the collision stopping power can be considered to be nearly equal [8].
1.1.2 Depth dose curve and Bragg peak

In medical applications what we are interested in is the physical absorbed dose $D$ released by a beam of particles in medium. The dose $D$ is defined as the energy absorbed per unit target mass:

$$D = \frac{dE}{dm} \quad \left[ Gy = \frac{J}{Kg} \right]$$  \hspace{1cm} (1.4)

Starting from the linear stopping power we can calculate the dose as:

$$D[Gy] = 1.6 \cdot 10^{-19} \cdot LET \left[ \frac{keV}{\mu m} \right] \cdot F[cm^{-2}] \cdot \frac{1}{\rho} \left[ \frac{cm^3}{g} \right]$$  \hspace{1cm} (1.5)

where $LET$ is the linear energy transfer, $F$ is the fluence of a monoenergetic beam of particles and $\rho$ is the medium density.

Once we know how to calculate the dose from the stopping power and fluence, we can calculate even the dose deposited along a certain depth in a direction (typically the direction of the beam). Fig.(1.6) shows the typical shape of the depth dose curve for a proton beam along the beam direction. We notice
Figure 1.6: Left: 75 proton beam depth dose curves calculated with Monte-carlo for energies from 59.4 to 255 MeV [6]. Right: spread out Bragg peak

the presence of a Bragg peak arising by the dependence of the stopping power by the inverse of the square velocity of the particle ($\beta^{-2}$) in formula (1.1). We notice that this peak has a certain width. When we are performing experiments or clinical practice we deal with beams of (quasi) monoenergetic particles directed onto the target and we do not obtain the same exact finite range for all of them. This phenomenon is the so called range straggling and it has different causes:

- Energy fluctuations in the incoming beam. Although the beam is nominally monoenergetic, there are fluctuation in the spectrum up to 1% that lead to range broadening;

- The nature of the interaction between particles and matter is stochastic and this leads to slight variations on energy losses and, as a consequence, on the range of the single particle, which increases with the distance traveled (i.e. as the particle initial energy increases);

We notice from Fig. (1.6) that the Bragg peak has a width of some millimeters given a certain beam energy. In radiotherapy we deal with tumors with the extent of several centimeters, thus the use of a single energy beam is not enough to cover with conformity the entire target region. The solution is the combination of different energy beams that, opportunely weighted in intensity, can cover the region to treat uniformly in the so-called spread out Bragg peak (SOBP). A SOBP (Fig. 1.6) has the advantage that we can in
principle release a very uniform dose to the target and, thanks to the distal fall off, very low doses to the distal organs at risk (OARs) that may be present in the patient anatomy. One of the major drawbacks is instead the increase of the dose in the entrance channel and thus on the body surface that may induce toxicity events related to the skin compared to the conventional use of photons (Fig. 1.7).

1.2 Biological damage

In addition to the physical advantage (Bragg peak) discussed in Sec 1.1, the use of charged particles in cancer treatment can be associated with distinct biological effects compared to X-ray. Heavy charged particles are considered high LET particles, since the energy released to the medium locally is high, compared to the lighter ones (Eq. 1.1). This property has the consequence that the ionization path of the charged particle is concentrated in a small localized region (densely ionizing particles) and thus, it is more probable to induce severe damages at the cellular level [6] (Fig. 1.8).

1.2.1 Biological damage of ionizing particles

Ionizing radiation is able to ionize molecules belonging to sensible structures inside the cells and the most sensible target to consider is the DNA inside
Figure 1.8: Simulated patterns of DSB distribution after photon and ion irradiation in a typical cell nucleus (radius of $\sim 5\mu m$). Protons are shown at the typical LET assumed in the entrance channel, resulting in a photon-like distribution of lesions (sparsely ionizing radiation). Low energy alpha particles and oxygen ions are also shown as representative of the typical target fragments produced in PT [10].
the cell nucleus. DNA is an helical double strand structure wrapped around itself to form chromosomes (Fig. 1.9). Chromosomes contain all the genetic information of the cell, essential for the cell replication (mitosis). Cells are in general able to repair the majority of damages to the DNA thanks to several dedicated proteins. The most severe damage that ionizing radiation can induce to the DNA is the double strand break (DBS), meaning that both the helical strands are broken by the radiation. This kind of damage is not always repairable, and may induce cell death, especially when several of such damages are occurring nearby (clustered DSBs). High LET particles, thanks to their dense ionization path, are able to cause more dense DSB damages to the DNA compared to photons, and thus a major probability to induce cell death. (Fig. 1.8).

Investigation of radiation induced cell death, intended as mitotic death (i.e. loss of proliferation capability) is one of the common methods used to study effects of ionizing radiation on cells. Cell lines are irradiated in vitro and then are seeded in culture flasks at appropriate density; a cell is classified as a survivor if it is able to produce at least 50 daughter cells within a time interval of 10-14 cell cycles. Irradiation of cells with different doses lead us to have several experimental points and fit them creating the so called cell survival curves which describe the survival fraction of cells as a function of the dose. Survival curves can depend in general on different parameters (cell type, cell cycle phase, radiation type, radiation energy, ..) but they all have similar
shape and thus rely on a similar mathematical description. The mathematical formulation for survival dose response $S(D)$ is based on the so-called linear-quadratic model:

$$S(D) = S_0 e^{-(\alpha D + \beta D^2)}$$  \hspace{1cm} (1.6)

Where $S_0$ is the survival probability for unirradiated sample and $\alpha$ and $\beta$ two parameters, the former associated to the linear behavior at low doses and the latter with the quadratic trend at higher doses. Typically what we are interested in is the ratio $\alpha/\beta$ that determines the trend of the survival curve with the dose, representing a dose where the linear and quadratic contributions are equal. Each tissue under study is generally labeled by a specific $\alpha/\beta$ based on some in vitro or in vivo study, that determines its response to radiation (e.g. a large part of the tumors have an $\alpha/\beta = 10$). In Fig.1.10 (left) we notice that sensitive cells, meaning that they are not proficient in repairing damages, show a linear trend compared to normal cell’s linear quadratic behavior. This fact indicates the possibility that the quadratic term in eq.1.6 is related to the ability of the cell to repair. Fig.1.10 (right) shows survival curves for different values of $\alpha$ and $\beta$. The repair of radiation damage takes a certain time interval, thus the damage to a biological object depends also on the temporal distribution of the dose delivery: at fixed dose, we expect a larger survival fraction for cell lines exposed to same dose but diluted in
Figure 1.11: Split dose recovery observed after irradiation of two human normal fibroblast cell lines. The total dose was given in 2 fractions of half the total dose with a time interval as indicated on the x-axis [11]

It is observed experimentally that the repair capability reaches a saturation when the time interval increases 1.11. This indicates that almost all the repairable damages have been repaired. This biological behavior is exploited in radiotherapy, where the dose is typically delivered in several fractions: as an example, a general schedule for a proton therapy treatment could be 30 fractions, over 6 weeks, i.e. 5 fractions per week. The advantage of such a schedule is to allow the repair of the healthy tissues surrounding the tumor volume which receive relatively high doses. In fact tumor cells have in general less repair capability, so that fractionation has less effect on them. When we are dealing with high LET particles, the LQ model is not more applicable and the shape of the survival curve is different compared to photons (Fig.1.12). In the logarithmic scale, the survival curve is a straight line, meaning the loss or the attenuation of the quadratic contribution in eq. (1.6). If we assume that the quadratic contribution is linked to the repair capacity of the cell after irradiation, as stated above, we can conclude that in the case of high LET radiation, where the damage is more localized and complex, the cell has more difficulties in repairing its structures, leading to cell death.
1.2.2 RBE

The way we quantify the enhanced biological effect described in Sec.1.2.1 is through the RBE (Relative Biological Effectiveness). This factor is defined as the ratio of absorbed doses, which have to be applied for the two radiation types to achieve the same biological effect:

\[
RBE := \frac{D_\gamma}{D_I} \bigg|_{Isoeffect} 
\]

Due to their different shape, the survival curves cannot be transformed into each other by simply applying a constant scaling factor to the dose (dose modifying factor). When we are dealing with charged particle radiations we calculate an RBE weighted dose \( D_{RBE} \), in order to account for the enhanced biological effectiveness, by multiplying the physical absorbed dose for the RBE \( (D_{RBE} = D_{phy} \cdot RBE) \). Since for high LET particles the survival curve can be described by a linear term \( S(D) = S_0 e^{-\alpha D} \) (Fig.1.12), the limit for \( D > 0 \) of the RBE is the ratio between the linear coefficients of the survival curves:

\[
RBE_{max} = \frac{\alpha_\gamma}{\alpha_I}
\]

When the dose increases the RBE decreases, down to the value of 1 for very high doses. This asymptotic behavior is in accordance with model of biological damage of radiations described in Sec.1.2.1, since for very high doses we expect that the damages to the cells reach a saturation and the initial enhanced biological effectiveness of ions compared to photons is reduced.

RBE strongly depends on physical characteristics of the particles (e.g. particle charge and LET). The dependence LET is shown in Fig.1.13, where we notice an initial increase of RBE with the LET and a following saturation trend. The increase of RBE from low to intermediate LET values can be attributed to increasing energy concentration within the particle tracks; this may lead to more complex damages into the cell and a consequent increase in the RBE. The drop of RBE at higher values of LET can instead be explained considering a saturation effect in the damage. RBE is a complex quantity and can in general depend on several parameters: physical (LET, energy, particle type) and biological (cell type, cell cycle phase, oxygenation level) ones.

Even if it is clear that the RBE is far from being a constant factor, in proton-therapy clinical practice it is assumed that is more safe to fix its value to 1.1.
Figure 1.12: Explanation of RBE. Experimental data: survival of CHO-K1 Chinese hamster cells. (Experimental data from [12])

Figure 1.13: Variation of RBE with linear energy transfer (LET). RBE$_\alpha$ represents the limiting RBE at very low doses, dened by the ratio $\alpha_I/\alpha_X$ of the linear coefficients. (Redrawn from [12] by [11])
Figure 1.14: Physical and RBE-weighted dose are shown, as obtained with a constant and with a variable RBE. Special emphasis is given to the differences at the distal fall-off, where OAR might be located [14].

In treatment plans in order to calculate RBE-weighted-dose calculation it is thus enough to increase the physical dose by a 10%, which is quite an easy task and does not require any additional computational power. The reason is that, despite the moderate experience in the therapeutic use of protons, there is still much to be clarified concerning the biological response of cells and tissues when irradiated with protons compared to photons, including tumor and normal tissue response [13]. This is reflected into the large uncertainties found in literature in the definition of RBE-LET relation (Fig.1.13). Thus a fixed value of 1.1, based in particular on in vivo results, seems to be a reasonable approximation for different studies [10]. In other words, this means that even if the assumption is wrong in principle, there is up to now no clear clinical evidence against it.

Even though clinically accepted, the 1.1 assumption for the RBE of protons over their whole range may lead to some drawbacks, first of all a possible underestimation of the biological dose deposited along the proton path. This might cause some extra dose, in particular in the distal fall-off part of the dose depth curve, where the LET of charged particles reaches the maximum and where an OAR might be located (Fig.1.14). Secondly, a complete knowl-
edge of the RBE along the proton range, could allow some dose sparing even at the level of the treatment plan doses, since we may lower the physical dose while fulfilling the same effective dose prescriptions.

1.3 TCP and NTCP modelling

In radiotherapy having models that describe the outcome of a treatment for what concerns both the tumor killing and the onset of complications in normal tissues are needed. Therefore tumor control probability (TCP) and normal tissue complication probability (NTCP) models were developed. These models, as the names suggest, describe the probability to control the tumor, meaning to stop the ability of tumor cell to proliferate, and the probability to develop some kind of toxicity in normal tissues, respectively. Such models are generally based on dose-volume histograms (DVH) of the different structures inside the body. DVHs represent a compact simplification of the 3D dose distributions both in target and normal tissues. Each point of the DVH represent the volume (relative or absolute) which receives at least a certain dose ($V_x$ is the volume receiving $D \geq x$ Gy, Fig 1.15, Left). If the NTCP and TCP vs. prescription doses are computed from their mathematical expressions, then shallow curves having sigmoidal shapes result as opposed to a binary situation (Fig.1.15, right).

1.3.1 TCP

Most of the TCP models are mechanistic descriptions that start from the cell survival model, based on the LQ approach for cell damage described in Sec.1.2. The sigmoidal shape of the dose-response curve (Fig.1.15,Right panel) is suitable for a description via Poisson distribution. In 1961, Munro and Gilbert [16] were the first to apply the Poisson statistic to a TCP model. They started from the assumption that the nature of cell damage is stochastic and that a full control of the tumor is obtained when all the malignant cells (clonogens) are not able to proliferate anymore. They derived an expression for the probability to control a tumor with N clonogens:

$$TCP = e^{-\lambda}$$

(1.8)

where $\lambda$ is the average number of surviving clonogens.
Figure 1.15: Left: dose-volume histogram (DVH) for clinical target volume (CTV) and organ at risk (OAR). Right: TCP and NTCP vs. prescription dose as computed from mathematical functions, whose parameters are derived from best fits to DVH-based binary clinical outcomes.[15]

Webb-Nahum’s TCP model

Over the years eq.1.8 has been further developed, allowing the equation to adapt to the new clinical and radiobiological features. In 1993 Webb and Nahum [17] proposed a TCP formulation that could benefit from the available 3D radiotherapy, where the dose to the tumor is known via DVH. They modify equation 1.8 using the LQ model to describe the $\lambda$ parameter:

$$TCP = \exp\left(-N_0\exp\left[-\alpha D\left(1 + \frac{\beta}{\alpha}d\right)\right]\right)$$  

where $N_0$ is the initial clonogenic cell number, $\alpha$ and $\beta$ are the parameters of the LQ model, $D = n \cdot d$ is the total dose given in $n$ fraction of dose $d$. In order to obtain a more realistic model for the TCP one has to consider
also that experimental data belong to a population of patients with their individual radiation sensitivity $\alpha$ distributed normally. Thus:

$$TCP = \sum_{i=1}^{K} g_i TCP_{\alpha_i}$$

with:

$$g_i = \exp \left[ - (\alpha_i - \alpha_m)^2 / 2\sigma_\alpha \right]$$

where $\alpha_m$ is the mean value of the radiosensitivity in the interpatient distribution, characterised by standard deviation $\sigma_\alpha$.

Up to this point it has been assumed that cells receive exactly the same dose $D$. In order to do this, one needs to how the number of clonogenic cells $N_{o,i}$ that receive a dose $D_i$. This is most conveniently obtained from DVH. One can generalize equation 1.9 to:

$$TCP = \frac{1}{\sigma_\alpha \sqrt{2\pi}} \int_0^\infty \left( \prod_i \exp \left( -\rho_i V_i \exp \left[ -\alpha D_i \left( 1 + \frac{\beta}{\alpha d_i} \right) \right] \right) \cdot \exp \left[ - (\alpha_i - \alpha_m)^2 / 2\sigma_\alpha \right] \right)$$

where $i$ is dose bin in the DVH, $\rho_i$ is the clonogenic cell density, $V_i$ is the volume of tissue in the $i$-th dose bin.

### 1.3.2 NTCP

On the other hand, NTCP models are needed in order to make treatment plans that either minimize the risk of developing some grade of side effect to normal tissues for a specified dose to the target, or individualize the tumor dose for an acceptable NTCP. The earliest NTCP models were based only on DVH and fractionation information, but several studies have demonstrated the importance of considering even clinical variables such as health status, surgery, chemotherapy, base-line organ function or organ co-dependence. In addition, the accuracy of the model can be further increased using biological and imaging predictors for radiation toxicity. Eventually, organs are in general not homogeneous, so a method that relies only on single DVH parameter is unlikely to be a faithful representation of the biological structure of the organ. [15]. Lyman-Kutcher-Burman (LKB) and relative seriality (RS) models are generally the most well known and accepted methods for predicting...
toxicity in normal tissues after RT. Eventually, even more phenomenological
models based on logistic regression are used.

Lyman-Kutcher-Burman (LKB) model

In 1985 Lyman argued that normal tissue complication depends upon the
volume irradiated as well as dose, and that they could be conveniently re-
presented by an error function in dose and volume. For organs that receive an
uniform dose, the NTCP can be expressed by:

\[
NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} e^{-t^{2}/2} dt \quad (1.12)
\]

\[
t = \frac{D - TD_{50}(V/V_{ref})}{mTD_{50}(V/V_{ref})} \quad (1.13)
\]

\[
TD_{50}(1) = TD_{50}(V/V_{ref})(V/V_{ref})^{n} \quad (1.14)
\]

where the fitting parameters are:

- \( TD_{50}(V/V_{ref}) \) is the dose to a fraction of the reference volume \( V_{ref} \) of
  the organ that may lead to a complication probability in the 50% of
  the population

- \( V_{ref} \) is the reference volume, generally taken as the whole organ volume

- \( m \) is a parameter indicating the steepness of the dose-response curve

- \( n \), is a parameter that relates the dose tolerances for the whole or partial
  volume organ uniform irradiation

The last parameter indicates the volume response of the organ, the *volume
effect*. Some organs can be describe by an \( n \) parameter near to 1, meaning
that they can be seriously injured even if a small part of them receive a
certain dose, while other organ may be compromised when a large portion
of them receive dose, and their \( n \) parameter will be close to 0. Thus, in this
framework, organs with \( n \sim 1 \) the dose response would be correlated with
the maximum dose \( D_{max} \), while in the case of \( n \sim 0 \) organs the mean dose
Figure 1.16: A 3D surface representation of the Lyman model for complication probability for uniform partial irradiation of the heart in this example, as a function of partial volume and dose. (From Lyman, J. T., Radiat. Res., 104, S13S19, 1985)

$D_{\text{mean}}$ would govern the outcome. Figure 1.16 is a 3D plot representing the LKB NTCP model (Eq.1.12) for heart as a function of both the dose and the partial volume irradiation.

**Relative seriality (RS) model**

In order to understand better the volume dependence of different organs to different organ distributions, it may be helpful to consider organs composed of smaller functional sub-units (FSUs) [18]. A serial arrangement of the FSUs means that the organ preserves its functionality only if all the FSUs survive the irradiation; on the contrary, parallel architecture preserve organ functions unless all the FSUs are inactivated by radiation. The so-called *relative seriality model* (Källman et al. 1992) represents an attempt to construct a quasi-mechanistic model for NTCP which takes into account the architecture of an organ; The organ is assumed to be arranged in a combination of parallel and series FSUs. Starting from equation1.15, derived from the linear quadratic model for cell survival after fractionated dose delivery, we obtain:

$$P(D_{\text{tot}}) = 2^{\exp[e\gamma(1-D_{\text{tot}}/TD_{50})]} \quad (1.15)$$

where $P(D)$ is the probability of no cell survival, $D_{\text{tot}}$ is the total dose delivered, $TD_{50}$ is the dose causing the 50% response rate and $\gamma$ is the normalized
dose response gradient. Then Poisson statistic is used to describe the probability to inactivate the organ. For an organ composed by \( m \) purely serial sub-units the probability of complication will be:

\[
NTCP = 1 - \prod_{i=1}^{m}(1 - P_i)
\]  

while for \( n \) purely parallel FSUs:

\[
NTCP = \prod_{j=1}^{n} P_j
\]  

and thus for an organ composed by \( m \times n \) matrix of serial and parallel FSUs:

\[
NTCP = \prod_{j=1}^{n} \left[ 1 - \prod_{i=1}^{m}(1 - P_{ij}) \right]
\]  

The final expression for the RS model is obtained by introducing the parameter \( s \) describing the relative seriality of the organ (fully parallel organ \( s = 0 \), fully serial organ \( s = 1 \)) which has been demonstrated to be equal to \( 1/n \) with \( n \) parameter of the LKB model (Eq.1.14). After some algebraic manipulation, it was found that for \( M \) functional volume of fractional volume \( \Delta v_i \) the NTCP expression is:

\[
NTCP = \left[ 1 - \prod_{i=1}^{M}(1 - P(D_i)s)\Delta v_i \right]^{1/s}
\]  

**Logistic regression**

A more phenomenological approach is found in the logistic regression. The sigmoidal relation between dose and response is suitable for a logistic regression model defined as:

\[
NTCP = \frac{1}{1 + e^{-g(x)}}
\]  

where:

\[
g(x) = \beta_0 + \sum_{i}^{n} \beta_i x_i
\]
with $x_1, x_2, ..., x_n$ different input variables and $\beta_0, \beta_1, ..., \beta_n$ the correspondent parameters of the regression.

Logistic regression is applicable whenever the dependent variable $g$ assumes dicotomic values, such as in the case we want to evaluate the probability to develop or not a certain toxicity endpoint. This model is now available in many commercial statistical package such as SPSS (statistical package for social science). Constructing the logistic model requires a pre-selection of the best combination variables, trying all the possible combination would be too computational expensive in many cases and may lead to some wrong estimates. The user generally selects the variables relying on a threshold of significance.

1.4 Monte Carlo beam transport simulation

In physics and also in radiotherapy applications it is often necessary to have methods to describe problems involving large number of particles and complex geometries, where analytic approaches fail to be efficient. Simulations with Monte Carlo methods are the most widespread numerical tools able to describe these kind of phenomena. Generally the more is the complexity of the problem, the more is advantageous the use of a Monte Carlo code as compared to analytic approaches (Fig. 1.17). Monte Carlo methods are mathematical tools to perform numerical calculation for physical and other scientific problems. They are based on statistical sampling experiments with random numbers and probability distributions. Monte Carlo simulations have been used in medical physics from the ‘60 and are nowadays widespread, since the power of the new calculators allows to use this method in many situations [19]. Nowadays, in both research and hospital structures there is an increasingly adoption of Monte Carlo methods and several codes dedicated to radiation physics are implemented (SHIELD-HIT, GEANT4, FLUKA, PHITS) in the TPS of the facilities [20], [21]. Monte Carlo simulation is particularly indicated for particle transport which is a stochastic process, where energy, position and direction of each particle are independent random variables. It is thus possible to track the particle history (i.e. the interactions) of particles traversing a medium. More in detail, a trajectory is discretized into small steps and the distance $s$ (step length) between two interactions in the medium is:

$$s = -\lambda \ln(1 - \epsilon) \quad (1.22)$$
where $\lambda$ is the mean free path which depends on the cross section $\sigma$ for the interaction and then on particle energy

$$\lambda = \frac{\rho N_A \sigma}{A}$$

(1.23)

where $\rho$ is the density of the medium, $N_A$ is the Avogadro’s number and $A$ is the atomic mass number, while $\epsilon$ is a real number ranging from 0 to 1. At each step the interaction characteristics are randomly sampled from appropriate probability density functions which are derived from experiment cross section for the interaction. As long as the physic model describing the interactions is reliable, many repeated sampling of the probability distribution for a sufficient number of particles, converge to a realistic result.

Monte Carlo codes in radiation research are divided in two main categories:

- Macroscopic radiation transport codes: they cover the entire irradiation volume, but are limited in spatial and energy resolution, i.e. down to 1 keV electrons (e.g. GEANT4, FLUKA, MCNP, EGS4);
- Track structures codes: they describe a small part of the track in its full
details, thus adopting very low thresholds for both spatial end energetic resolution i.e. down to 1 eV (e.g. TRAX, OREC, PARTRAC);

1.4.1 GEANT4

Geant4 (geometry and tracking) is a software tool based on MC code for the simulation of macroscopic radiation transport of particles traversing matter. Geant4 is completely implemented in C++ programming language and since its first version released in 1998 it has been continuously upgraded. Geant4 covers applications in all physics areas which requires simulation particle interaction (e.g. astro-particle physics, nuclear physics, medical applications, radiation protection). Geant4 is able to simulate particles in the whole irradiation taking into account also filters, scatterers, collimators, etc. (Fig. ??). Geant4 is composed by a broad collection of library classes assembled in 17 major categories. For example, geometry category permits the creation of the volume and the coordinate system where the user intend to propagate the particles. This volume can be composed by non-conflicting sub-volumes of different shapes and materials. Physics category instead manages the physical processes involved in the simulation. Several physical models are implemented in Geant4 depending on energy range, particle type and medium, including physics of photons, electrons, hadrons and ions up to energies of $10^{12}$ eV. For an overview of the all different categories we refer to the Geant4 userguide [23].

![Figure 1.18: Example of a geometry implemented in G4 [22].](image)
Chapter 2

Material and Methods

This study is based on a set of patients treated at the proton therapy center in Trento (IT) for brain tumors. Aim of the work is to find dosimetric predictors able to determine the onset of toxicity events after a proton therapy treatment and to develop an NTCP model based on multivariate logistic regression for these endpoints. In our study the radiation induced fatigue (RIF) and radiation induced alopecia (RIA) endpoints were considered. Different dose metrics were extracted from the dose maps of the patients and statistical tests were employed to find statistically significant correlations between dose metrics and toxicity outcomes prior to develop the NTCP model. A subsequent study on two subsets of the initial patient set was carried out in order to account for differences in dose distributions when using the McNamara [24] variable model for RBE. Therefore a description of the proton therapy facility and of the set of patients considered for the analysis will be given in the first part of this chapter. Furthermore, the procedure adopted for dose metrics extraction and of the statistical analysis employed will be presented in detail. Validation of the RBE calculation and the application of the variable RBE model to the subsets of patients considered will be also presented.
2.1 Materials

2.1.1 Trento proton center facility

The patient database analyzed in this work was produced at the proton therapy facility of Trento (I), which is one of the three hadron therapy structures actually available in Italy, together with the CNAO center in Pavia and the CATANA center in Catania. Trento started the activity in October 2014, and, up to now has treated about 300 patients [2]. The center was born in collaboration with AtreP (Agenzia Provinciale per la Protonterapia) and was constructed by IBA (ion beam applications) company and it is now part of the Trentino healthcare agency APSS (Azienda Provinciale per i Servizi Sanitari). The structure (Fig.2.1) relies on a cyclotron able to accelerate protons up to about 230 MeV, and distribute them with the beam line to the two gantries where patients are treated, or to the experimental room, where experiments are mainly conducted in collaboration with TIFPA (Trento Institute for Fundamental Physics and Applications) which is a part of the INFN (Istituto Nazionale di Fisica Nucleare).

Beam line

The accelerator used in the Trento facility is an isochronous cyclotron produced by IBA (ion beam applications), able to accelerate protons up to an
energy of about 230 MeV. A cyclotron is called *isochronus* if it keeps the same orbital period independently on the energy and radius of the particles, thus a single RF is needed during the acceleration process. The cyclotron is composed by a proton source located at the center, a radiofrequency RF electric field orthogonal to a strong magnetic field produced by a magnet (Fig.2.2). Protons produced by the source are accelerated in the gap between the dees by an RF electric field, then they cross a region were a constant magnetic field curves their trajectory thanks to the Lorentz force, \( \vec{F} = q\vec{v} \times \vec{B} \). The particle velocity increases at each transition between the plates thanks to the potential difference applied and the radius of curvature \( R \) increases as well, since it is proportional to the particle velocity \( (R = \frac{mv}{qB}) \). When the protons reach the maximum energy, an extraction system collects the particles and guide them into the beam line. In order to achieve the energies used for therapeutic purposes (70 to 230 MeV), an energy selection system (ESS) is included into the beam line. ESS is composed by a proton degrader followed by a beam analyzer to select the energy and energy spread of the beam. In the proton degrader we have beam attenuation and spread, thanks to a degrader material. In order to set the outgoing energy, the material thickness must be adjusted and a carbon wedge, "rolled up" along the surface of a wheel, is used to this purpose. The degrader can have two functions. Firstly, it can be used as a range shifter to set the maximum needed energy in a certain treatment field, where the energy modulation is performed in the treatment nozzle just before the patient. Secondly, it can be used directly as an energy modulator, which then requires a fast response of the magnets \cite{25}. Figure 2.3 shows a the degrader unit and an example of a degraded beam spectrum.
acquired at the proton therapy facility at the Center of Proton Therapy of the Paul Scherrer Institute (PSI) [26].

The momentum selection is performed by a beam analyzer behind the degrader composed by two large dipoles bending the beam around 45°. The beam optics is designed to have a dispersive focus halfway between the bending magnets. At this location a slit system select the energy and energy spread that are accepted for the treatment. Eventually the second bending magnet compensate for the dispersion and makes the beam independent on the beam energy. After the ESS the beam line divides into three paths, one for each treatment room (gantries) and one for the experimental room. For the two gantries the beam reaches the nozzle composed by two fast scanning magnets able to scan the $xy$-plane orthogonal to the beam direction $z$ (Fig.2.1.1).

**Scanning technique**

The technique used in Trento for shaping the dose distribution is the pencil beam scanning (PBS), which is currently the most flexible available solution. Compared to a passive scattering technique, the pencil beam scanning allows
Figure 2.4: Scheme of the nozzle. a) beam being bent by the 135° magnet in the gantry; b) movable ionization chamber (IC) to check beam properties; c) 2 quadrupoles to focus the beam at the isocenter; d) 2 fast scanning magnets; e) movable x-ray tube to allow beam eye view x-ray shots; f) vacuum chamber; g) set of ICs; h) drawer to install range shifter

a better covering of the tumor volume (Fig.2.5) and a better modulation of the intensity. Dose delivery is achieved by two fast scanning magnets in the nozzle, that must yield a velocity for the pencil beam displacement of 1cm/ms. Fast magnets scan in the plan orthogonal to the beam direction, while scanning in depth is achieved by ESS described above. For shallow seated tumors (i.e. depth lower than 4.1 cm), an additional range shifter can be installed right before the nozzle exit at different distances from it.

2.1.2 Patients and outcome

In this study a set of 85 patients undergoing proton therapy (PT) for brain tumor (BT) was considered. Patients were treated in the Trento proton center facility between 2015 and 2017. Patient median age was 55 years (range 30 to 84 years) and their median follow up was 5 months (range 1 to 19 months). The technique used for the irradiation was the pencil beam scanning (PBS), releasing the prescription dose D to the tumor (D ranging from 20-72 Gy) in fractions \( d = 1.8 - 2.2 \) Gy, for a number of fractions \( n \) from 12 to 36. Patient related characteristics such as age, gender, chemotherapy (CHT), re-irradiation, were taken into account in the analysis. The RT plans generated following dose prescriptions with the Raystation v.6 software [27] used at the Trento proton therapy center, were available for exporting.
Furthermore, clinical data and toxicity events observed during the follow-up were scored and organized by clinicians in the clinical Mosaiq database of the facility. We considered Radiation induced fatigue (RIF) and radiation induced alopecia (RIA) as endpoints for the analysis. Both RIF and RIA were previously scored according to the CTCAE v.4 (common terminology criteria for adverse events) scoring system. RIF was scored from grade 0 to 3 while RIA from grade 0 to 2. Figure 2.6 reports description of the scoring used in accordance with the CTCAE. We separated toxicity outcome in acute and late events. An acute events occurs within 90 days after the end of the treatment, while an event is classified to be late if it occurs after 90 days from the end of the treatment. The analysis of late events is in general of great interest, since it is related to a non-temporary toxicity, which may become even permanent. Skin was not considered an OAR in the plan and no dose boundary were imposed to this structure, while for brainstem standard doses boundary were adopted.

2.2 Method

2.2.1 Dose metrics extraction

The dicom CT, RT structures and RT doses were firstly exported from Raystation and they were converted using CERR (computational environment for radiotherapy research) software into MatLab readable format (Math-
Figure 2.6: CTCAE v.4.03 scoring system for fatigue and alopecia [28].

Works, Natick, MA, USA). CERR is an open source, freely available general treatment plan analysis package based on MatLab. CERR capabilities for radiotherapy treatment response modeling include the ability to import full treatment planning data sets from treatment planning systems, a convenient graphical review of the data, manipulation of the structures and ability to derive dose-volume histograms (DVH) and dose surface histograms (DSH) [29]. Brain stem maximum dose, mean dose and the $V_x$ points of the DVHs were extracted for the fatigue analysis. In the analysis of the RIA skin maximum dose, mean dose and $S_x$ points of the DSHs were extracted. $V_x$ and $S_x$ are the volumes and the surface of the considered organs receiving at least $x$ Gy of dose, respectively. Both $V_x$ and $S_x$ were extracted in steps of 5 Gy.

**DVH and DSH**

Dose volume histograms are often considered in literature as representative of an organ irradiation and then they are considered in development of NTCP model (e.g. LKB model, sec.1.3). DVH condenses the complex 3D dose pattern on the organ considered to a one dimensional curve, where each of its points $V_x$ is the volume of the organ that receives at least $x$ Gy of dose. This approach of course reduces the complexity of the analysis, but leaks of representative power in case of not homogeneous irradiation. On the other hand dose surface histograms (DSH) extracted in the analysis of the RIA, were considered to be representative of the irradiation of thin cutaneous layer of the scalp. These histograms have the same meaning of the dose volume histograms described above, with the difference that we are now considering the organ surface instead of volume. This choice is particularly indicated
in this case where the organ to be investigated is the skin, which is best modeled by a surface than a volume. This procedure was first adopted in 2016 (Pastore et al.[30]) in evaluating the risk of severe acute skin toxicity in breast cancer patient. To calculate absolute DSH, they extracted the relative complement in the skin contouring structure (body) of its 3D erosion defined by a spherical structuring element of radius $r \sim 3$mm (i.e. the order of magnitude of mean skin thickness). On such shell, the absolute dose-volume histogram was regularly computed and then divided by $r$ to obtain the DSH (Fig. 2.7).

In the same way we extracted the DSH, starting from the body structure of the scalp and taking the complement of its 3D eroded structure, with spherical structural element $r$ of 4 mm, mean depth of human hair follicle, which is considered to be the sensible target for RIA. An example of a patient from our set is shown in figure (2.8). DVH and DSH were then normalized in order to be independent on the individual characteristic. DVH for brain stem and HCT were normalized with the total volume of their respective structure. Relative DSH were instead obtained normalizing the absolute DSH with the surface of the healthy cerebral tissue (HCT). The reason for this choice relies in the fact that the skin of the scalp is not a well defined organ in this context,
so we considered an organ, with a smaller surface, but that scales similarly to the skin in the scalp region. This may lead to $S_x > 1$, but it should not represent a problem if we know how the relative DSH has been built.

### 2.2.2 Statistical analysis and NTCP model

The statistical analysis was developed in collaboration with the IBB (Institute of Biostructure and Bioimaging) of the CNR (Consiglio Nazionale Ricerche) of Naples (IT). SPSS (statistical package for social science) commercial software was employed for statistical analysis.

Chi-squared test and Mann-Whitney test were employed for univariate statistical analysis. Chi-square tests were performed in order to determine if there are significant relations between patient and treatment-related characteristics (age, gender, CHT, re-irradiation), and toxicity outcomes.

Chi-square tests are statistical hypothesis tests where the sampling distribution of the test statistic is a chi-squared distribution when the null hypothesis is true. The chi-squared test is generally used to determine whether there is a significant difference between the expected frequencies and the observed frequencies of one or more categories. For a sample with $k$ possible events,
the chi-square variable is:

\[ \chi^2 = \sum_{i=1}^{k} \frac{(o_i - e_i)^2}{e_i} \]  (2.1)

where \( o_i \) are the observed frequencies, while \( e_i \) the expected ones. Once the value of \( \chi^2 \) is known, tables of significance lead us to the eventual rejection of the null hypothesis, for a choice of the significance value. The significance threshold for the test was set to \( p = 0.05 \).

Mann-Whitney U-tests were employed to evaluate if there is a statistical significance that dose metrics are differently distributed among two samples of the patient population based on the outcome. Mann-Whitney U-test is a non parametric statistical test for independent continuous data. Non parametric statistical analysis is adopted in cases where the variable is not distributed normally. For normally distributed variables Mann-Whitney test is substituted by the parametric Student \( t \)-test. A normality test was thus performed before the test analysis. Assumptions of the Mann-Whitney U-test are:

- the two samples under study have to be reciprocally independent and each observation inside the sample is independent from the others;
- the observations can be compared;

the \( U \)-test calculates the ranks of the whole population, then divide the population in 2 subsets, based on the outcome. Thus a statistic \( U \) is calculated for each subset as \( U = R - \frac{n(n+1)}{2} \), where \( R \) is the rank sum of the subset and \( n \) the number of observations for the subset. Eventually the lower value of \( U \) is used when looking to the significance tables.

\( U \)-test highlights possible dosimetric variables that correlate with a certain outcome. The p-value was set to \( p = 0.05 \) also in this case.

In our case population is divided in 2 sub-population discriminated by a dichotomous variable relative to the grade of fatigue or alopecia developed by the patients (e.g. 1 if patient developed alopecia, 0 if not). Then the tests establishes if some of the dose metric extracted or clinical variables correlates with the outcome.
Figure 2.9: ROC curve explanation for a random guess: as the AUC ROC approaches 1, the model increases its predictive power. Blue points represent possible (FP, TP) rate couples in the ROC space.

In case we found statistically significant variables we proceed in developing an NTCP model based on a multivariate logistic regression, described in Sect. 1.3. Logistic regression model, being a phenomenological model, is more versatile than LKB or RS models, which generally require a larger set of data to be accurate. Again the SPSS software was employed for the model computation.

Model performance was measured by the area under the ROC curve (AUC-ROC). The ROC (receiver operating curve) is a graphical scheme used in decision theory to describe the predictive power of a model (Fig. 2.9). On the y-axis it represents the probability of having a true positive (TP) outcome from the model, also called sensitivity, while, on the x-axis the probability that the model returns a false positive (FP), also called 1− specificity. Therefore the points of the ROC curve are the couple (FP, TP) rates for the data under study when varying a classifying parameter. The AUC-ROC parameter describes the predictive power of the model, which increases as
Figure 2.10: Scheme of the procedure adopted for statistical analysis.

The AUC-ROC approaches 1. The Youden’s $J$ index was calculated. The index was suggested by W.J. Youden in 1950 [31] as a way of summarizing the performance of a diagnostic test. Its value ranges from -1 to 1, and has a zero value when a diagnostic test gives the same proportion of positive results for groups with and without the disease, i.e the test is useless. It is defined for each point of the ROC as:

$$ J = \text{sensitivity} + \text{specificity} - 1 $$

The maximum value of the index may be used as a criterion for selecting the optimum cut-off point when a diagnostic test gives a numeric rather than a dichotomous result.
A schematic summary of the procedure described above is depicted in Fig. 2.10.

### 2.2.3 RBE weighted dose maps recalculation

Recently the proton therapy center of Trento obtained the released research version of *Raystation v. 7*, which performs calculations of dose averaged LET ($\text{LET}_d$) maps from treatment plans, thanks to a Monte Carlo internal module which simulates the particle transport.
When we deal with monochromatic beams, the LET calculation is easily achieved because the kinetic energy is well defined. On the contrary, clinical
beams are not mono-energetic and possess a kinetic spectrum at a certain depth. Therefore is more meaningful to introduce the concept of LET distribution and hence, to deal with mean LET value. LET$_d$ is thus defined as

$$\text{LET}_d^j = \frac{\int_0^\infty S_d^j(E)\psi_E^j(z)dE}{\int_0^\infty \psi_E^j(z)dE}$$

(2.3)

where $\psi$ is the energy spectrum of the particles at depth $z$. LET$_d$ maps can be employed to calculate maps of variable RBE and thus new RBE weighted dose maps. Several variable RBE models are found in literature (e.g. LEM, Wedenberg, McNamara, Carabe) and going into the details of all is beyond the scope of this work. However it is worth to say that RBE models can be in general based on the full spectrum of particles and energies participating in the irradiation. They are based on radial dose distribution of ions traversing the medium and they consider the local damage induced by these ions (LEM [33], MKM [34]). On the other hand, simpler analytical approaches rely only on macroscopic quantities, such as LET$_d$ and Dose $D$, obtaining their analytical equation by fitting experimental data (McNamara [24], Wedenberg [35], Carabe [36]). damage that each particle can The model we rely on the one introduced by McNamara.

Figure 2.11: The RBE for cell survival as a function of LET$_{x}$ and $(\alpha/\beta)_x$ for a dose of 2 Gy (left panel) and 8 Gy (right panel) [24].
McNamara model

The McNamara variable model of RBE is based on experimental data of 76 studies for a total of 369 data points, presented in Paganetti (2014) [13]. These data were extracted and analyzed in the framework of the linear-quadratic (LQ) model, in order to parameterize the dependence of the RBE on the LET\(_d\) and \((\alpha/\beta)_x\) for proton therapy. For each experimental data set the following parameters were extracted: \(\alpha_x\), \(\beta_x\) and \(\alpha\), \(\beta\), to describe the tissue response to photon radiation and proton radiation respectively and LET\(_d\) at the position of the biological sample. McNamara restricted the values to be taken into account to LET\(_d\) < 20 keV/\(\mu\)m and \((\alpha/\beta)_x\) < 30 Gy in the fit. This restriction is intended to collect only the data which fall into the clinical relevant LET\(_d\) range, where the relation between RBE and LET\(_d\) may be approximately linear.

\[
\text{RBE}\left[D_p, \left(\frac{\alpha}{\beta}\right)_x, \text{LET}_d\right] = \frac{1}{2D_p} \cdot \left[\left(\frac{\alpha}{\beta}\right)_x^2 + 4D_p\left(\frac{\alpha}{\beta}\right)_x \left(0.999064 + \frac{0.35605}{(\alpha/\beta)} \text{LET}\right) + 4D_p^2 \left(1.1012 - 0.0038703 \sqrt{(\frac{\alpha}{\beta})_x \text{LET}_d}\right)^2 - (\frac{\alpha}{\beta})_x\right]
\]

The formulation given in equation 2.4 depends on the proton dose \(D_p\), the ratio \((\alpha/\beta)_x\) and the dose averaged linear energy transfer (LET\(_d\)). Dependence of the RBE for cell survival on LET\(_d\) and \((\alpha/\beta)_x\) is shown in Fig.2.11 for \(D_p\) of 2 Gy and 8 Gy as predicted by the model. The RBE is expected to increase as the LET\(_d\) increase and as the \((\alpha/\beta)_x\) decreases in accordance with the biological model described in Sec.1.2.2. Dependence of the RBE on the Dose \(D_p\) is shown in Fig. 2.2.3, for different \((\alpha/\beta)_x\) ratios and LET\(_d\) = 2.5 KeV/\(\mu\)m. The RBE decreases with increasing dose for \((\alpha/\beta)_x\) ≤ 2 Gy and approaches 1 for high doses. For large \((\alpha/\beta)_x\) values, the slope the McNamara model converges to zero with RBE ~ 1.08 and 1.05 for \((\alpha/\beta)_x\) = 10 and 15 Gy, respectively. Other similar radiobiological models are found in literature: Carabe et al. model [36] and Wedenberg et al. model [35] which are both based on a smaller set of data compared to the model described so far. A comparison between models is found in Fig.2.13 and in Fig. 2.2.3, where we notice a good agreement between McNamara et al. model and
Figure 2.12: The RBE as a function of dose for different $(\alpha/\beta)_x$ values. Three different models predict the RBE: McNamara et al. model (blue solid line), the Carabe et al. model (green dashed line) and the Wedenberg et al. model (pink dotted line). Adapted from [24].
Wedenberg et al. model for low $D_p$, in particular for low LET$_d$ values.

Figure 2.13: RBE for cell survival as a function of $\alpha/\beta$ for different LET$d$ values and a dose of 2 Gy. Three different models predict the RBE: our model (blue solid line), the Carabe et al model (green dashed line) and the Wedenberg et al model (pink dotted line). Adapted from [24]

**LET$_d$ validation**

LET$_d$ calculation is not a trivial task and rely on a Monte Carlo computation which simulates the components of the irradiation field and the geometry of the system. Therefore, Raystation LET$_d$ calculation was firstly compared to a Monte Carlo simulation performed by Geant4 to validate it. The validation was performed in a simulated water box phantom of 15x15x15 cm$^3$, voxel size was set to 0.1 cm. A beam of $E = 120$ MeV and $\Delta E = 0.8$ MeV was chosen for the comparison. Raystation simulated $10^9$ protons, while with Geant4 we are able to simulate $10^6$ protons otherwise it would have been computationally too expensive. For the simulation in Geant4 we adopted the Hadrontherapy class developed by the LNS (Laboratori Nazionali del Sud) group of INFN [37]. Dose maps were firstly compared for the spatial
distribution and the IDD (integrated depth dose) curve along the beam direction. Since the doses of Raystation and Geant4 are clearly different due to the different statistics, they were properly normalized with respect to their maximum. After that LET \(_d\) spatial distribution maps were compared between Raystation and Geant4 simulations. Employing LET \(_d\) distributions, RBE maps were then computed following the McNamara model for physical doses of 1 Gy and \(\alpha/\beta = 2\) in order to highlight discrepancies (Fig. 2.11). RBE weighted doses were finally calculated and their IDD curves were compared.

**Application to a patient subset**

We considered two subsets of 10 patients, one for RIF and one for RIA. Patients for RIF were selected among the patients with \(D > 0\) to the brainstem, differently the patients for RIA were chosen between the patients having the higher \(RS_{20Gy}\) in order to highlight the differences in dose maps. The calculation of the new dose maps relies on dose averaged LET (LET \(_d\)), \(\alpha/\beta\) value and on spatial physical dose distributions. Dose distribution were already extracted for the first part of the work. LET \(_d\) maps were instead calculated using the new research version of *Raystation v.7*. A Raystation script based on *Python* language was then developed in order to calculate the RBE maps and the RBE weighted dose maps directly on Raystation, avoiding subsequent exporting and importing of patient plans from Raystation to other softwares. A recent work reports \(\alpha/\beta = 2.5 Gy\) for the brainstem structure [?], while it is not uniquely reported in literature a clear indication for the value of \(\alpha/\beta\) for the body structure we have considered for RIA. Therefore we conducted a sensitivity analysis varying \(\alpha/\beta\) from 2 to 10 Gy, which are generally the most extreme cases. The procedure is depicted in Fig.2.14.

From the new dose maps DVH and DSH metrics were extracted with the same procedure described in described in Sec. 2.2.1. Then, mean DVH and mean DSH were compared for different \(\alpha/\beta\) values. Finally Wincoxon W-test were employed for the 10 patients in order to search for statistically significant differences between the metrics extracted. Wilcoxon W-test is a non parametric statistical test for paired data. It is the statistical test corresponding to the Mann-Whitney U-test described in Sec. 2.2.2 for non independent data. In this case the data were paired since we were looking for differences in dose metrics extracted from different dose maps belonging to
Figure 2.14: Procedure steps from the left to the right: starting from the original plan, we calculate the LET_d map, from which we derive the RBE maps for different $\alpha/\beta$ ratios. Finally we calculate the new RBE weighted dose maps.

the same patients. The p-value chosen as the significance level was $p = 0.05$. 
Chapter 3

Results and discussion

This chapter presents and discusses the results of the work. First part will be dedicated to the statistical analysis outcomes, concerning RIF and RIA, and the NTCP model for RIA derived from multivariate logistic regression. Secondly, results concerning the application of the McNamara model of RBE on dose maps will be presented, focusing firstly on the validation of the LET\(_d\) calculation of Raystation and then on the application of the model in recalculating dose maps of brainstem and body structures on two subsets of 10 selected patients.

3.1 Statistical analysis

3.1.1 RIF and RIA Outcomes

Outcomes for RIF and RIA are reported in table 3.1. We divided the various grades in dichotomous outcomes (i.e. 1 for grade \(\geq G1\) and 0 otherwise, or 1

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RIF</th>
<th>RIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\geq G1) Acute</td>
<td>69 of 83 (83%)</td>
<td>47 of 78 (60%)</td>
</tr>
<tr>
<td>(\geq G2) Acute</td>
<td>1 of 83 (&lt; 2%)</td>
<td>38 of 78 (49%)</td>
</tr>
<tr>
<td>(\geq G1) Late</td>
<td>29 of 62 (47%)</td>
<td>32 of 59 (54%)</td>
</tr>
<tr>
<td>(\geq G2) Late</td>
<td>2 of 62 (&lt; 4%)</td>
<td>19 of 59 (33%)</td>
</tr>
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</table>

Table 3.1: Acute and late outcomes for RIF and RIA.
Table 3.2: p-values for differences between mean $V_x$ points between patients developing or not acute or late G1 RIF

<table>
<thead>
<tr>
<th></th>
<th>V10</th>
<th>V15</th>
<th>V20</th>
<th>V25</th>
<th>V30</th>
<th>V35</th>
<th>V40</th>
<th>V45</th>
<th>V50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td>0.728</td>
<td>0.432</td>
<td>0.349</td>
<td>0.154</td>
<td>0.265</td>
<td>0.254</td>
<td>0.304</td>
<td>0.334</td>
<td>0.352</td>
</tr>
<tr>
<td>Late</td>
<td>0.901</td>
<td>0.918</td>
<td>0.930</td>
<td>0.971</td>
<td>0.928</td>
<td>0.982</td>
<td>0.994</td>
<td>0.939</td>
<td>0.900</td>
</tr>
</tbody>
</table>

for grade $\geq G2$ and 0 otherwise. According to the CTCAEv.4 classification (Fig. 2.6), we notice that the great majority of the toxicity events associated to fatigue, for both acute and late events, are grade 1 (G1) toxicities. More severe grade of RIF are found in very few patients, in particular, the most severe grade 3 is not even present. On the contrary, alopecia events are more severe. Maximum grade 2 of RIA is present with a substantial percentage in both acute and late analysis. Acute G1 RIF was observed at a median time $t_m = 38$ days after the end of PT (6-84 days), while late G1 RIF at a $t_m = 114.5$ days (91-497 days). Acute G2 2 RIA was found at a $t_m = 37$ days after the end of the treatment (range 6 to 58 days), while Late Grade 2 RIA was found at a $t_m$ of 112 days (91 to 264 days).

3.1.2 RIF analysis

No clinical variable considered is associated with acute or late G1 grade of RIF. Neither $D_{mean}$ nor $D_{max}$ correlate with the outcome. Mean DVH comparison for the brainstem structure between patient developing or not G1 RIF is reported in Fig. 3.1. DVH comparison shows a shift of the mean DVH points towards higher values for patients developing acute RIF, which is not present for patients developing late RIF. Nevertheless, the shift was not found to be significant at the univariate statistical analysis. $P$-values for acute G1 RIF are reported in table 3.2. Since results show no clinical or dosimetric variables significantly associated with the outcome, we did not proceed to the multivariate statistical analysis for RIF. This result is in contrast with results of similar studies with photons which report significant increase in $D_{mean}$ or $D_{max}$ to the brainstem in patients developing RIF ([38], [39]).
Figure 3.1: Top: brainstem mean DVH comparison between patients who developed G1 or G2 acute RIF vs. those who did not. Dashed lines represent standard deviations $\sigma$ of the distribution of the $V_x$ points of the patient’s data set. Bottom: same comparison in the case of late RIF events.
Clinical variables significantly associated with acute G2 RIA were CHT ($p = 0.01$) and age ($p = 0.02$). Age association with the acute outcome is depicted in Fig 3.1.3. We notice that younger age is more probable to determine the onset of G2 RIA in the acute phase. Furthermore, clinical variables significantly associated with late G2 RIA were CHT ($p = 0.04$) and acute G2 RIA ($p < 0.0001$), the latter meaning that a certain persistence of toxicity exist from the acute to the late phase.

Both $D_{mean}$ $D_{max}$ metrics are significantly associated with the G2 outcome in both acute and late phase ($p < 0.001$). Fig. 3.1.3 shows the comparison between mean DSH for the body structure for patients developing or not acute or late G2 RIA. We notice that in both acute and late phase, mean DSHs are well separated, also considering standard deviations $\sigma$ of the $S_x$ distributions. $P-values$ relative to the $S_x$ points of the DVH are reported in Table 3.3.

It turns out that all the dose metrics extracted from the DSHs ($S_x, D_{mean}, D_{max}$) are significantly associated ($p < 0.001$) with the onset of both acute
Figure 3.3: Top: body mean DSH comparison between patients who developed acute G2 RIA vs. those who did not. Dashed lines represent standard deviations $\sigma$ of the distribution of the $S_x$ points of the patient’s data set. Bottom: same comparison in the case of late RIA events.
Table 3.3: p-values for differences between mean $S_x$ points between patients developing or not acute or late G2 RIA

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<th>S15</th>
<th>S20</th>
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<th>S30</th>
<th>S35</th>
<th>S40</th>
<th>S45</th>
<th>S50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Late</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
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and late G2 RIA. Hence we proceeded to the multivariate analysis for these endpoints.

**NTCP model for acute RIA**

In the acute phase, at the multivariate analysis, age, CHT, clinical variables and $D_{\text{max}}$ metric remain significant within the NTCP model. $D_{\text{max}}$ distribution of the two populations of patients are reported in Fig. 3.4. Multivariate logistic regression parameters are reported in in table 3.4. Odds Ratios represents the exponentiation of the coefficients $\beta_i$ in the eq. 1.21. Area under the ROC curve (AUC-ROC) was used to measure model performance, giving: AUC-ROC = 0.878 ± 0.038. Furthermore Youden index was measured to find the optimal cut-off for determining the onset of acute G2 RIA and results: $J = 45$ Gy. ROC curve for the NTCP model described above is shown in Fig. 3.5.

The model has good prediction performance (AUC > 0.8) in predicting the onset of severe alopecia (G2) induced by radiation in our patient database. $D_{\text{max}}$, the dosimetric predicting variable of the model, suggests a serial behavior of the skin in the scalp region. This is in contrast with more parallel behavior found in study for acute skin toxicity in patients treated with photons. ([30]). Further studies are needed to determine whether the injury is local or not to.

<table>
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<tr>
<th></th>
<th>Odds ratio</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>$D_{\text{max}}$</td>
<td>1.112</td>
<td>1.050-1.178</td>
</tr>
<tr>
<td>Age</td>
<td>0.952</td>
<td>0.910-0.996</td>
</tr>
<tr>
<td>CHT</td>
<td>0.213</td>
<td>0.050-0.910</td>
</tr>
<tr>
<td>Constant</td>
<td>0.398</td>
<td></td>
</tr>
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</table>

Table 3.4: Logistic regression G2 RIA acute
Figure 3.4: Whisker box plot for the $D_{\text{mean}}$ distribution for patients developing (1) or not (0) acute G2 RIA. Box represents 25 and 75 percentiles, with the median in the middle of the box.

Figure 3.5: ROC curve of NTCP model derived for acute G2 RIA
**NTCP model for late RIA**

Concerning the toxicity in the late phase, at the multivariate analysis, only S20 remains significant within the NTCP model. SPSS returns for logistic regression NTCP model the following parameters: Odds Ratio = 1.163, 95% CI 1.071-1.262; constant = 2.352. Representation of the model is shown in Fig. 3.6. We can there notice the typical sigmoidal shape of the NTCP models described in Sect. 1.3.

Area under the ROC curve to measure model performance results AUC-ROC = 0.893 ± 0.041. ROC curve is shown in Fig. 3.7. Youden J-index establishes the optimum cut-off for determining the onset of late G2 RIA to S20 = 9.9%. The model we obtained has good prediction performance in determining the onset of grade 2 radiation induced alopecia. Nevertheless, the possibility to extend the database of patients may lead to a more robust NTCP model and make it suitable for a comparison with different models (e.g. LKB).

![NTCP model representation](image_url)

**Figure 3.6:** Representation of the NTCP model derived from multivariate logistic regression for late G2 RIA. Red points represent S20 for patient with outcome 1 for late G2 RIA. Blue points are S20 of patients with outcome 0.
Figure 3.7: ROC curve of NTCP model derived for late G2 RIA.
3.2 RBE maps

3.2.1 LET validation

Dose calculated with Raystation and Geant4 shows good agreement for spatial distribution (Fig. 3.8, 3.9). Curves shown in Fig. 3.9, are two orthogonal profiles of the bragg peak, and they are similarly distributed. We impute the differences to the lower statistic of the Geant4 simulation compared to the one of Raystation.

Figure 3.8: Dose simulation. Left: Raystation. Right: Geant4

Figure 3.9: comparison of bragg peak dose profiles on directions orthogonal to the beam direction between Raystation and Geant4.
Also idd curves along the beam direction are reported, normalized with respect to their maximum, and show a very good agreement (Fig. 3.10). On the other hand, when looking at the LET\textsubscript{d} distributions we find a discrepancy between Raystation and Geant4 simulations. Fig. 3.11 and 3.12 shows the spatial distribution of the LET\textsubscript{d} for Raystation and Geant4. We notice that spatial distribution of Geant4 is wider in the entrance channel. Furthermore, Raystation simulates a uniform arched distribution, which is not present in Geant4. We impute this behavior to the different models adopted by the two Monte Carlo codes for particle tracking, in particular in cut’s thresholds for electromagnetic nuclear interactions, rather than to the different statistics of the simulations. This because, even with lower statistics, Geant4 simulates particles in regions not populated by Raystation simulation. This is clearly visible yet in the entrance channel and also in the lateral spread at the Bragg peak depth (Fig. 3.11). Missing statistics does not seem to contribute to fill a sharp arched front as in Raystation, but rather to fill a more flat front. Furthermore, transverse cuts of Fig. 3.12. Despite the different spatial distribution of the LET\textsubscript{d}, dose maps, show very good agreement. This because the LET\textsubscript{d} is not weighted for the dose, in fact, regions showing major discrepancies in LET\textsubscript{d}, are populated by few particles, resulting in a negligible dose.
Figure 3.11: LET$_d$ distributions over a central plane parallel to the beam direction.

Figure 3.12: LET$_d$ distributions over transverse planes at different depths.
In order to remove the dependence on different spatial distributions we calculated at each depth an average LET\textsubscript{d} value over the plan orthogonal to the beam direction at that depth in analogy to a planar dose integration (PDD-IDD). It is important to note that, the non additivity of the LET\textsubscript{d} would make a standard IDD curve for the LET senseless. Therefore, calling \( P(z) \) the plans at different depths, the averaged LET\textsubscript{d} is calculated as an additional dose average, i.e.:

\[
< \text{LET}_{d}(z) > = \frac{\sum_{i \in P(z)} \text{LET}_{d}^{i} \cdot D_{i}}{\sum_{i \in P(z)} D_{i}}
\]  

(3.1)

Where \( i \) is the voxel indices belonging to the plane \( P \), while \( \text{LET}_{d}^{i} \) and \( D_{i} \) are the LET\textsubscript{d} and physical dose in the voxel \( i \), respectively. Therefore a \( \text{LET}_{i} \) value at each depth is obtained, which condenses the 3-dimensional information on the spatial distribution on a mono-dimensional curve. Fig.3.13 shows quite good agreement between the two simulations, even though Raystation curve results \( \sim 8\% \) higher in the peak region.

Differences in LET\textsubscript{d} maps are reflected in the RBE weighted dose (\( D_{RBE} \)) maps calculated with the McNamara model. Here IDD calculations with

![Figure 3.13: LET\textsubscript{d} averaged over plans orthogonal to the beam direction for Raystation and Geant4 simulations.](image)

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Figure 3.14: RBE weighted dose maps calculated from Raystation and Geant4 simulations of LET$_d$. Parameters: $D_p = 1$ Gy, $\alpha/\beta = 2$ Gy. $
\alpha/\beta = 2$ are shown (Fig. 3.14). Physical doses $D_p$ are peaked at 1 Gy. Calculation of $D_{RBE}$ relative to Geant4 simulation shows a peak $\sim 10\%$ higher compared to Raystation.

Even if we expect the RBE in the McNamara model to increase monotonically with LET$_d$ from Sec. 2.2.3, and hence the $D_{RBE}$ for Raystation to be slightly higher than the Geant4 one, here it the opposite happens. We attribute this to the more flat distribution at the peak position resulting in Geant4. Therefore, although Raystation presents on average slightly higher LET$_d$ values and hence RBE values, the integration of the IDD favors the Geant4 simulation at the Bragg peak depth. Furthermore, the $\alpha/\beta = 2$ Gy adopted maximizes the differences between the two $D_{RBE}$, since the RBE has a more steep response to LET variation for low $\alpha/\beta$ values (Fig. 2.11).

It is worth noticing that in clinical practice, a combination of several quasi mono-energetic beams, weighted in intensity, are adopted to build the SOBP. A comparison on a SOBP would tell us if these discrepancies are somehow compensated and leveled out. We point out that a simulation of a SOBP is an challenging task to achieve and requires non trivial implementation in Geant4. Nevertheless, the calculation of RBE we rely on seems to be reasonable, also considering that in experiments, biological variability of samples leads to uncertainties larger than 10\%. 

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3.2.2 Application to a patient subset

We then apply the McNamara model to two subsets of 10 patients from the initial database. Starting from the original treatment plan we assess first the LET$_{d}$ maps. Then we calculate compute RBE maps thanks to which we calculate new RBE weighted dose maps. Fig. 3.15 is a pictorial representation of the procedure on one patient of the database.

**Brainstem**

We recalculated the RBE dose maps on the brainstem with the McNamara model on a sub population of 10 patients receiving non-zero dose to that structure. We considered $\alpha/\beta$ parameter equal to 2 and 10 Gy. Mean DVHs are compared in Fig. 3.16. We notice a clear shift towards higher $V_x$ points for low $(\alpha/\beta)_x = 2$, in particular $D_{\max}$ increases of more than 10%, while for $(\alpha/\beta)_x = 10$ the $V_x$ differences are shallower to the dose map with RBE = 1.1. Nonetheless, differences are found to be significant for several of the $V_x$ points. Wilcoxon W-test for paired data shown in Fig. 3.17 and Fig. 3.18, reports the p-values relative to the $V_x$ points extracted.

Results of the W-test imply the need to extend the recalculation to the whole initial set of patients, in order to see whether a shift to $V_x$ points may lead to variation in the univariate statistical analysis previously performed for RIF. Brainstem is an interesting structure for RBE weighted dose recalculation, since, due its deep position, it is often subject to the distal part of the beams.
Figure 3.16: Mean DVHs of the brainstem for 10 patients. Comparison between dose maps recalculated with McNamara RBE model for $(\alpha/\beta)_x = 2$ and 10 Gy, compared with the original map with RBE = 1.1.

Figure 3.17: Wilcoxon W-test between $V_x$ of the brainstem extracted from dose maps calculated with $(\alpha/\beta)_x = 2$ and constant RBE = 1.1
Figure 3.18: Wilcoxon W-test between $V_x$ of the brainstem extracted from dose maps calculated with $(\alpha/\beta)_x = 10$ and constant RBE = 1.1

characterized by high LET values and hence steeper gradients RBE values and thus RBE weighted dose, according to the model adopted. Therefore differences between constant or variable model of RBE are maximized for this structure.

**Body**

The procedure described above for brainstem was applied also for the body structure to other 10 patients selected among the patients with higher values of $S_{20}$ from the initial database. Mean DSH comparison is reported in Fig. 3.19. We notice a shift towards higher $S_x$ values and an increase of $D_{max}$ of $\sim 10\%$ for $(\alpha/\beta)_x = 2$. On the contrary, mean DSH of $(\alpha/\beta)_x = 10$ shows a slight shift towards lower $S_x$ values. Wilcoxon W-test returns significant differences in several $S_x$ values between original dose maps and those recalculated with $(\alpha/\beta)_x = 2$ or $(\alpha/\beta)_x = 10$ (Fig. 3.20, Fig. 3.21).

Also in this case, the result of the W-test suggests the need to extend the RBE recalculation to the whole database of patients. A significant increase of the DSH point may lead to variations in the statistical analysis previously performed and thus on the parameters of the NTCP model derived from logistic regression.
Figure 3.19: mean DVHs of the body structure for 10 patients. Comparison between dose maps recalculated with McNamara RBE model for $(\alpha/\beta)_x = 2$ and 10 Gy, compared with the original map with RBE = 1.1.

Figure 3.20: Wilcoxon W-test between $S_x$ of the body structure extracted from dose maps calculated with $(\alpha/\beta)_x = 2$ and constant RBE = 1.1
Figure 3.21: Wilcoxon W-test between $S_x$ of the body structure extracted from dose maps calculated with $(\alpha/\beta)_x = 10$ and constant RBE = 1.1
Chapter 4
Conclusions

A set of 85 consecutive brain tumor patients treated in the Trento proton therapy center for brain tumor was analyzed in a retrospective analysis. We assessed acute (≤ 90 days) and late (> 90 days) toxicity events concerning radiation induced fatigue and radiation induced alopecia. We considered clinical variables and treatment related characteristics such age, gender, CHT, re-irradiation, and we extracted DVH and DSH dose metrics for brainstem and body structure respectively, in addition to $D_{\text{max}}$, $D_{\text{mean}}$ metrics. Analysis of RIF does not show any significant association between variables considered and toxicity outcomes. It is worth noticing that scoring of RIF records almost only G1 toxicity in both acute and late phase, in contrast with other works reporting most severe outcomes. Further work is thus needed to understand whether patients may benefit from therapy with protons compared to photons concerning fatigue outcome. Therefore, assessing data coming from a different cohort of patients treated with photons, with similar dose distribution, may indicate if there are notable differences in RIF outcome.

On the other hand, analysis of RIA exhibits more interesting results. All the dose metrics extracted are significantly associated with the most severe toxicity (G2) and thus NTCP models based on logistic regression were developed. In the NTCP model for the acute phase, CHT, age, and $D_{\text{max}}$ are the independent significant predictive quantities, while $S_{20Gy}$ is found for the late phase. Both models have good prediction performance (acute AUC = 0.878, late AUC = 0.893). Next move will be dedicated to widen the patient’s database, reaching about 130 patients, to make the models derived more robust.
Furthermore, RBE calculation following the McNamara model was implemented into Raystation v.7 research version. A validation of the Monte Carlo code adopted by Raystation for the LET_d maps simulation, adopted in the RBE calculation, was firstly performed with the help of the Geant4 toolkit. A quite good agreement between RBE weighted doses for the two simulations is found, even though spatial distributions of LET_d result a bit different.

Recalculating the RBE weighted dose maps for two subset of 10 patients selected among the initial database, we notice that DVH and DSH points exhibit a significant shifts, in particular for lower $\alpha/\beta$ ratio ($\alpha/\beta = 2$ Gy). We conclude that the application of the McNamara model to the whole patient’s database considered for this work is needed in order to snatch possible variations in the NTCP models derived so far. In particular brainstem, which is generally affected by higher LET_d, and hence, RBE values, due to its inner position, may be affected by substantial variations at the statistical analysis level.
Bibliography


[36] Alejandro Carabe, Maryam Moteabbed, Nicolas Depauw, Jan Schuemann, and Harald Paganetti. Range uncertainty in proton therapy


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3.21 Wilcoxon W-test between S_x of the body structure extracted from dose maps calculated with (α/β)_x = 10 and constant RBE = 1.1.