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Assessment of Dose Correlation Models Considering Total Toxicity in Re-irradiation with Ions, Focused on Voxel by Voxel Biological Effective Dose Calculation and Total Dose Accumulation

Diploma Thesis

Technische Universität Wien

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Abstract

EN

Radiation therapy has proven to be an effective method in the treatment of tumors for decades and modern developments improve the impact on tumors while reducing the strain on healthy tissue in the surrounding area. Estimating the effect of radiation on human tissue is a complicated issue but an important factor in treatment planning. In the scope of this thesis, scripts for the treatment planning system RayStation were written, which evaluate the 'Biological Effective Dose' (BED) and the 'Equivalent Dose in 2 Gray Fractions' EQD_2. They calculate these fractionation dependent parameters voxelwise from a planed relative biological effective dose distribution and save the resulting BED- or EQD_2-dose distributions for comparative purposes.
These scripts were used to evaluate the biological effect of multiple radiation therapy treatments on organs at risk, of 18 patients, which had recurrent tumors. All patients were re-irradiated at MedAustron Ion Therapy Center after initial treatments with photons or electrons. For a numerically description of the dose distributions in high risk structures, dose volume histogram parameters were taken from the brain, brainstem, eye nerves and chiasm and saved into a database.
When being continuously extended, this database could provide statistically meaningful indications that re-irradiated patients accumulate less toxicity in organs at risk than anticipated by currently used measurement standards. These results are already indicated by the biologically effective dose distributions and associated dose volume histogram-parameters presented in this thesis. By adjusting the restrictions given in therapy planning due to possibly upcoming indications, the success rate of tumor treatments in radiation therapy could be further improved.

DE

Strahlentherapie mit ionisierender Strahlung wird bereits seit Jahrzehnten als effektive Methode zur Behandlung von Tumoren genutzt, wobei neue wissenschaftliche Erkenntnisse und moderne Technologie die Erfolgsraten der Tumorbekämpfung stetig erhöhen, während die Belastung des gesunden Gewebes, welches den Tumor umgibt, veringert werden kann. Ein wichtige Rolle in der Therapieplanung spielt deswegen die korrekte Beschreibung der Wirkung von ionisierender Strahlung auf menschliches Gewebe, diese stellt aber eine fortwährende Herausforderung dar.
Im Rahmen dieser Arbeit wurden Skripten für die Bestrahlungsplanungs-Software Raystation geschrieben, welche die "Biologisch Effektive Dosis"(BED) und die "Äquivalente Dosis in 2 Gray Fraktionen" (EQD_2) berechnen. Diese fraktionierungsabhängigen Parameter werden Voxel für Voxel aus einer vorliegenden, relativ biologisch wirksamen Dosisverteilung berechnet und die resultierende Dosisverteilung gespeichert, damit beide Verteilungen im Anschluss verglichen werden können. Diese Skripten wurden verwendet um die Toxizität der therapeutischen Strahlung in Risikoorganen von 18 Patienten mit rezidivierenden Tumoren zu untersuchen welche mehrmals Strahlentherapie verschrieben bekamen. Alle Patienten wurden am MedAustron Ionentherapiezentrum mit Ionen wiederbestrahlt, nachdem ursprüngliche Tumore mit Photonen- oder Elektronenbestrahlung behandelt wurden. Zur numerischen Beschreibung der Dosisverteilungen wurden Dosis-Volumen-Histogram-Parameter vom Gehirn, dem Hirnstamm, den Augennerven und des Chiasm opticums eruiert und in einer Datenbank gespeichert.
Wird diese Datenbank künftig stetig erweitert, so könnte sie statistisch relevante Hinweise darauf geben, dass die zugeführte Dosis in Risikoorganen, bei Patienten welche mehrmals mit ionisierenden Strahlen behandelt wurden, weniger Schaden verursacht als derzeitige Evaluierungsparameter vorraussagen. Werden die in der Therapieplanung geltenden Restriktionen an etwaig dafürsprechende Daten angepasst, so würden die Wahrscheinlichkeiten von erfolgreichen Tumorbehandlungen durch Radiotherapie weiter steigen.

Contents

1. Introduction

Radiotherapy uses the destructive effect of ionizing radiation on biological cells to stop the growth of tumors and to kill cancer cells. The aim of radiation oncologists and medical physicists is to induce high levels of radiation dose in the malignant tumor cells while keeping the healthy tissue around the tumor as clear of radiation as possible. External radiotherapy includes treating patients with beams of accelerated photons, electrons or hadrons (protons, neutrons or heavy ions). The advantages of ion therapy over the use of photons or electrons are due to the distinctive characteristics of the interaction between accelerated ions and tissue, which make it easier to spare healthy tissue while also having a slightly higher relative biological effectiveness on tumor cells. Due to the dose they already received in tissue and organs around the tumor during their preceding treatment, patients with recurring tumors have to be taken into special consideration when the best or only option for treatment is radiotherapy because any amount of accumulated dose increases the possibility of complications. In order to prevent excessive strain on healthy tissue during re-irradiation and due to its biological effectiveness, the use of ion therapy is recommended for many indications. This is getting more common and is also encouraged by the growing amount of ion therapy centers.

Getting a realistic estimation of the biological effects of re-irradiation on sensitive tissue and organs during treatment planning is of high importance in order to be able to utilize the radiation beam characteristics in the most efficient way. In many cases the initial and second treatment are not carried out by the same facilities, which makes calculating the total radiation effects on the patient more complicated and requires complex treatment planning and risk estimations. Aside from the total dose applied to patient, potential repair mechanisms can additionally influence decisions concerning the safe amount of radiation during the second re-irradiation. Finding matching mathematical models which describe the biological effects of radiation in tissue proves to be difficult due to the complexity of biological systems and missing clinical data to confirm proposed ones. In fractionated radiotherapy, a linear quadratic model is well-established. It yields comprehensible results when using its parameter α and β to calculate the biologically effective dose (BED), which quantitatively indicates the biological effect of a fractioned radiotherapy treatment, taking the dose per fractions and the total dose into account.

Clinically used treatment planning systems do not include a tool for the calculation of the BED of dose distributions provided by the system.

1.1. Purpose of this Thesis

For an estimation of a re-irradiation's toxicity on organs at risk, a script for calculating the BED in RayStation (RaySearch Laboratories AB (publ)), which provides a scripting interface based on Ironpython (v2.7 – Jim Hugunin, Microsoft, USA) and the .NET framework has to be be written as a first step. It should calculate the BED for a treatment plans evaluated dose distribution Voxel by Voxel and provide a time-dependent recovery factor for the first treatment.

At the Ion Therapy Center MedAustron, around 40 patients with tumors in the brainstem/spinal cord region who have been treated with radiation therapy before were treated with ion therapy after disease recurrence. These patients' treatment plans were inspected for their significance in studying the strain on the brainstem, the brain, the spinal cord and the eye nerves. For the 18 patients who meet the requirements for this study, dose distributions of the initial and the second treatment and a summed up distribution are provided by the institute or have to be evaluated. Using this data as basis, the scripts which should be created in the range of this work, should be used for the evaluation of BED distributions and a database containing descriptive parameters of the 18 patients accumulated dose should be created for later references when estimating biological effects of radiation therapy treatments in organs at risk.

2. Theoretical Background

2.1. Physical Interaction of Ionizing Radiation with Matter

Ionizing radiation describes accelerated particles or photons which remove electrons of atoms or molecules and leave them as positively charged ions when interacting with a target material. [1]

The amount of energy which is deposited into the target during these collisions between particles is a measurement for the so-called energy dose, which is usually displayed in the unit Gray [1 Gy = 1 J/kg]. [2]

One can distinguish between directly and indirectly ionizing radiation:

- **Indirectly ionizing radiation** used in medical fields mainly consists of photons, like gamma- or x-rays. During an impact with matter, two kinds of interactions take place. Some of the incident photons are absorbed, meaning that they lose their entire kinetic energy through collisions (photoelectric effect, compton effect, pair production) and do not permeate the body. The other photons are getting scattered, a process during which they lose part of their kinetic energy and change direction every time they interact with particles within the target, but have enough velocity left to leave the body. Both interactions create free, electrically charged secondary particles, like electrons or positrons, which are able to ionize their surroundings themselves.

- **Directly ionizing radiation** consists of electrically charged particles like electrons, protons or ions. Due to them being charged, the probability of them interacting with the shells or cores of atoms, dispensing energy and ionizing them is higher compared to uncharged particles. [3]

2.2. Radiation Therapy using Photons

The most common form of radiation therapy uses photon beams with energies of 6-20MeV, which are produced using linear accelerators or radioactive sources (^{60}Co)

which are focused onto the area of the tumor. The curve describing the behavior of the deposited dose over distance in the tissue shows a fast increase shortly after entrance, due to mainly secondary electrons which are responsible for the energy transfer. After a short distance it reaches a maximum and drops exponentially afterwards, along with the intensity of the photon beam, as shown in figure 2.1. [4]

This results in tumors receiving lower doses than the tissues up front. In order to still be able to inflict most of the damage to the cells of the tumor, multiple angles are used to get a conformal dose distribution with the maximum dose in the tumor while keeping damages to the surrounding, healthy tissue to a minimum.

Also, tumors typically respond more intensely to deposed doses, so they suffer more damage as healthy tissue at the same deposited dose (see sections 2.4, 2.6).

Invasive forms of photon therapy like brachy-therapy or nuclide therapy are common medical treatments as well but will not be discussed in this paper in more detail.

2.3. Radiation Therapy using Ions

In order to be able to use accelerated ions for therapeutic purposes, the beam energies need to be up to 300 MeV. This can be achieved using iso-cyclotron- or synchrotron accelerators, which use electric- and magnetic-fields to interact with charged particles.

Faster and heavier particles form a beam which is more focused and has sharper edges than beams made of light particles or photons. The behavior of the dose, which is deposited in the tissue, over distance shows a slow ascent after entry, followed by a steep rise to a short, high maximum, the so-called Bragg peak and drops almost immediately to the zero dose level afterwards. Figure 2.1 shows this percentage depth dose curve. This behavior is controlled by the high masses, energies and the charge of the incident ions. At the start of their way through the body, they deposit low amounts of energy to the fundamental components of the tissue by means of inelastic scattering until their kinetic energy is in the range of the atoms' and molecules' ionization energy. At this point, they rapidly deposit their remaining energy while intensely ionizing the target material. Heavier ions like carbons have a larger 'tail' after their Bragg peak than protons due to secondary ionizing particles, which result from the breakup of the heavy ions while interacting with the target material's particles, leading to a resulting energy deposition in the following tissue. This phenomenon is described by the Bethe-Bloch-formula [4]

This form of the percentage depth dose curve has major advantages when treating some applications of tumors compared to photon beams, due to the tissue being exposed to much lower doses prior to the Bragg peak and almost dose free afterwards. With the

sharp-edged, narrow ion beam, an exact selection of the acceleration energy and precise adjustable magnetic deflection, it is possible to scan tumors point wise, a method called pencil beam scanning. Another possibility called passive scattering uses multiple overlapping beams with different energies to create a Spread-Out Bragg peak, which length is adjusted to the tumor's length and the width of the beam fits its diameter. Both methods achieve a very precise ionization of the tumor while comparably sparing the surrounding tissue from damage.

The currently most commonly used particles in ion therapy are protons, harvested as the nuclei of hydrogen atoms. In recent years, research and medical institutions also started focusing on carbon ions, consisting of 6 protons and 6 neutrons. Experimental results indicate an up to three times higher biological effectiveness for carbon ions compared to protons, due to a much higher ionization rate in the Bragg peak. There are also promising studies which show that carbons are able to treat many tumors which are largely resistant to common treatment techniques, like bone- and soft tissue tumors, un-oxygenated tumors, tumors with low growth-rates and relapse tumors after initial photon radiation treatment. [5]

Even though treatment with ions holds a lot of advantages medically, photon therapy is still a lot more common. On the one hand, its technology was heavily improved over decades and there are a lot of cases where photon treatment is the better option, for example when the irradiation of surrounding tissue is done on purpose due to it not only affecting healthy tissue but also possibly infected lymph nodes. On the other hand, there are substantial financial expenses necessary to provide ion therapy for the general public. The costs of high-tech devices like ion accelerators and the equipment needed to deploy these beams in a medically correct way, including a lot of necessary safety precautions, are enormous due to the need of specifically manufactured components and the expertise of technical personnel. Additional effort of medical personnel and the need of imaging devices during treatment planning lead to increased treatment costs as well. This is why one has to carefully choose which treatment method will deliver the best results for each individual patient.

2.4. Effects of Ionizing Radiation in Organic Tissue

In organic tissue, radiation causes two kinds of effects:

- **Direct effects** describe a damage to an organic cell by accelerated particles hitting its components.
- **Indirect effects** appear due to radicals which harm the cells. Radicals are created by radiation particles or photons colliding with atoms or molecules which lose

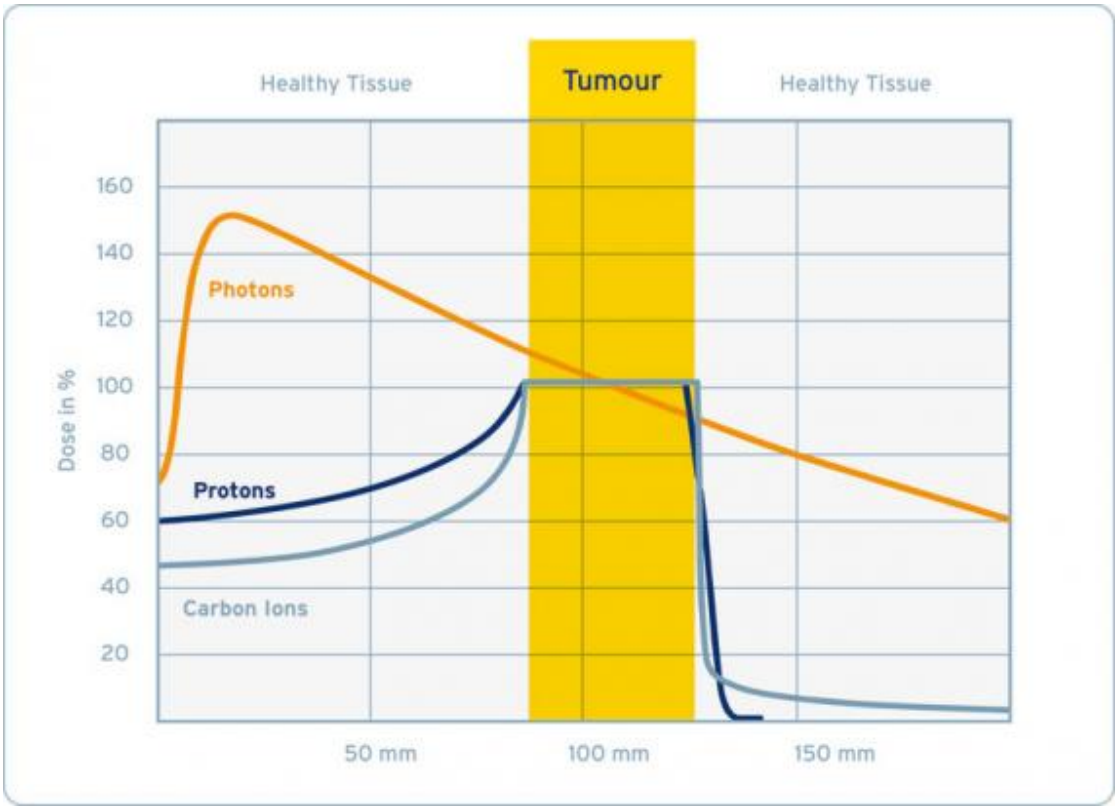

Figure 2.1.: Percentage Depth Dose Curves for Photons, Protons and Carbons. Proton and Carbon Curves are shown with a spread-out Bragg Peak, Photons as a Single Energy Beam [6]

shell electrons and afterwards tend to change or destroy other molecules and organic complexes in order to compensate their lack of electrons. It proves difficult to estimate the amount of radicals which is produced by incident radiation. One of the most important elements in the formation of radicals is oxygen, so hypoxic cells tend to be less sensitive to radiation than well-oxygenized ones. [7]

In clinical routines, it is not necessary to differentiate between direct and indirect effects in vivo. They both affect organic components of cells like proteins, the membrane and - what is particularly important in radiation therapy - nucleic acids. Incident radiation can damage the bases of DNA and lead to single or double-strand breaks. The vast majority of damages in cells are successfully repaired by enzymatic reactions but some rare ones, like double-strand breaks, fail to repair and eventually lead to cell death. It is the killing of stem cells and consequently the inability to form new cells which causes early manifestations of tissue damages. These are required in tumors but can lead to a breakdown of the skin or mucosa, denudation of the intestine and haemopoietic damage in healthy tissue shortly after exposure to radiation. Late reactions which may become issues are fibrosis and telangiectasia of the skin, nerve and blood vessel damage and radiation induced tumors, which can form even many years later. [8] An important factor of the cells' radiation sensitivity is their current phase in the cell cycle. These can be divided into the G_1 phase, during which the cell increases in size, the S phase, during which DNA replication takes place, the G_2 phase, where the cell continues to grow, the M phase, during which the cell stops growing and its energy is focused on the orderly division into two daughter cells, and finally the G_0 phase, where the cell has left the cycle and has stopped dividing. They are most sensitive in the M and late G_2 phase and most resistant in the late S phase. Cells which have a greater reproductive activity, like tumor cells, cells of the gonads or in growing organisms (children) tend to be more sensitive to radiation than the majority of body cells. An exact description of sensitivity proves to be very difficult due to additional influencing parameters like type, oxygenation and metabolism of the individual cell. [7]

2.5. Quantifying Cell Kill and Cell Survival

A simple way of picturing how radiation might kill cells is the idea that their reproductive ability depends on certain regions of the DNA. These sensitive parts can be thought of as specific targets the radiation needs to damage to ensure the cell's death. This leads to a cell survival theory called 'single-target single-hit ', which proposes that just one hit by radiation on a single sensitive target will lead to the death of the cell. Using this theory to plot a cell survival curve, which displays cell survival plotted over accumulated dose, would lead to an exponential dependency (i.e. a straight line

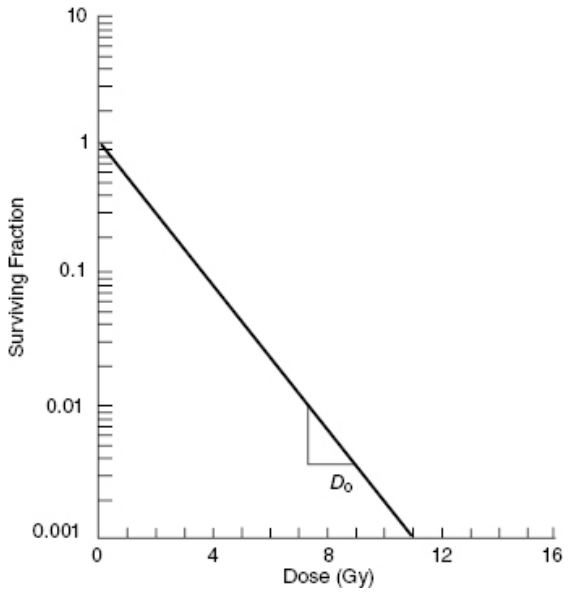

Figure 2.2.: 'Single-Target Single-Hit' Cell Survival Curve with the Surviving Fraction on a Logarythmic Scale [9]

in a semi-logarithmic plot as shown in figure 2.2). Deriving an equation from this is possible using Poisson statistics. The presumption is that during irradiation, there is a very large number of hits on different cells, but the probability (p) of the next hit occurring in a certain cell is very small. Thus equation 2.1, with D_0 as the dose that gives an average of one hit per target, can be derived to describe the survival rate.

$$p(\text{survival}) = p(0 \text{ hits}) = e^{-\frac{D}{D_0}} \tag{2.1}$$

This survival curve fits sufficiently when describing the radiation response of noncomplex or sensitive cells or when high LET radiation (see section 2.6) is applied. This curve form is actually valid outside the target framework due to it describing the simple situation where an individual cell will die if it receives an amount of radiation greater than D_0, otherwise it will survive. [10]

For more complex scenarios, the survival curve needs to be adjusted and is usually described as a 'shouldered' curve. To model this type of response, the target model was further developed by proposing the 'multi-target, single-hit' inactivation. Thus, one hit of radiation on each of n sensitive targets in one cell is required for the death of the cell. Lines 2.2 to 2.4 show how to mathematically derive the new model's equation 2.5 displayed in figure 2.3.

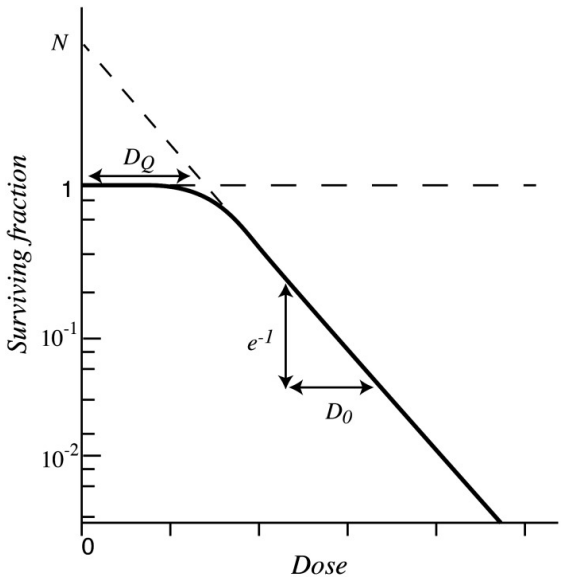

Figure 2.3.: 'Multi-Target Single-Hit' Cell Survival Curve with the Surviving Fraction on a Logarythmic Scale [9]

$$p(0 \text{ hits on a specific target}) = e^{-\frac{D}{D_0}} \tag{2.2}$$

thus

$$p(\text{specific target inactivated}) = 1 - e^{-\frac{D}{D_0}} \tag{2.3}$$

as there are n targets in the cell

$$p(\text{all n targets inactivated}) = (1 - e^{-\frac{D}{D_0}})^n \tag{2.4}$$

thus

$$p(\text{survival}) = 1 - (1 - e^{-\frac{D}{D_0}})^n \tag{2.5}$$

A problem with the target model description is that so far, the specific radiation targets have not been identified for mammalian cells, despite considerable effort to search for them. Therefore, the key role of DNA strand breaks (see section 2.4) and their repair, with sites for such damage being generally dispersed throughout the cell nucleus, is getting more into focus. The more obvious problem of the multitarget model is that it

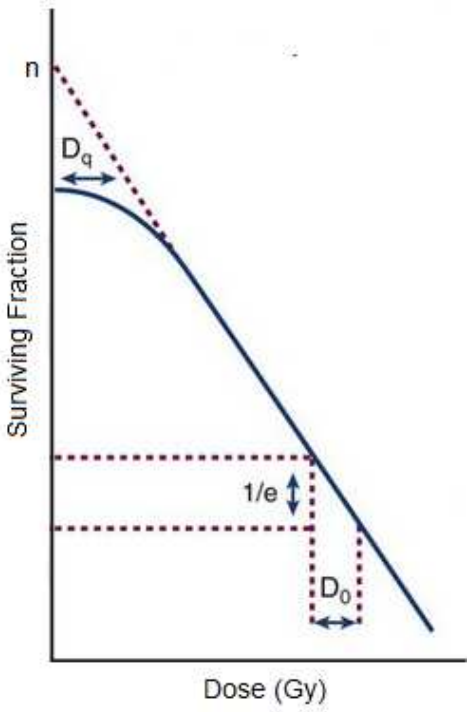

Figure 2.4.: 'Multi-Target Single-Hit' Cell Survival Curve with the Surviving Fraction on a Logarythmic Scale with the Improved Initial Slope [9]

predicts a flat response for very low doses, as can be seen in figure 2.3. Experimental data has given overwhelming evidence for significant cell killing even at low doses and therefore demands for cell survival curves with a finite initial slope. In order to take these results into account, the multitarget model was adjusted by adding an additional single-target component leading to equation 2.6

$$p(\text{survival}) = e^{-\frac{D}{D_1}} * (1 - (1 - e^{D(\frac{1}{D_0} - \frac{1}{D_1})})^n) \tag{2.6}$$

This survival curve is illustrated in figure 2.4. The parameter D_1 fixes the initial slope, and describes the dose required in the low-dose regime to reduce survival from 1 to $\frac{1}{e}$. This curve now correctly predicts finite cell killing in the low-dose region but has the drawback that the change in cell survival in this range occurs almost linearly, which does not match the discovered effects of fractionation (see section 2.8). Using a multitarget approach as the initial slope could make a better fit but would make the model much more complicated and therefore be of little value in helping to understand the fundamental mechanism determining radiation effects. [11]

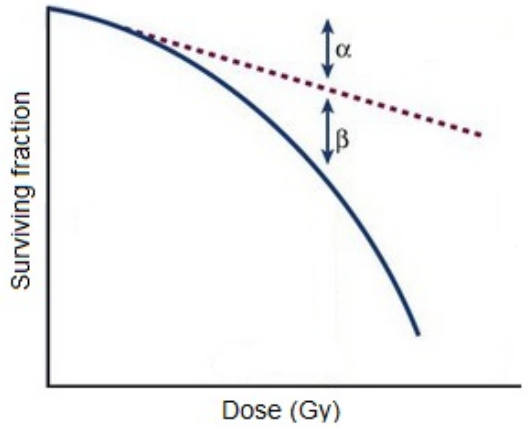

Figure 2.5.: The Linear Quadratic Cell Survival Curve with its Parameters α and β Defining the Linear and Quadratic Shares [11]

This continually downward bending form of the cell survival curve can be well fitted mathematically by a second-order polynomial with a zero constant term to ensure that survival probability is 1 at zero dose. This formulation is called the linear-quadratic (LQ) model. Although it is based purely on mathematical assumptions, equation 2.7 is not only superficially similar to the mathematically more complicated, two-component model (see figure 2.5), in fact, its description of radiation in the lower response region is even more accurate.

$$p(\text{survival}) = e^{-\alpha D - \beta D^2} \tag{2.7}$$

α and β determine the shape or 'bendiness' of the curve. They do not describe known physical or biological parameters directly. α's dimension is Gy^{-1} and β's Gy^{-2}, indicating that their ratio has the dimension of Gy, which describes the dose at which the linear factor's contribution to damage (αD on the logarithmic scale) equals the quadratic factor's contribution (βD^2). The LQ model is now widely used for biological effect estimation purposes, although there are still ongoing debates and studies about the interpretation of α and β. [11]

2.6. Linear Energy Transfer (LET) and Relative Biological Effectiveness (RBE)

X-rays, γ-rays and electron beams have similar biological effects per unit dose, although there is a small energy dependency, with lower energies being slightly more effective (see section 2.8). Heavier particles tend to have a larger biological effect on tissue per unit dose and can be classified into two classes. One consists of the light particles like protons, neutrons and α-particles and the other one of heavy particles like fully striped carbon, neon, silicon or argon ions. The linear energy transfer (LET) describes the density of ionization in a particle beam's track. High LET particle beams move through tissue in a fairly linear and more focused path than low-LET particle beams, which produce a high number of sparse tracks per gray. With increasing LET, the survival curves become steeper, straighter and less shouldered, which indicates either a higher ratio of lethal to potentially lethal lesions or that high-LET radiation damage is less likely to be repaired correctly (see section 2.4). [12]

The relative biological effectiveness (RBE) of a specific kind of radiation is defined as

$$\text{RBE} = \frac{\text{dose of reference radiation}}{\text{dose of test radiation}} \tag{2.8}$$

It describes the biological effect of a specific type of radiation by comparing it to a reference radiation, which is commonly 250 kVp x-rays or ^{60}Co γ-rays since these are usually available whenever RBE is being evaluated. [13]

2.7. Tumor Control Probability (TCP) and Normal Tissue Complication Probability (NTCP)

Radiation effects on tumors under clinical as well as experimental conditions can lead to different desired endpoints including local tumor control, tumor regrowth delay and tumor regression. In radiotherapy, local tumor control, describing a stabilization of the tumor volume, is the main goal, which hopefully leads to a longer survival of the cancer patient. A tumor is considered locally controlled when all of its clonogenic cells (see section 2.4) have been inactivated. The probability of achieving this goal is dose-dependent. If not only a single, but a group of tumors is considered, the local tumor control probability (TCP) is defined by the amount of cell kills as function of radiation dose. The dose-response relationship curves can be derived from clinically obtained survival curves, with effect thresholds and a maximum number of affected cells as boundary conditions. They have a sigmoid shape, with the incidence of radiation effects

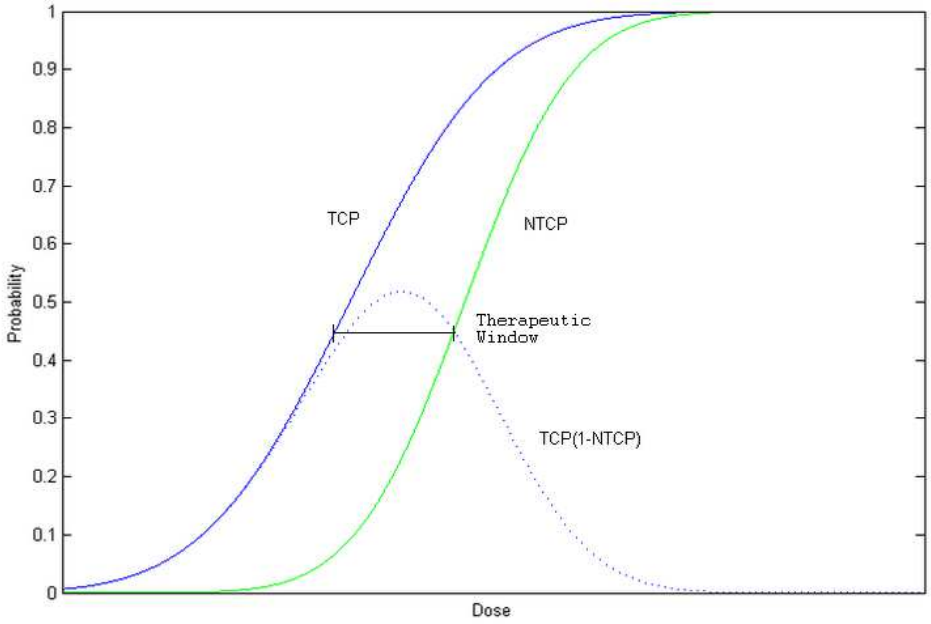

Figure 2.6.: Dose-Response Diagram with TCP, NTCP and the Therapeutic Window [15]

tending to zero as no dose is applied and going up to 100% at very large doses, as shown in figure 2.6. The form of the response curve was derived from experimental data long ago and scientists and physicians have been using it ever since to describe the effect of radiation on biological tissue. However, finding an exact mathematical model to explain and predict the curve turned out to be very difficult due to the quantity of influential parameters (see sections 2.4, 2.5).

In healthy tissue, the curve takes the same shape but has a higher dose threshold due to its divergent radiation sensitivity (see section 2.4). This effect defines the goal for treatment planners. They try to apply enough radiation so the TCP is at its maximum while keeping the NTCP as low as possible. The area in between the two curves in the dose-response graph is called the therapeutic window (see figure 2.6).[14]

2.8. Fractionation and the Biological Effective Dose (BED)

Fractionation in radiotherapy is the process of dividing the treatment total dose into multiple 'fractions', given in a specific time interval over the treatment course, which

then usually lasts multiple weeks. This practice seeks to maximize the destruction of malignant cells while minimizing damage to healthy tissues. Its effectivity was discovered experimentally and although it is hard to precisely explain the underlying mechanisms, there are multiple factors which seem to have an influence. First, having multiple treatments raises the chance to irradiate the cell during the correct phase in its cell circle (see section 2.4). Secondly, the intervening time gives hypoxic cells a chance to supply themselves with more oxygen (see section 2.4). Also, cells are given a time frame to repair their received damage, which benefits the healthy tissue as its cells have improved repair mechanisms compared to tumor cells. [16, 17]

Taking the target model as basis for cell survival, the surviving fraction after a dose per fraction d is given as $SF_d = e^{-\alpha d - \beta d^2}$ (see section 2.5). Studies have shown that each successive fraction is equally effective, so the same effect (E) on tissue by treatment courses with a different number of fractions n can be expressed as written in equation 2.9, with D being the total radiation dose $D = nd$.

$$E = -log_e(SF_d)^n = -nlog_e(SF_d) = n(\alpha d + \beta d^2) = \alpha D + \beta dD \tag{2.9}$$

This equation can be rearranged into equation 2.10 where E/α is denoted as the biological effect dose BED.

$$E/\alpha = D(1 + \frac{d}{\alpha/\beta}) = BED \tag{2.10}$$

It is a measure of the effect (E) of a course of fractionated or continuous irradiation. Due to the division by α it has the unit of dose, usually expressed in Gray. If the dose per fraction (d) is reduced towards zero, BED becomes $nd = D$, the total radiation dose. Thus, BED is the theoretical total dose that would be required to produce the isoeffect E using an infinitely large number of infinitesimally small dose fractions. It is highly suitable for comparing the quantitative biological effects of treatments in many modalities. A disadvantage of BED as a measure of treatment intensity is that it is numerically much greater than any prescribed dose and is therefore difficult to relate to everyday clinical practice if its backgrounds are unknown. [18]

2.9. The Equivalent Dose in 2 Gray Fractions (EQD_2)

The Equivalent Dose in 2 Gray fractions (EQD_2) describes the dose delivered in 2 Gy fractions, which is biologically equivalent to a total dose. Like the BED, it is based on the linear quadratic function and therefore denotes a similar effect as the BED. It

contains the total dose D, the fraction dose d and the α/β ratio and its formula and relationship to the BED is displayed in equation 2.11. [19]

$$EQD_2 = D * (\frac{d + \alpha/\beta}{2 + \alpha/\beta}) = \frac{BED}{1 + \frac{2}{\alpha/\beta}} \tag{2.11}$$

Although BED and EQD_2 provide similar information, the EQD_2 is more common in everyday clinical use due to its values being in the same range as RBE dose values, while BED values are not directly comparable to RBE dose values.

2.10. The Dose Volume Histogram (DVH)

A dose-volume histogram (DVH) relates radiation dose to tissue volume and is often used as an indicator for the dose distribution in specific volumes in radiation therapy planning when comparing different plans' dose distributions in target areas or organs at risk. They can be visualized in two ways, either as differential DVHs or cumulative DVHs. For creating a DVH, the size of the dose bins, which are sorted along the horizontal axis, has to be determined. In a differential DVH, each bar's height indicates the volume of the structure receiving the corresponding dose given by the bin. The affected volume is either given on a relative basis or in absolute values. In therapy planning, the use of cumulative DVHs is more common where the height of each bar displays the share of the structure's volume which received a dose as high or higher than fixed by the bin. With very fine bin sizes, the cumulative DVH takes the form of a smooth line graph which will always slope and go from the top-left to the bottom-right corner. A structure receiving a very homogenous dose will result in a DVH with a horizontal line at the top of the graph and an almost vertical drop at the end (see figure 2.7). Evaluating specific DVH-parameters like the dose at 2% Volume ($D_{2\%}$) denoting the maximum dose which is deposited in 2% of the structure's volume, provides comparable dose distribution describing values. It is important to take the spatial distribution into account as well as DVH parameters do not provide any information concerning the location of dose minima and maxima. [20]

2.11. Medical Images and Treatment Planning Systems

The necessary tumor dose and boundary conditions are chosen by a radiation oncologist based on the histology of the tumor. For evaluating the optimal radiotherapy for a patient, it is necessary to adjust the distribution of the prescribed dose to his or her

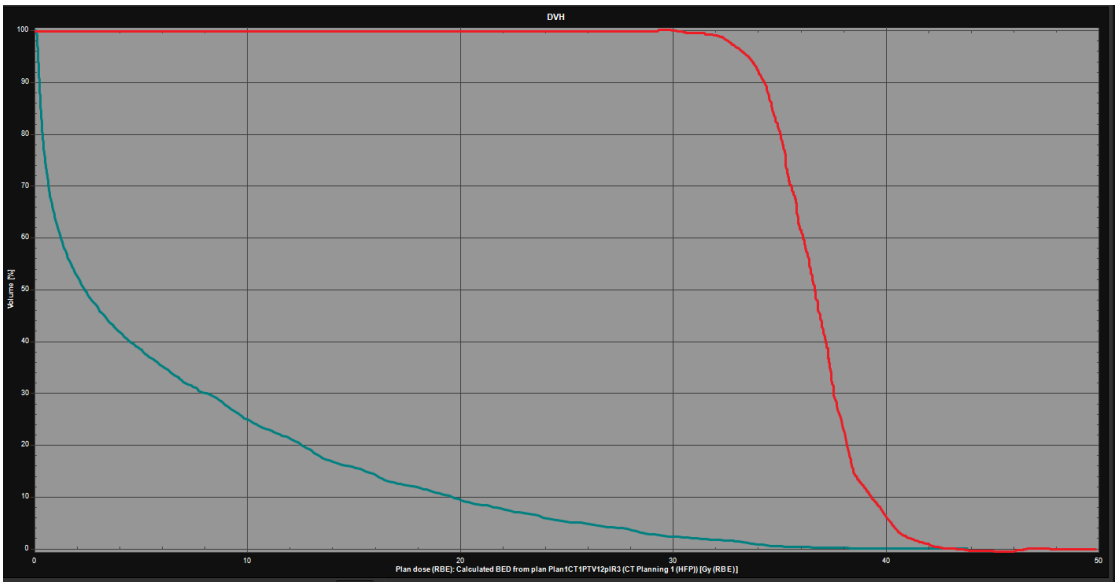

Figure 2.7.: DVH of the Brainstem of an Anonymized Patient. The Red Line Represents a Typical Target Dose Distribution, the Blue Line a Typical Structure Lying Close to the Target. The y-Axis refers to the Structure's Volume in % and the x-Axis to the Planed Dose. Patient Data Provided by MedAustron and DVHs Exportet from Raystation Therapy Planning System

individual anatomy as precisely as possible. This means that high contrast anatomic images of the patient's body, which do not only register the outer body but also visualize interior structures, are necessary. For the creation of treatment plans, computer tomography (CT) image stacks are typically used as anatomical and also physical reference. Computer tomography creates data slices of the human body by performing x-ray scans at multiple angles and in predefined steps along the longitudinal axis of the patient. Afterwards, the data is reconstructed digitally. These data stacks are saved as files in DICOM (Digital Image and COmmunications in Medicine) format where additional information like segmentation, patient data, pathology or image registrations can be attached.

The merged stacks are sorted into voxels, which are small cubic subdivisions of the whole body and can be understood as pixels in 3D. Their size is mostly defined by the in-plane resolution of the slices and the distance between them. Each of these voxels has an assigned value describing its relative x-ray attenuation coefficient. This parameter describes the permeability of a material when hit by ionizing radiation, which, in the case of CT, consists of x-rays. The relative attenuation coefficient's values are distributed on a linear scale in Hounsfield Units (HU). On the Hounsfield unit scale, water is defined as 0 HU while air is set as -1000 HU. Assigning a gray color scale to the Hounsfield scale allows visualizing the data stacks as image stacks in black and

white or through computer rendering, even the formation of 3D-Models is possible. Having a data matrix which contains the spatially correctly assigned relative attenuation coefficient's values is essential for treatment planning systems. These programs can not only view and process DICOM image stacks and provide tools to segment the images into anatomical areas of interest, they are also able to calculate and visualize dose distributions of virtual radiation beams, which simulate the clinically existing beams' properties. Modern therapy planning systems use powerful computational algorithms like Colapsed Cone or Monte-Carlo simulations to calculate the predicted dose distribution voxel by voxel using medium qualities extracted from the HU and taking the relative biological effectiveness (see section 2.8) of different particle beams into account. These dose distributions can also be extracted and saved as DICOM files. A number of calculated physical and biological parameters help medical physicists and physicians to choose the best treatment plan for each patient, although the complexity of the influences on the treatment raises a desire for further improvement of existing programs and the development of additional tools. [21]

3. Material and Methods

The aim of this thesis is to create a script for the treatment planning system RayStation (RS v8B – RaySearch Laboratories AB, Sweden), which calculates the BED distribution of a treatment plan voxel by voxel using the RBE dose distribution as basis. For 18 patients of interest, who were re-irradiated with protons at MedAustron after developing a recurrent tumor in the head and neck region, specific DVH-parameters of organs at risk will be evaluated from the BED and RBE dose distributions of each treatment and for the summed distribution of both treatments. The data is stored in order to start a database of re-irradiation cases for future reference and statistical evaluations. This database will provide helpful information on the toxicity of multiple radiation therapy treatments in organs at risk, as well as insight on the validity of the BED as a parameter describing the effect of radiation in tissue.

3.1. The Patients

At MedAustron, Ion Therapy Center, 41 patients with recurrent tumors close to the brainstem and spinal cord were treated with ion therapy after the initial tumor was treated with photon radiation therapy. The scripts, which were developed in the course of this thesis, evaluate RBE, BED and EQD_2 parameters in the brainstem, spinal cord, brain and the optic nerves from dose distributions saved in DICOM format. Therefore, only patients with available DICOM plans for both treatments can be included. This leads to an exclusion of 14 patients. Another important factor in this study is that the two treatments' dose distributions overlap in at least one of the organs of interest, otherwise the data would not contain any significant information regarding the re-irradiation of these structures. Therefore, another 9 patients have to be excluded. This leaves 18 patients whose characteristics are summarized in table 3.1.

The selection of the patients qualifying for the study was done by Yasuhito Hagiwara MD, PhD and provided as basis for this thesis.

Characteristic		Value
Sex	M/F	12(67%)/6(33%)
Age	Median/Range	51y.o./7-78y.o.
Time between Treatments	Median/Range	30m/14-81m
Initial Treatment	Median Total Dose/Fractions	60 Gy [RBE]/ 30
Second Treatment	Median Total Dose/Fractions	66 Gy [RBE]/ 31

Table 3.1.: Patients Statistics

3.2. RayStation

RayStation is a treatment planning system developed by RaySearch Laboratories AB (publ), which provides a graphical user interface and the necessary tools and implementations needed for evaluating appropriate treatment plans in radiation therapy. The program is updated frequently and the version used in this thesis is RayStation 8B SP1. It provides features for visualizing images, tools for marking patient geometry, algorithms for the calculation of photon, proton and carbon dose distributions, treatment plan optimization tools and implementations for the evaluation of biological effects. Additionally, it includes a scripting interface which gives users the possibility to automate tasks or access and process data of treatment plans.

The scripting interface is based on Ironpython (v2.7 – Jim Hugunin, Microsoft, USA) and the .NET framework and additionally includes some RayStation-specific functions, which can be displayed in the "state tree", a scripted guide to the implemented functions which can be accessed in the scripting interface. These are very helpful for accessing common objects and performing frequently needed Raystation tasks with short commands instead of complex functions in the Python language.

In Raystation, all created plans, which include DICOM image files, segmentations, dose distributions and patient and treatment data, are stored in RayStations own local database. It is possible to export DICOM files to an external folder or import files, although these will be labeled by the program. [22, 23]

3.3. Summing up Dose Distributions of Initial and Second Treatments

RayStation's plan evaluation section provides a tool for summing up different dose distributions. In order to do so, they need to be registered to the same image stack. So the initial treatment's dose distributions have to be imported into the respective

patient's database in RayStation and registered to the new CT image set. This task was already done by Yasuhito Hagiwara MD, PhD and Mgr Inż. Piotr Andrzejewski, PhD who wrote a registration manual which can be found in the MedAustron database.

3.4. Creating Scripts for the Evaluation of BED and EQD_2 Distributions in RayStation

The necessary modules which need to be imported are '*' from connect, to connect the script to Raystation and being able to use functions implemented in the treatment planning system, 'platform' to access the underlying platform's identifying data, 'math' for mathematical operations, 'wpf' from 'System.Windows': '*' for being able to access the windows .NET framework and from 'System.Window.Controls': '*' for having access to the windows GUI functions.

At the beginning of the script, the variables 'recovery', 'alpha_beta' and 'number_fractions_input' are defined and their most common values 0, 2 and 1 are assigned to them. These values will later be replaced by values provided via GUI or read out of a treatment plan by a function.

Two winform structures which open a GUI when the script is run in RayStation are defined. The first one is called 'MyWindow' and will call the xaml-file 'BEDinput', which provides a winform window in Raystation asking the user to choose a recovery factor in % and the α/β ratio in [Gy]. The provided values will replace the originally defined values of the associated variables. The second winform structure calls the 'BEDinputrf' xaml-file and asks the user to type in the number of fractions manually. This window only pops up when the fractionation scheme is not defined in the current treatment plan.

Now the currently opened patient, case, plan, examination and machine database will be assigned to variables, so all built-in functions related to them can quickly be accessed later. The script recalculates the currently open plan into its BED distribution.

The creation of a new plan is defined, with the naming convention 'Calculated BED from plan' and the name of the original plan, with the percentage of recovery displayed in brackets, in case there was one defined.

The next structure, called 'compute_bed' defines the equation for calculating the BED from the provided variables 'fraction_dose', 'number_fractions' and 'alpha_beta' (see 2.10).

As the dose grid of the BED plan has to be the same as the one of the original plan, it needs to be updated, so the size and number of voxels is the same in both plans.

In the next paragraph, the beamsets of the original plan are copied. It is necessary to define various exceptions because the provided 'AddNewBeamSet'-function requires an input for the treatment modality and the beam forming machine's name. Unfortunately deprecated machines and modalities or machines, which are not registered in the utilized copy of RayStation, result in a function error. This has to be avoided by changing these parameters into ones which are accepted by the function. In order to prevent confusion when looking at the BED plans later on, a comment about the change of modality or treatment machine will be added to the plan by the script.

Now the fraction dose is read out of the old beamset voxelwise, fed into the 'compute_bed'-function, which calculates the BED value, and saved into a spatially equivalent position in an array. This array is now assigned to the newly created beamset of the BED-plan. This process is repeated until all beamsets of the old plan are converted into BED distributions for the new BED-plan.

It should be noted that in case the dose distribution was imported, it is possible that multiple beamsets are already summed up to a single dose distribution. In this case, the calculated BED distribution is not correct as the voxel-wise BED calculation can only result in correct values when each beamset was evaluated individually and summed up afterwards. Otherwise wrong fraction numbers are assigned to specific areas and lead to wrong distributions. For example, even if both beamsets have the same fractionation schemes of 14 fractions, simply taking 28 fractions as the functions fraction number gives wrong results for voxels in areas where the beamset's distributions do not overlap, as only 14 fractions were delivered here.

A similar script which calculates the EQD_2 instead of the BED was created as well. Here the 'cumpute_bed' function is substituted for a 'compute_eqd2' function containing the EQD_2 formula (see 2.9). For this script the same restrictions apply as for the BED calculating script.

The scripts are provided in appendices B and C.

3.5. MICE Toolkit

MICE Toolkit (Medical Interactive Creative Environment - NONPI Medical AB, Sweden) is a graphical programming user interface which aims to be user friendly while still being highly flexible. It provides tools to perform complex image analysis, to visualize images and to extract data and resulting images in various forms. It enables users to perform programming steps without having a background in writing code in any programming language, although for those who want and need to perform additional programming operations, the premium version provides the implementation of Python

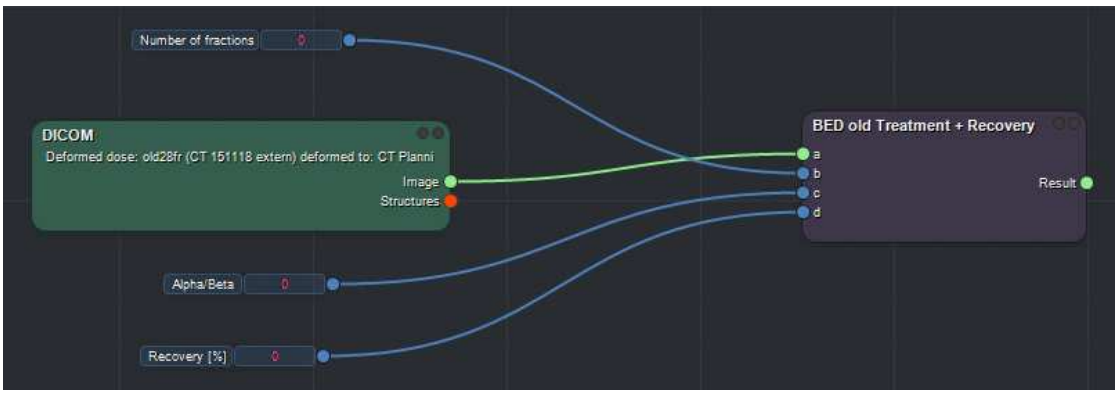

Figure 3.1.: The Structure of Image-Data, Input-Values and the BED calculating Expression Node

or Matlab code. The graphical user interface comes in the form of nodes, each representing a DICOM image set or some sort of operation. The operation nodes are put into different categories which are differentiated by the type of data they work on. The nodes' categories are image, mask, structure, data, values, vector and complex. All of them have subcategories like mathematical expressions or even complex algorithms implemented in order to lighten the user's workload.

For script validation purposes (see 3.8), a BED node calculating structure set was built in MICE Toolkit. The resulting structure is shown in figure 3.1.

3.6. Creating a Script in RayStation for Reading out DVH-Parameters

The modules which need to be imported into this script are 'xlsxwriter' for writing the read out parameters into an excel file, 'numpy' for mathematical operations and from 'connect' '*' to connect the script to RayStation and being able to use functions implemented in the treatment planning system. Two functions will be defined in the beginning of the script - one to create an array where the data will be stored in and one that defines where the resulting values will be written in the excel table.

As a next step five variables need to be created. The first one defines the index number for the correct fraction evaluations, the second one defines the index number of the correct examination and the other three define the index numbers assigned to the evaluation doses of the old, new and summed up RBE dose and BED distributions. In case this script is used for other purposes, any evaluation dose can be assigned. The respective variables have to be adjusted for each patient so the correct dose distributions

will be accessed. The index number, which is assigned to a specific evaluation dose, can be looked up with a script called state tree script provided by Raystation. It shows a list of all variables which are accessible by scripts. Figure 3.2 shows the pathway to the evaluation doses.

The next lines use functions provided by the RayStation scripting interface to assign the currently opened patient, case, plan and beamset to variables.

The 'plan_dose' variable is a shortcut to the plan's total dose function in the state tree which contains information on the dose grid and regions of interest's parameters. The 'structure_set' variable loads all the segmented structures from the patient's data.

The following code snippet loads the patients name and reforms it, so it will be displayed without additional signs in the excel sheet.

Now the dose names and distributions for the assigned dose evaluations are being read out and assigned to variables, the first ones are used for a clear structure in the excel sheet, the second ones for calculation of the DVH-parameters.

Organs at risk which should be inspected need to be written into the 'oar_names' list. A small utility afterwards converts camelCase afterwards; however; correct naming, which is consistent with RayStation data, is still necessary. The chosen structures for this thesis are the brain, brainstem, spinal cord, chiasm and the left and right optic nerve.

Thereafter the saving path for the excel file needs to be assigned and all headers and descriptors, which are necessary in order to have a well-structured excel sheet, need to be defined and assigned to rows and columns.

Creating an array containing the organs of interest provides a structure, which assists in reading out in the 'for'-loop.

The 'for'-loop runs through all previously defined structures and calculates the chosen DVH-parameters. The built-in 'TotalVolume'-function of RayStation provides the structures' volume in centimeters and the 'GetDoseAtRelativeVolumes'-function reads out the maximum dose value, which covers a defined relative volume. In order to convert absolute volumes (e.g. d2cc, d1cc, do.7cc,...) into relative volumes, they have to be divided through the total volume of the considered organ. It should be noted that the Raystation scripting interface issues an error if the relative volume is outside 0 and 1, so exceptions should be included in the code for organs which are smaller than a volume of interest for evaluating a DVH-parameter.

Finally, the calculated values are assigned to the previously defined array and written into the excel-sheet's cells.

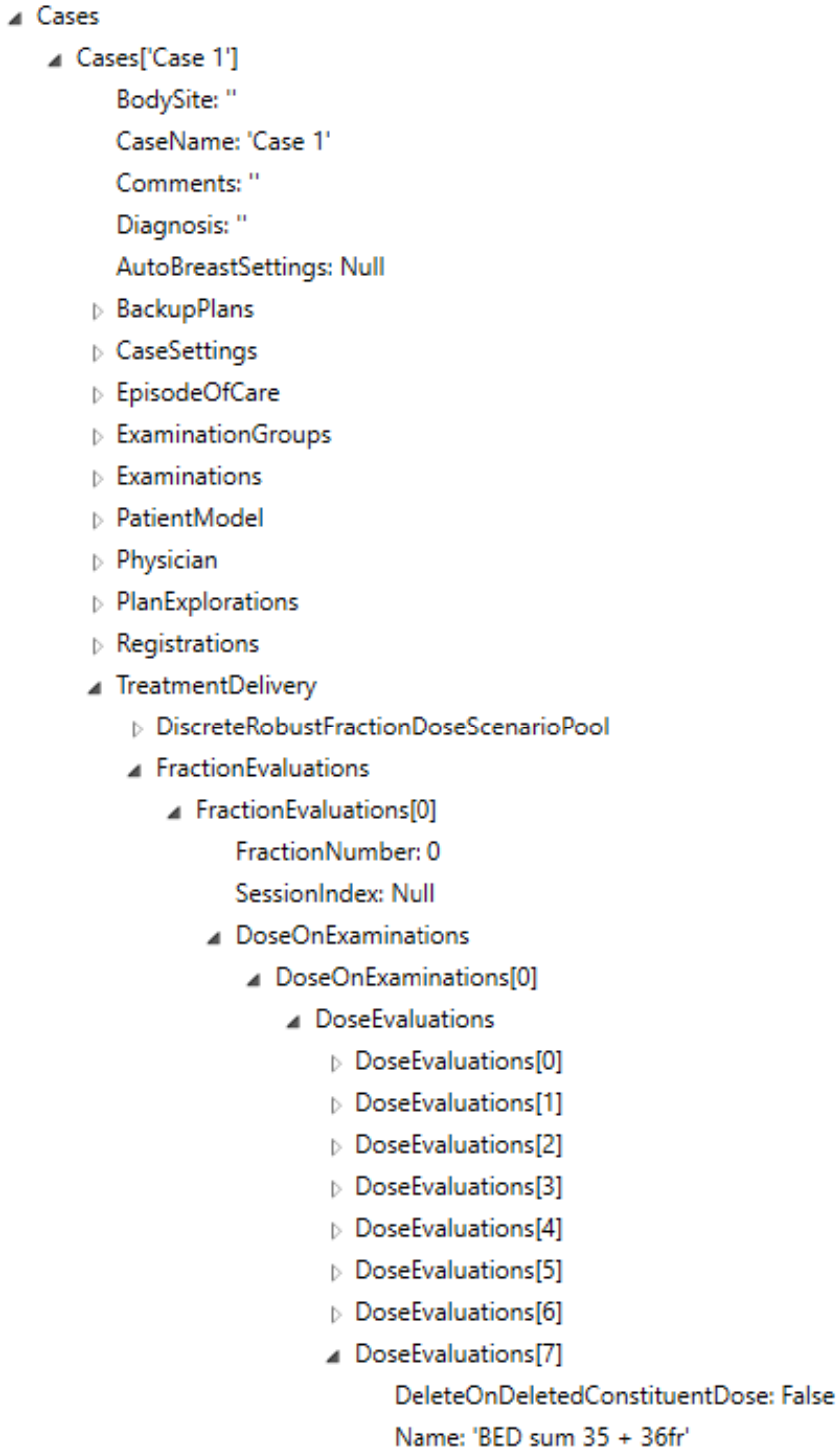

Figure 3.2.: Raystation Scripting Interface's Statetree with the Pathway opened up to find the Evaluation Doses

The whole process, starting from the definition and writing of the headers has to be done for all three evaluation dose distributions - the old one, the new one and the sum of both.

At the end, the name of the excel sheet has to be defined and its workbook closed. This file will now contain the name of the patient alongside the DVH-parameters and their descriptions.

The script is provided in appendix D.

3.7. Workflow for Data Acquisition

The complete workflow for collecting patients' RBE, BED and EQD_2 DVH-parameters of an initial, a re-treatment and the summed up dose of both consists of the following steps:

- Open the patient in RayStation and make sure all treatment plans are saved in his/her data profile. If a treatment's plan is missing, import the associated DICOM files as a new plan.
- Use the provided BED and EQD_2 scripts in RayStation's scripting interface to create BED- and EQD_2-plans from all RBE-plans that contain beamsets which were actually delivered in a treatment.
- Create evaluation doses of the old and new treatments RBE dose and BED distributions.
- If the initial and re-treatment are not registered to the same reference image set, register one of the dose distributions to the other image set.
- Use the 'Sum Doses' tool to sum up the old and new RBE dose distributions and the BED distributions.
- Look up the correct 'FractionEvaluations', 'DoseOnExaminations' and 'DoseEvaluations' indices from the RayStation scripting interface's state tree and assign them to the variables in the 'DVH_parameters'-script (see 3.6).
- Adjust the DVH-parameters in the 'DVH_parameters'-script to the desired values and set the path where the resulting excel file should be saved.
- Run the script in the scripting interface.
- Copy the obtained data into the patient database excel file (see attachment E).

3.8. Validation of the BED script for Clinical Use

For future use, the BED calculating script was validated in terms of MedAustron policy standards for script validation. The validation report is attached in G.

4. Results

4.1. The Developed Scripts

All developed scripts operate as intended and the BED script was validated according to MedAustron script validation standards. The validation protocol is added as appendix G.

The distributions resulting from the EQD_2 script were validated using random test-voxels in multiple patient's dose distributions. Every time the original dose distribution, consisting of a simple fractionation scheme, was opened in RayStation's dose evaluation viewer next to its associated EQD_2 distribution. A dose value of a voxel in the original distribution was read out, its EQD_2 value calculated manually and compared to the value of the same voxel in the EQD_2 distribution. The maximum dose value can also be taken as reference.

The DVH-parameter evaluation script's outputs were validated by looking up the same parameters in the DVH-tool provided by RayStation and checking their correctness. Small deviations can occur here since different bin sizes are used. The DVH tool works with specific minimal volume sizes, which leads to it taking median dose values distributed over this volume. The developed script uses the smallest volume possible - a single voxel - as minimal volume so every voxel's assigned dose value is taken into account individually.

4.2. Patient Database

The created database is attached as appendix E. It contains a patient number, the prescribed dose to the target volume and the fractionation schemes of each treatment, the recovery time in months, the histology and the evaluated DVH-parameters which contain the D2.0cc, D0.7cc and D1.0cc for the brainstem and the spinal cord, the D5.0cc, D2.0cc and D1.0cc for the brain and the D2% for the chiasm and the right and left eye nerve evaluated from the RBE, BED and EQD_2 distributions. The patient number was assigned in the list of the initial 40 patients (see 3.1) and is also used in the RayStation

patient database. Thus, all patients are anonymized. The columns containing the data of the second treatment are colored in yellow and columns containing data of the summed up dose distributions are colored in green.

A second database which only focuses on specific parameters was also created and attached as appendix F. Only data describing the total radiation exposure is listed here, with the intermediate dose volume DVH-parameter's column from each structure marked in yellow and the smallest volume colored in green. Additionally, the differences between RBE and EQD_2 parameters were calculated at the right end of the table, with the minimum and maximum always at the bottom of a column.

5. Discussion

5.1. Resulting BED and EQD_2 Distributions

When comparing a resulting BED distribution with their associated RBE distribution, the first noticeable effect is the shift of equivalent dose levels towards the center of the target volume in BED distributions (see figure 5.1). This effect is caused by the nature of the BED formula (see section 2.8), which shows a quadratic dependency on the dose per fraction received by a specific voxel. This correlation is paired with the typical shape of a dose distribution: In most treatments only voxels in the target volume receive the planned fraction dose and further out the dose drops in either a steep or a gentle gradient, depending on the treatment method (see sections 2.2 and 2.3). As the EQD_2 is linearly dependent on the BED, $EQD_2 = \frac{BED}{1+\frac{2}{\alpha/\beta}}$ when the α/β-ratio is kept constant in all volumes, its distribution looks similar to the BED distribution. This concentration to the center and relief of outer areas implies that on a biological effective level, the stress put on organs surrounding the tumor is less than an absolute RBE dose comparison implies. Especially in ion therapy, the steep dose gradients at the edges of the target volume are enhanced when looking at the biological effect of the treatment. Having the biological parameters calculated voxelwise is especially helpful when inspecting the dose distribution in small structures because even a small area of sensitive structures like nerves being exposed to high effective dose levels can lead to major health restrictions and can therefore be an important factor in treatment planning.

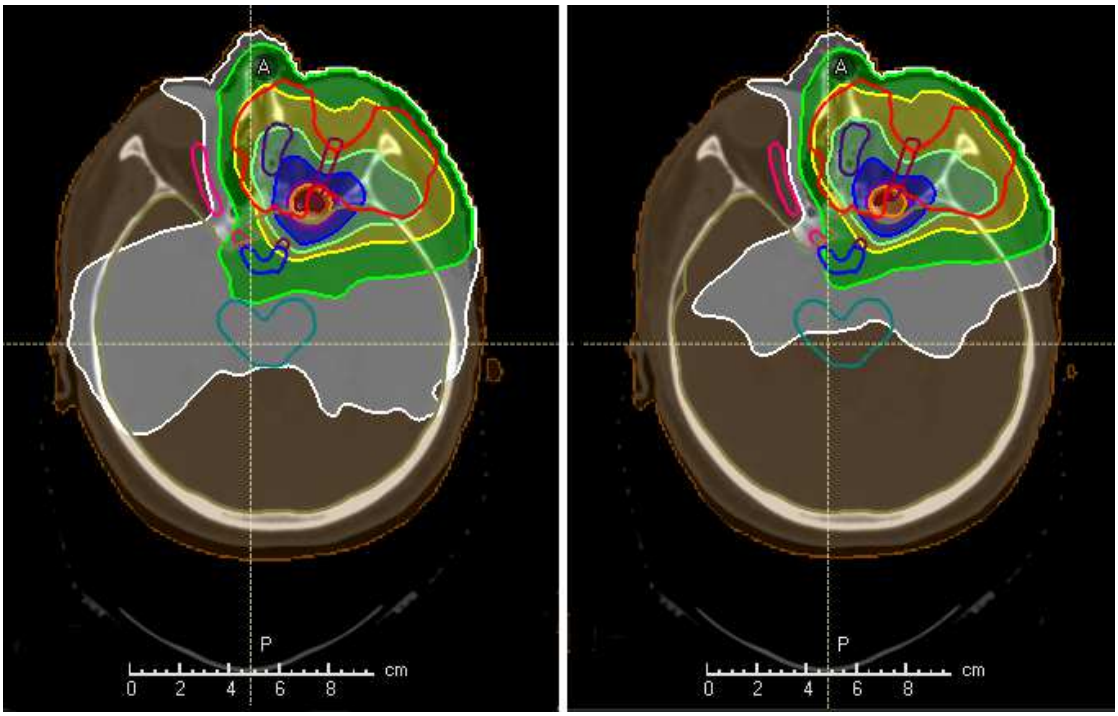

Figure 5.1.: Patient 12's RBE Dose Distribution (left) and BED Distribution (right). Colormap Scaled to Percentage of Maximum Dose with Red Indicating 95-100%, orange 90-95% Purple 85-90%, Blue 75-85%, Yellow 50-75%, Green 25-50%, White 10-25% and Brown 1-10% of the maximum dose

5.2. Patient Evaluation Results

Due to the dose values being in the same range, only RBE dose and EQD_2 DVH-parameters can be directly compared. In datasheet F, parameters for the organs of interest considering the total applied dose of all treatments are listed. As expected, most EQD_2 parameters are lower than their corresponding RBE dose values. Sometimes there is a difference of up to 18 Gy, which is a substantial variation when considering treatment planning. These lower values are a result of the above-mentioned contracted form of the dose distributions, as in most cases, the inspected structures are not in the epicenter of the treatment.

Nevertheless, some EQD_2 values turn out to be higher than their corresponding RBE values. This appears in volumes which lie in or close to the planning target center where a lot of the voxel's fraction dose exceeds 2 Gy, which indicates a severe strain on the structure, with the EQD_2's DVH-parameter being up to 10 Gy higher than the RBE dose value.

Patient number 15 was treated twice using a gammaknife. Due to the dose being applied in just one fraction in this method, calculating the BED or EQD_2 leads to incredibly large values, as the underlying model only corresponds to fractionated therapy. This is why the patient was left out when maxima and minima were calculated of the RBE-EQD_2 differences.

From a biologically effective point of view, the data indicates that there is less strain on organs at risk than anticipated so far. These predictions lead to the mandatory restrictions in treatment planning. Accumulating more data on similar patients could lead to statistically significant indications showing that dose restrictions can be adjusted so the tumor control probability rises with still safe levels of dose achieved for organs at risk (see 2.7). This data accumulation should be promoted at the moment because the number of patients who have similar medical histories as the ones occurring in this thesis is rising, due to modern radiation therapy treatments sparing healthy tissue enough for recurrent tumors to be treated with radiation therapy as well.

6. Summary and Conclusion

The first aim of this thesis was to develop a script compatible with the RayStation scripting interface which evaluates biological effective dose values from treatment dose distributions voxel by voxel. Due to the equivalent dose in 2 Gy fractions being more intuitive for a lot of people working in the field of radiation therapy, an according script was developed as well. The second goal was to use these scripts on the treatment data of 18 patients with tumors in the head and neck area, who were treated at MedAustron with ion therapy after growing a recurrent tumor, in order to evaluate BED and EQD_2 distributions. Relative biological effective dose, biologically equivalent dose and equivalent dose in 2 Gy fractions distributions of the initial treatment, the re-irradiation and a summed up distribution of both were created and dose volume histogram parameters for specific organs were read out. These parameters were saved in a table in order to start a database describing the radiation toxicity in high risk organs in patients who received multiple radiation therapy treatments. For DVH-parameter readout an additional script was developed. For future use, the BED evaluating script was validated and stored in MedAustron's script database.

The BED and EQD_2 evaluating scripts work as intended and provide the desired results. When using them, their working mechanism and results should be thoroughly understood, especially the regulations for evaluating BED and EQD_2 distributions. The limits and shortcomings of these parameters should be kept in mind when using them for either research or clinical purposes.

These scripts can provide valuable help in data processing for future research on the toxicity of radiation therapy. The evaluation of the 18 patients already show promising results, indicating the possibility of organs at risk being able to tolerate higher doses during treatment than the current restrictions allow. For more precise results, a larger number of patients should be evaluated and added to the database. Extending the script with a feature to assign different α/β-values to individual structures, or using the included recovery factor could lead to more precise data. Neither of these factors were applied in this thesis due to it focusing on providing a very constant and efficient workflow. Additionally, both the assignment of α/β-values and the actual recovery between treatments still very much depend on an expert's estimate rather than a fixed dependence as there are no precise and validated mathematical models yet and would have to be assigned for each patient individually.

Appendix A.

List of Abbrevations

BED	Biologically Effective Dose
DICOM	Digital Image and COmmunications in Medicine
DNA	DesoxyriboNucleic Acid
EQD_2	Equivalent Dose in 2 Gy fractions
GUI	Graphical User Interface
Gy	Gray
HU	Hounsfield Units
MICE	Medical Interactive Creative Environment
RBE	Relative Effective Dose

Appendix B.

BED Script

```
from connect import *

import platform
import math
import wpf

from System.Windows import *
from System.Windows.Controls import *

recovery = 0
alpha_beta = 2
number_fractions_input = 1

class MyWindow(Window) :
    def __init__(self):
        wpf.LoadComponent(self, 'X:\Documents\Masterthesis\Scripts\
            BEDinput.xaml')

        self.dose = plan.TreatmentCourse.TotalDose

    def ComputeClicked(self, sender, event):

       global alpha_beta
       global recovery

       alpha_beta = float(self.alphabeta.Text)
       recovery = float(self.recoveryfactor.Text)


       self.DialogResult = True


    def CloseClicked(self, sender, event):
       exit()
       self.DialogResult = True
```

```
class MyWindowrf(Window) :
    def __init__(self):
        wpf.LoadComponent(self, 'X:\Documents\Masterthesis\Scripts\
            BEDinputrf.xaml')

        self.dose = plan.TreatmentCourse.TotalDose

    def ComputeClickedrf(self, sender, event):

       global number_fractions_input

       number_fractions_input = float(self.numberfractions.Text)


       self.DialogResult = True


    def CloseClickedrf(self, sender, event):
       exit()
       self.DialogResult = True

patient = get_current('Patient')
case = get_current('Case')
plan = get_current('Plan')
machine_db = get_current('MachineDB')

examination = plan.BeamSets[0].GetPlanningExamination()


window = MyWindow()
window.ShowDialog()



if recovery > 0:

    case.AddNewPlan(PlanName  = 'Calculated BED from plan ' + str(plan.
        Name) + ' (' + str(recovery) + '% recovery)', Comment = 'Voxel by
        Voxel calculated BED, will be shown as Uniform Scanning
        Protontherpy Plan, if Modality and Treatment Technique are unknown
        ', ExaminationName = examination.Name)

    bed_plan = case.TreatmentPlans['Calculated BED from plan ' + str(plan
        .Name) + ' (' + str(recovery) + '% recovery)']

else:

    case.AddNewPlan(PlanName  = 'Calculated BED from plan ' + str(plan.
```

```
        Name), Comment = 'Voxel by Voxel calculated BED, will be shown as
        Uniform Scanning Protontherpy Plan, if Modality and Treatment
        Technique are unknown', ExaminationName = examination.Name)

    bed_plan = case.TreatmentPlans['Calculated BED from plan ' + str(plan
        .Name)]


def compute_bed(fraction_dose, number_fractions, alpha_beta):
    if number_fractions < 2:

        windowrf = MyWindowrf()
        windowrf.ShowDialog()

        calc = [(1-recovery*0.01)*(i * (100 + i/(number_fractions_input *
            alpha_beta)))/(100) for i in fraction_dose]
        return calc

    else:
        calc = [(1-recovery*0.01)*(i * (100 + i / alpha_beta))/(100) for
            i in fraction_dose]
        return calc

dose_grid = plan.GetDoseGrid()
bed_plan.UpdateDoseGrid(Corner = { 'x': dose_grid.Corner.x , 'y':
    dose_grid.Corner.y , 'z': dose_grid.Corner.z}, NumberOfVoxels = { 'x':
     dose_grid.NrVoxels.x , 'y': dose_grid.NrVoxels.y , 'z': dose_grid.
    NrVoxels.z}, VoxelSize = { 'x': dose_grid.VoxelSize.x , 'y': dose_grid
    .VoxelSize.y , 'z': dose_grid.VoxelSize.z})

number_beamsets = plan.BeamSets.Count


for i in range(number_beamsets):


    beam_set = plan.BeamSets[i]

    number_fractions = beam_set.FractionationPattern.NumberOfFractions

    if beam_set.Modality in ['UnknownIon', 'Unknown']:

        bed_plan.AddNewBeamSet(Name = str(beam_set.DicomPlanLabel),
            ExaminationName = examination.Name, NumberOfFractions =
            number_fractions, Modality = 'Protons', TreatmentTechnique = '
            UniformScanning',PatientPosition = beam_set.PatientPosition,
            MachineName = 'IR2')

    elif str(machine_db.GetTreatmentMachine(machineName = beam_set.
        MachineReference.MachineName, lockMode=None)) in ['None']:
```

```
if beam_set.Modality in ['Photons']:

    bed_plan.AddNewBeamSet(Name = str(beam_set.DicomPlanLabel),
        Comment= 'Treatment machine was changed to available
        machine', ExaminationName = examination.Name,
        NumberOfFractions = number_fractions, Modality = beam_set.
        Modality, TreatmentTechnique = beam_set.
        GetTreatmentTechniqueType(),PatientPosition = beam_set.
        PatientPosition, MachineName = 'RSL_SynergyAgil')

elif beam_set.Modality in ['Protons']:

    bed_plan.AddNewBeamSet(Name = str(beam_set.DicomPlanLabel),
        Comment= 'Treatment machine was changed to available
        machine', ExaminationName = examination.Name,
        NumberOfFractions = number_fractions, Modality = beam_set.
        Modality, TreatmentTechnique = beam_set.
        GetTreatmentTechniqueType(),PatientPosition = beam_set.
        PatientPosition, MachineName = 'IR2')

elif beam_set.Modality in ['Carbons']:

    bed_plan.AddNewBeamSet(Name = str(beam_set.DicomPlanLabel),
        Comment= 'Treatment machine was changed to available
        machine', ExaminationName = examination.Name,
        NumberOfFractions = number_fractions, Modality = beam_set.
        Modality, TreatmentTechnique = beam_set.
        GetTreatmentTechniqueType(),PatientPosition = beam_set.
        PatientPosition, MachineName = 'RSL_Carbon_2')

elif beam_set.Modality in ['Neutrons']:

    bed_plan.AddNewBeamSet(Name =  str(beam_set.DicomPlanLabel),
        Comment= 'Treatment modality and machine were changed to
        available ones', ExaminationName = examination.Name,
        NumberOfFractions = number_fractions, Modality = 'Protons'
        , TreatmentTechnique = 'UniformScanning',PatientPosition =
         beam_set.PatientPosition, MachineName = 'IR2')

else:

    bed_plan.AddNewBeamSet(Name = str(beam_set.DicomPlanLabel),
        Comment= 'Treatment modality and machine were changed to
        available ones', ExaminationName = examination.Name,
        NumberOfFractions = number_fractions, Modality = 'Protons'
        , TreatmentTechnique = 'UniformScanning',PatientPosition =
         beam_set.PatientPosition, MachineName = 'IR2')
```

```
    else:

        bed_plan.AddNewBeamSet(Name = str(beam_set.DicomPlanLabel),
            ExaminationName = examination.Name, NumberOfFractions =
            number_fractions, Modality = beam_set.Modality,
            TreatmentTechnique = beam_set.GetTreatmentTechniqueType(),
            PatientPosition = beam_set.PatientPosition, MachineName =
            beam_set.MachineReference.MachineName)


    beam_set_new = bed_plan.BeamSets[i]

    fraction_dose0 = list(beam_set.FractionDose.DoseValues.DoseData)
    fraction_dose = [float(j) for j in fraction_dose0]

    bed = compute_bed(fraction_dose, number_fractions, alpha_beta)

    beam_set_new.FractionDose.SetDoseValues(Array=bed, CalculationInfo='
        Voxel by Voxel calculated BED')


patient.Save()
```

Appendix C.

EQD_2 Script

```
from connect import *

import platform
import math
import wpf

from System.Windows import *
from System.Windows.Controls import *

recovery = 0
alpha_beta = 2
number_fractions_input = 1

class MyWindow(Window) :
    def __init__(self):
        wpf.LoadComponent(self, 'X:\Documents\Masterthesis\Scripts\
            EQD2input.xaml')

        self.dose = plan.TreatmentCourse.TotalDose

    def ComputeClicked(self, sender, event):

       global alpha_beta
       global recovery

       alpha_beta = float(self.alphabeta.Text)
       recovery = float(self.recoveryfactor.Text)


       self.DialogResult = True


    def CloseClicked(self, sender, event):
       exit()
       self.DialogResult = True
```

```
class MyWindowrf(Window) :
    def __init__(self):
        wpf.LoadComponent(self, 'X:\Documents\Masterthesis\Scripts\
            EQD2inputrf.xaml')

        self.dose = plan.TreatmentCourse.TotalDose

    def ComputeClickedrf(self, sender, event):

       global number_fractions_input

       number_fractions_input = float(self.numberfractions.Text)


       self.DialogResult = True


    def CloseClickedrf(self, sender, event):
       exit()
       self.DialogResult = True

patient = get_current('Patient')
case = get_current('Case')
plan = get_current('Plan')
machine_db = get_current('MachineDB')

window = MyWindow()
window.ShowDialog()

examination = plan.BeamSets[0].GetPlanningExamination()

if recovery > 0:

    case.AddNewPlan(PlanName  = 'Calculated EQD2 from plan ' + str(plan.
        Name) + ' (' + str(recovery) + '% recovery)', Comment = 'Voxel by
        Voxel calculated EQD2, will be shown as Uniform Scanning
        Protontherpy Plan, if Modality and Treatment Technique are unknown
        ', ExaminationName = examination.Name)

    bed_plan = case.TreatmentPlans['Calculated EQD2 from plan ' + str(
        plan.Name) + ' (' + str(recovery) + '% recovery)']

else:

    case.AddNewPlan(PlanName  = 'Calculated EQD2 from plan ' + str(plan.
        Name), Comment = 'Voxel by Voxel calculated EQD2, will be shown as
         Uniform Scanning Protontherpy Plan, if Modality and Treatment
        Technique are unknown', ExaminationName = examination.Name)
```

```
    eqd2_plan = case.TreatmentPlans['Calculated EQD2 from plan ' + str(
        plan.Name)]


def compute_eqd2(fraction_dose, number_fractions, alpha_beta):
    if number_fractions < 2:

        windowrf = MyWindowrf()
        windowrf.ShowDialog()

        calc = [(1-recovery*0.01)*(1/(1+2/alpha_beta))*(i * (100 + i/(
            number_fractions_input * alpha_beta)))/(100) for i in
            fraction_dose]
        return calc

    else:
        calc = [(1-recovery*0.01)*(1/(1+2/alpha_beta))*(i * (100 + i /
            alpha_beta))/(100) for i in fraction_dose]
        return calc

number_beamsets = plan.BeamSets.Count
dose_grid = plan.GetDoseGrid()

eqd2_plan.UpdateDoseGrid(Corner = { 'x': dose_grid.Corner.x , 'y':
    dose_grid.Corner.y , 'z': dose_grid.Corner.z}, NumberOfVoxels = { 'x':
     dose_grid.NrVoxels.x , 'y': dose_grid.NrVoxels.y , 'z': dose_grid.
    NrVoxels.z}, VoxelSize = { 'x': dose_grid.VoxelSize.x , 'y': dose_grid
    .VoxelSize.y , 'z': dose_grid.VoxelSize.z})


for i in range(number_beamsets):


    beam_set = plan.BeamSets[i]

    number_fractions = beam_set.FractionationPattern.NumberOfFractions

    if beam_set.Modality in ['UnknownIon', 'Unknown']:

        eqd2_plan.AddNewBeamSet(Name = str(beam_set.DicomPlanLabel),
            ExaminationName = examination.Name, NumberOfFractions =
            number_fractions, Modality = 'Protons', TreatmentTechnique = '
            UniformScanning',PatientPosition = beam_set.PatientPosition,
            MachineName = 'IR2')

    elif str(machine_db.GetTreatmentMachine(machineName = beam_set.
        MachineReference.MachineName, lockMode=None)) in ['None']:

        if beam_set.Modality in ['Photons']:
```

```
            eqd2_plan.AddNewBeamSet(Name = str(beam_set.DicomPlanLabel),
                Comment= 'Treatment machine was changed to available
                machine', ExaminationName = examination.Name,
                NumberOfFractions = number_fractions, Modality = beam_set.
                Modality, TreatmentTechnique = beam_set.
                GetTreatmentTechniqueType(),PatientPosition = beam_set.
                PatientPosition, MachineName = 'RSL_SynergyAgil')

        elif beam_set.Modality in ['Protons']:

            eqd2_plan.AddNewBeamSet(Name = str(beam_set.DicomPlanLabel),
                Comment= 'Treatment machine was changed to available
                machine', ExaminationName = examination.Name,
                NumberOfFractions = number_fractions, Modality = beam_set.
                Modality, TreatmentTechnique = beam_set.
                GetTreatmentTechniqueType(),PatientPosition = beam_set.
                PatientPosition, MachineName = 'IR2')

        elif beam_set.Modality in ['Carbons']:

            eqd2_plan.AddNewBeamSet(Name = str(beam_set.DicomPlanLabel),
                Comment= 'Treatment machine was changed to available
                machine', ExaminationName = examination.Name,
                NumberOfFractions = number_fractions, Modality = beam_set.
                Modality, TreatmentTechnique = beam_set.
                GetTreatmentTechniqueType(),PatientPosition = beam_set.
                PatientPosition, MachineName = 'RSL_Carbon_2')

        elif beam_set.Modality in ['Neutrons']:

            eqd2_plan.AddNewBeamSet(Name =  str(beam_set.DicomPlanLabel),
                 Comment= 'Treatment modality and machine were changed to
                available ones', ExaminationName = examination.Name,
                NumberOfFractions = number_fractions, Modality = 'Protons'
                , TreatmentTechnique = 'UniformScanning',PatientPosition =
                 beam_set.PatientPosition, MachineName = 'IR2')

        else:

            eqd2_plan.AddNewBeamSet(Name = str(beam_set.DicomPlanLabel),
                Comment= 'Treatment modality and machine were changed to
                available ones', ExaminationName = examination.Name,
                NumberOfFractions = number_fractions, Modality = 'Protons'
                , TreatmentTechnique = 'UniformScanning',PatientPosition =
                 beam_set.PatientPosition, MachineName = 'IR2')


    else:
```

```
            eqd2_plan.AddNewBeamSet(Name = str(beam_set.DicomPlanLabel),
                ExaminationName = examination.Name, NumberOfFractions =
                number_fractions, Modality = beam_set.Modality,
                TreatmentTechnique = beam_set.GetTreatmentTechniqueType(),
                PatientPosition = beam_set.PatientPosition, MachineName =
                beam_set.MachineReference.MachineName)


        beam_set_new = bed_plan.BeamSets[i]

        fraction_dose0 = list(beam_set.FractionDose.DoseValues.DoseData)
        fraction_dose = [float(j) for j in fraction_dose0]

        eqd2 = compute_eqd2(fraction_dose, number_fractions, alpha_beta)

        beam_set_new.FractionDose.SetDoseValues(Array=eqd2, CalculationInfo='
            Voxel by Voxel calculated EQD2')


patient.Save()
```

Appendix D.

DVH Parameter Evaluating Script

```
import re, sys
import numpy as np

import xlsxwriter

from connect import *


def create_array(m, n, type):
    return np.empty(shape=(m,n),  dtype=type)

def write_cells(start_row, start_column, write_data, worksheet_name):
    print (write_data)
    for col, data in enumerate(write_data):
        worksheet.write_column(start_row, start_column+col, data)

fraceval = 0
exam = 0

evdosenumbero = 18
evdosenumbern = 16
evdosenumbers = 19

patient = get_current('Patient')
case = get_current('Case')
plan = get_current('Plan')
beamset = get_current('BeamSet')

plan_dose = plan.TreatmentCourse.TotalDose

structure_set = plan.GetStructureSet()

patient_name_caretencoding = patient.Name
patient_name = patient_name_caretencoding.replace("^"," ")
```

```
dose_nameo = case.TreatmentDelivery.FractionEvaluations[fraceval].
    DoseOnExaminations[exam].DoseEvaluations[evdosenumbero].Name
dose_namen = case.TreatmentDelivery.FractionEvaluations[fraceval].
    DoseOnExaminations[exam].DoseEvaluations[evdosenumbern].Name
dose_names = case.TreatmentDelivery.FractionEvaluations[fraceval].
    DoseOnExaminations[exam].DoseEvaluations[evdosenumbers].Name

eval_doseo = case.TreatmentDelivery.FractionEvaluations[0].
    DoseOnExaminations[exam].DoseEvaluations[evdosenumbero]
eval_dosen = case.TreatmentDelivery.FractionEvaluations[0].
    DoseOnExaminations[exam].DoseEvaluations[evdosenumbern]
eval_doses = case.TreatmentDelivery.FractionEvaluations[0].
    DoseOnExaminations[exam].DoseEvaluations[evdosenumbers]


oar_names = ['brainstem', 'spinalcord', 'chiasm', 'opticusLEFT', '
    opticusRIGHT', 'brain']


# Small utility to convert camelcase
def convert(name):
    s1 = re.sub('(.)([A-Z][a-z]+)', r'\1 \2', name)
    return re.sub('([a-z0-9])([A-Z])', r'\1 \2', s1).lower()

workbook = xlsxwriter.Workbook('X:\Documents\Masterthesis\DVH_parameters.
    xlsx')
worksheet = workbook.add_worksheet()

# Add patient data
patient_data = create_array(2,2, object)
patient_data[0,0] = 'Patient Name'
patient_data[0,1] = patient_name
patient_data[1,0] = 'Doses'
patient_data[1,1] = dose_nameo + dose_namen + dose_names

write_cells(0,0,patient_data, workbook)

header_row = create_array(1,8, object)
header_row[0,0] = str(dose_nameo)
header_row[0,1] = 'Volume [cm^3]'
header_row[0,2] = 'D2cc [Gy(RBE)]'
header_row[0,3] = 'D0.7cc [Gy(RBE)]'
header_row[0,4] = 'D0.1cc [Gy(RBE)]'
header_row[0,5] = 'D2% [Gy(RBE)]'
header_row[0,6] = 'D1cc [Gy(RBE)]'
header_row[0,7] = 'D5cc [Gy(RBE)]'


write_cells(4,0,header_row, workbook)
```

```
data_array = create_array(len(oar_names),8, object)

for idx, roi in enumerate(oar_names): # Edit this if other dose
    statistics are desired
    volume = plan_dose.GetDoseGridRoi(RoiName=roi).RoiVolumeDistribution.
        TotalVolume

    if 2/float(volume) > 1 or 2/float(volume) > 1 or 2/float(volume) > 1:
        d2cc, d07cc, d01cc, d2p, d1cc, d5cc = eval_doseo.
            GetDoseAtRelativeVolumes(RoiName=roi, RelativeVolumes=[0, 0,
            0, .02, 0, 0])

    else:
        d2cc, d07cc, d01cc, d2p, d1cc, d5cc = eval_doseo.
            GetDoseAtRelativeVolumes(RoiName=roi, RelativeVolumes=[2/float
            (volume), 0.7/float(volume), 0.1/float(volume), .02, 1/float(
            volume), 5/float(volume)])

    average = eval_doseo.GetDoseStatistic(RoiName=roi, DoseType='Average'
        )
    data_array[idx,0] = roi
    data_array[idx,1] = ("%.2f" % volume)
    data_array[idx,2] = ("%.2f" % (float(d2cc)/100))
    data_array[idx,3] = ("%.2f" % (float(d07cc)/100))
    data_array[idx,4] = ("%.2f" % (float(d01cc)/100))
    data_array[idx,5] = ("%.2f" % (float(d2p)/100))
    data_array[idx,6] = ("%.2f" % (float(d1cc)/100))
    data_array[idx,7] = ("%.2f" % (float(d5cc)/100))



write_cells(4,1,data_array, workbook)



header2_row = create_array(1,8, object)
header2_row[0,0] = str(dose_namen)
header2_row[0,1] = 'Volume [cm^3]'
header2_row[0,2] = 'D2cc [Gy(RBE)]'
header2_row[0,3] = 'D0.7cc [Gy(RBE)]'
header2_row[0,4] = 'D0.1cc [Gy(RBE)]'
header2_row[0,5] = 'D2% [Gy(RBE)]'
header2_row[0,6] = 'D1cc [Gy(RBE)]'
header2_row[0,7] = 'D5cc [Gy(RBE)]'


write_cells(14,0,header2_row, workbook)
```

```
data_array2 = create_array(len(oar_names),8, object)

for idx, roi in enumerate(oar_names): # Edit this if other dose
    statistics are desired
    volume = plan_dose.GetDoseGridRoi(RoiName=roi).RoiVolumeDistribution.
        TotalVolume

    if 2/float(volume) > 1 or 2/float(volume) > 1 or 2/float(volume) > 1:
        d2cc, d07cc, d01cc, d2p, d1cc, d5cc = eval_dosen.
            GetDoseAtRelativeVolumes(RoiName=roi, RelativeVolumes=[0, 0,
            0, .02, 0, 0])

    else:
        d2cc, d07cc, d01cc, d2p, d1cc, d5cc = eval_dosen.
            GetDoseAtRelativeVolumes(RoiName=roi, RelativeVolumes=[2/float
            (volume), 0.7/float(volume), 0.1/float(volume), .02, 1/float(
            volume), 5/float(volume)])

    average = eval_dosen.GetDoseStatistic(RoiName=roi, DoseType='Average'
        )
    data_array2[idx,0] = roi
    data_array2[idx,1] = ("%.2f" % volume)
    data_array2[idx,2] = ("%.2f" % (float(d2cc)/100))
    data_array2[idx,3] = ("%.2f" % (float(d07cc)/100))
    data_array2[idx,4] = ("%.2f" % (float(d01cc)/100))
    data_array2[idx,5] = ("%.2f" % (float(d2p)/100))
    data_array2[idx,6] = ("%.2f" % (float(d1cc)/100))
    data_array2[idx,7] = ("%.2f" % (float(d5cc)/100))

write_cells(14,1,data_array2, workbook)

header3_row = create_array(1,8, object)
header3_row[0,0] = str(dose_names)
header3_row[0,1] = 'Volume [cm^3]'
header3_row[0,2] = 'D2cc [Gy(RBE)]'
header3_row[0,3] = 'D0.7cc [Gy(RBE)]'
header3_row[0,4] = 'D0.1cc [Gy(RBE)]'
header3_row[0,5] = 'D2% [Gy(RBE)]'
header3_row[0,6] = 'D1cc [Gy(RBE)]'
header3_row[0,7] = 'D5cc [Gy(RBE)]'

write_cells(24,0,header3_row, workbook)


data_array3 = create_array(len(oar_names),8, object)

for idx, roi in enumerate(oar_names): # Edit this if other dose
    statistics are desired
    volume = plan_dose.GetDoseGridRoi(RoiName=roi).RoiVolumeDistribution.
        TotalVolume
```

```
    if 2/float(volume) > 1 or 2/float(volume) > 1 or 2/float(volume) > 1:
        d2cc, d07cc, d01cc, d2p, d1cc, d5cc = eval_doses.
            GetDoseAtRelativeVolumes(RoiName=roi, RelativeVolumes=[0, 0,
            0, .02, 0, 0])

    else:
        d2cc, d07cc, d01cc, d2p, d1cc, d5cc = eval_doses.
            GetDoseAtRelativeVolumes(RoiName=roi, RelativeVolumes=[2/float
            (volume), 0.7/float(volume), 0.1/float(volume), .02, 1/float(
            volume), 5/float(volume)])

    average = eval_doses.GetDoseStatistic(RoiName=roi, DoseType='Average'
        )
    data_array3[idx,0] = roi
    data_array3[idx,1] = ("%.2f" % volume)
    data_array3[idx,2] = ("%.2f" % (float(d2cc)/100))
    data_array3[idx,3] = ("%.2f" % (float(d07cc)/100))
    data_array3[idx,4] = ("%.2f" % (float(d01cc)/100))
    data_array3[idx,5] = ("%.2f" % (float(d2p)/100))
    data_array3[idx,6] = ("%.2f" % (float(d1cc)/100))
    data_array3[idx,7] = ("%.2f" % (float(d5cc)/100))


write_cells(24,1,data_array3, workbook)

filename = r".\DoseStatistics.xlsx"

workbook.close()
```

Appendix E.

Complete Patient Database

Patient Number	Patient Name	First Treatment	Re-irradiation Treatment	Recovery Time [m]	Histology	BED Brainstem D2.0cc old	BED Brainstem D0.7cc old	BED Brainstem D0.1cc old	BED Brainstem D2.0cc new	BED Brainstem D0.7cc new	BED Brainstem D0.1cc new	BED Brainstem D2.0cc sum	BED Brainstem D0.7cc sum	BED Brainstem D0.1cc sum
7		70Gy/35fr	72Gy/36fr/3D+6	55	PLECA	56,23	62,87	70,36	17,97	46,00	90,81	62,34	76,73	122,88
8		70Gy/35fr	70Gy/35fr/4+13+13+5	27	PLECA G3	37,38	43,55	50,29	6,04	14,30	28,32	43,50	50,96	67,35
10		69.6Gy/58fr	70Gy/35fr/15+15+3+2	27	PLECA G3	42,84	53,51	79,41	0,55	1,10	2,33	43,13	54,06	74,12
11		60Gy/30fr(25+5)	70Gy/35fr/15+15+3+2	15	PLECA G3	23,87	36,56	51,08	77,25	95,08	107,31	81,53	98,68	111,44
12		54Gy/30fr/30	60Gy/30fr/15+15	80	Beninges Meningeom	15,66	25,72	55,22	3,13	8,30	23,37	18,82	33,50	76,91
14		66Gy/33fr(25+5+3)	70Gy/35fr/15+15+5	42	PLECA G2	40,03	43,89	47,80	0,21	0,36	0,58	40,15	43,83	47,94
15		2xGammaknife 14Gy at edge	36Gy/20fr & 22Gy/11fr/ 10+10 & 9+1+1	57	Beninges Meningeom	8,66	10,99	14,77	237,30	454,12	715,01	245,55	462,94	727,70
18		60Gy/30fr(25+5)	70Gy/35fr/15+15+5	16	PLECA G3	46,65	50,05	52,37	16,30	30,49	49,82	54,51	70,87	94,99
19		59.4Gy/33fr(28+5)	66Gy/33fr/7+14+4+5+3	40	Synovialsarkom	55,28	62,36	67,72	28,93	32,68	41,64	76,36	87,42	102,95
20		50Gy/25fr + 70Gy/35fr	70Gy/35fr/8+8+5+4+10	28	PLECA G2	1,83	8,21	12,01	58,66	77,25	94,76	74,63	94,53	117,14
21		60Gy/30fr	69Gy/30fr/15+15	12	PLECA G3	0,57	0,74	0,94	12,49	21,45	34,49	13,25	22,10	35,50
22		50.4Gy/28fr(23+5)	54Gy/18fr/	13	Undifferenziertes Sarkom	0,45	1,76	7,67	0,00	0,01	0,07	0,47	1,86	7,90
26		70Gy/35fr	67.5Gy/30fr/2+1+13+14	29	Adeno G2	78,36	86,85	99,32	0,27	0,57	1,45	78,64	87,23	100,25
32		60Gy/30fr + 45Gy/25fr	50Gy/25fr/12+13	27	PLECA	63,49	75,29	85,46	1,86	4,41	10,38	56,17	78,16	90,12
33		60Gy/30fr(25+5)	62Gy/22fr/11+11	14	PLECA G3	39,70	45,78	50,70	7,57	17,43	37,44	41,63	47,40	54,90
34		60Gy/30fr?	60Gy/30fr/7+7+8+8	91	GBM	91,96	94,53	97,30	4,46	9,34	17,32	94,82	101,55	111,31
35		56Gy/28fr	60Gy/30fr/15+15	32	Astro III	112,20	112,56	112,91	31,19	44,33	56,74	114,42	118,80	125,23
39		66Gy/33fr	66Gy/30fr/6+5+5+3+11	29	Adeno G2	64,78	73,56	80,12	0,00	0,00	0,04	63,63	71,45	78,61

Patient Number	BED Brain D5cc old	BED Brain D2cc old	BED Brain D1cc old	BED Brain D5cc new	BED Brain D2cc new	BED Brain D1cc new	BED Brain D5cc sum	BED Brain D2cc sum	BED Brain D1cc sum	BED Chiasm D2% old	BED Chiasm D2% new	BED Chiasm D2% sum	BED OpticL D2% old	BED OpticL D2% new	BED OpticL D2% sum	BED OpticR D2% old	BED OpticR D2% new	BED OpticR D2% sum
7	73,43	81,04	86,11	120,09	125,09	133,81	157,37	175,19	187,57	26,13	91,57	100,28	29,41	28,24	49,39	53,06	112,79	154,26
8	79,36	89,72	97,56	126,73	136,22	139,95	148,71	175,48	189,40	5,69	74,60	83,62	6,10	81,57	97,57	6,75	33,10	41,89
10	112,06	113,63	114,53	123,91	132,90	135,56	200,80	227,46	237,92	107,77	9,26	114,60	116,69	137,30	248,17	66,32	13,66	74,02
11	46,12	55,89	62,58	139,90	140,82	141,58	142,52	144,51	147,18	1,85	101,04	98,99	2,21	96,55	100,15	2,26	142,70	144,33
12	73,48	88,28	93,42	88,64	104,93	113,41	155,85	184,54	199,77	79,85	12,88	92,90	98,81	26,00	126,42	23,66	1,40	24,36
14	102,85	117,97	127,23	98,52	112,23	122,35	186,00	219,32	235,31	94,61	4,95	93,06	59,18	10,15	67,32	133,54	34,27	154,70
15	94,80	127,98	148,26	1104,38	1120,13	1128,10	1195,51	1284,80	1374,14	41,37	554,23	601,31	8,12	152,20	120,64	38,71	1130,13	1153,17
18	82,36	100,95	110,60	136,91	140,43	141,63	208,31	232,29	244,48	21,82	91,53	107,63	7,31	43,70	54,26	10,30	125,99	132,28
19	65,59	85,00	91,98	125,62	130,83	131,87	168,63	209,63	225,35	3,02	23,81	27,47	5,64	59,02	64,97	3,73	3,20	5,75
20	8,03	11,21	13,59	129,42	136,79	139,87	150,06	178,86	195,44	0,51	85,36	92,69	0,87	34,80	39,62	0,84	94,15	96,67
21	0,97	1,45	1,79	57,44	79,72	90,89	58,69	79,73	91,17	0,00	0,53	0,56	0,21	0,67	0,83	0,00	1,75	2,31
22	94,54	95,83	96,26	112,88	125,80	131,33	205,98	221,08	226,74	0,00	0,00	0,00	0,00	0,01	0,01	0,00	0,10	0,09
26	144,94	147,02	148,51	146,54	148,03	149,11	286,35	289,60	291,02	142,86	60,19	200,21	147,13	15,67	155,13	149,42	147,85	292,20
32	129,03	135,31	138,72	98,90	101,17	102,06	221,04	240,77	252,78	49,33	34,11	83,06	33,04	33,28	66,61	134,73	102,39	326,41
33	77,52	86,96	91,46	149,98	163,01	166,82	180,88	198,66	211,94	20,70	112,49	138,08	14,77	54,27	66,46	0,00	0,00	0,00
34	125,98	126,51	127,10	123,15	124,69	126,04	245,67	246,73	247,39	101,07	17,99	117,30	101,15	17,45	112,50	72,87	18,04	82,79
35	125,05	125,41	125,56	124,19	124,95	125,47	217,36	223,45	227,01	113,56	0,03	113,36	111,55	0,02	117,27	90,67	0,01	107,38
39	119,20	127,46	131,86	23,98	39,50	49,57	137,36	162,32	176,38	94,26	2,20	91,66	62,13	10,13	61,67	97,59	43,26	99,05

Patient Number	RBE Brainstem D2.0cc old	RBE Brainstem D0.7cc old	RBE Brainstem D0.1cc old	RBE Brainstem D2.0cc new	RBE Brainstem D0.7cc new	RBE Brainstem D0.1cc new	RBE Brainstem D2.0cc sum	RBE Brainstem D0.7cc sum	RBE Brainstem D0.1cc sum	RBE Brain D5cc old	RBE Brain D2cc old	RBE Brain D1cc old	RBE Brain D5cc new	RBE Brain D2cc new	RBE Brain D1cc new	RBE Brain D5cc sum	RBE Brain D2cc sum	RBE Brain D1cc sum
7	35,35	38,12	41,01	12,07	28,09	51,45	38,85	51,10	74,48	43,89	47,28	49,80	60,84	65,81	68,65	89,48	98,21	103,40
8	26,94	30,15	33,63	5,51	11,82	20,97	31,59	37,36	48,61	47,27	51,55	54,67	65,21	68,68	69,95	84,35	97,69	103,89
10	31,90	39,56	51,59	0,55	1,08	2,24	33,38	40,25	52,00	70,07	70,93	73,13	64,40	67,56	68,50	119,06	130,52	134,72
11	17,63	24,74	32,90	46,17	53,73	58,41	50,52	57,29	62,54	29,46	34,02	36,78	69,96	70,26	70,52	72,99	74,73	81,47
12	12,87	19,27	35,00	2,89	7,35	17,75	15,75	26,26	51,37	42,99	48,91	50,75	48,85	54,90	57,83	88,82	100,17	105,88
14	27,55	29,47	31,40	0,21	0,36	0,58	27,70	29,47	31,52	55,19	60,75	64,05	54,95	60,23	63,93	103,67	116,66	122,79
15	3,28	3,79	4,53	19,56	32,77	45,19	23,21	37,16	49,90	12,81	15,03	16,25	57,76	58,53	58,95	73,96	82,35	88,26
18	30,75	32,38	33,52	13,27	22,40	33,00	39,12	49,78	62,91	46,41	53,40	56,82	68,94	70,13	70,54	110,93	120,05	124,62
19	35,52	38,89	41,34	20,24	23,84	28,91	51,11	58,25	66,84	40,41	48,10	51,04	63,82	65,61	65,96	92,93	110,54	117,59
20	18,90	22,45	25,69	37,71	46,22	53,53	50,53	61,06	72,92	39,05	46,23	49,99	66,38	68,89	71,32	87,34	101,12	108,25
21	0,76	0,91	0,93	10,55	16,62	24,11	11,14	17,04	24,95	2,44	3,22	3,76	35,40	45,16	49,57	36,37	45,48	50,35
22	0,45	1,69	6,71	0,00	0,01	0,07	0,46	1,79	6,86	49,96	50,42	50,58	48,24	51,67	53,08	97,73	101,90	103,39
26	46,89	50,75	54,84	0,27	0,57	1,41	47,16	50,92	56,48	71,71	72,41	72,90	68,45	68,90	69,23	138,45	139,49	139,95
32	38,80	43,59	47,81	1,79	4,08	8,85	40,53	46,03	53,74	63,08	65,16	66,24	49,63	50,39	50,68	118,72	128,51	134,09
33	26,30	29,24	31,48	6,39	13,03	23,92	27,69	30,46	37,91	42,59	46,06	47,68	62,14	65,65	66,80	87,14	94,51	98,67
34	50,07	51,03	52,04	4,12	8,10	13,94	53,15	57,82	64,13	62,03	62,21	62,35	61,04	61,55	61,04	121,87	122,21	122,44
35	56,06	56,18	56,32	22,61	29,63	35,61	60,55	63,96	68,61	60,30	60,40	60,46	61,39	61,64	61,80	110,97	113,10	114,35
39	40,91	44,86	47,41	0,00	0,00	0,04	39,69	43,16	46,22	62,25	64,91	66,83	16,90	24,59	29,12	75,77	86,93	93,09

Patient Number	RBE Chiasm D2% old	RBE Chiasm D2% new	RBE Chiasm D2% sum	RBE OpticL D2% old	RBE OpticL D2% new	RBE OpticL D2% sum	RBE OpticR D2% old	RBE OpticR D2% new	RBE OpticR D2% sum
7	19,78	41,94	62,06	21,66	19,74	32,66	63,28	57,98	89,34
8	5,29	43,46	50,03	5,64	48,27	57,70	6,20	23,58	30,71
10	67,33	8,21	74,87	73,29	69,09	138,59	47,95	11,59	53,91
11	1,79	56,04	55,79	2,17	54,30	56,61	2,22	70,89	72,80
12	45,50	11,05	56,78	52,74	19,62	73,49	18,28	1,37	18,87
14	52,16	4,64	53,92	37,22	8,99	45,01	66,28	25,20	85,31
15	8,15	39,62	48,30	3,15	15,63	15,47	7,86	59,07	67,02
18	16,71	51,83	63,27	6,57	29,06	37,58	8,91	63,49	70,28
19	2,89	17,79	20,84	50,18	37,25	42,07	3,54	3,01	5,43
20	2,30	49,75	54,09	2,63	23,14	27,05	3,07	53,38	56,06
21	0,00	0,53	0,56	0,22	0,66	0,82	0,00	1,69	2,21
22	0,00	0,00	0,00	0,00	0,01	0,01	0,00	0,10	0,09
26	70,11	36,72	106,44	72,44	12,10	81,32	73,19	68,85	140,38
32	33,05	23,27	56,34	22,46	22,82	47,31	64,84	50,79	162,10
33	15,83	50,50	69,22	11,98	31,64	41,93	0,00	0,00	0,00
34	53,40	14,16	66,88	53,66	14,08	64,77	41,81	14,41	50,76
35	56,45	0,04	56,45	55,79	0,02	55,76	51,13	0,01	54,45
39	52,26	1,98	51,59	40,50	7,63	39,80	55,31	29,04	62,55

Patient Number	EQD_2 Brainstem D2.0cc old	EQD_2 Brainstem D0.7cc old	EQD_2 Brainstem D0.1cc old	EQD_2 Brainstem D2.0cc new	EQD_2 Brainstem D0.7cc new	EQD_2 Brainstem D0.1cc new	EQD_2 Brainstem D2.0cc sum	EQD_2 Brainstem D0.7cc sum	EQD_2 Brainstem D0.1cc sum	EQD_2 Brain D5cc old	EQD_2 Brain D2cc old	EQD_2 Brain D1cc old	EQD_2 Brain D5cc new	EQD_2 Brain D2cc new	EQD_2 Brain D1cc new	EQD_2 Brain D5cc sum	EQD_2 Brain D2cc sum	EQD_2 Brain D1cc sum
7	28,12	31,44	35,18	8,99	23,00	45,41	31,17	38,37	61,44	36,72	40,52	43,06	60,05	62,55	66,91	78,69	87,60	93,79
8	18,69	21,78	25,15	3,02	7,15	14,16	21,75	25,48	33,68	39,68	44,86	48,78	63,37	68,11	69,98	74,36	87,74	94,70
10	21,42	26,76	39,71	0,28	0,55	1,17	21,57	27,03	37,06	56,03	56,82	57,27	61,96	66,45	67,78	100,40	113,73	118,96
11	11,94	18,28	25,54	38,63	47,54	53,66	40,77	49,34	55,72	23,06	27,95	31,29	69,95	70,41	70,79	71,26	72,26	73,59
12	7,83	12,86	27,61	1,57	4,15	11,69	9,41	16,75	38,46	36,74	44,14	46,71	44,32	52,47	56,71	77,93	92,27	99,89
14	20,02	21,95	23,90	0,11	0,18	0,29	20,08	21,92	23,97	51,43	58,99	63,62	49,26	56,12	61,18	93,00	109,66	117,66
15	4,33	5,50	7,39	118,65	227,06	357,51	122,78	231,47	363,85	47,40	63,99	74,13	552,19	560,07	564,05	597,76	642,40	687,07
18	23,33	25,03	26,19	8,15	15,25	24,91	27,26	35,44	47,50	41,18	50,48	55,30	68,46	70,22	70,82	104,16	116,15	122,24
19	27,64	31,18	33,86	13,47	16,33	20,82	37,68	43,71	51,48	32,80	42,50	45,99	62,81	65,42	65,94	84,32	104,82	112,68
20	0,92	4,11	6,01	29,33	38,63	47,38	37,32	47,27	58,57	4,02	5,61	6,80	64,71	68,40	69,94	75,03	89,43	97,72
21	0,29	0,37	0,47	6,25	10,73	17,25	6,63	11,05	17,75	0,49	0,73	0,90	28,72	39,86	45,45	29,35	39,87	45,59
22	0,23	0,88	3,84	0,00	0,01	0,04	0,24	0,93	3,95	47,27	47,92	48,13	56,44	62,90	65,67	102,99	110,54	113,37
26	39,18	43,43	49,66	0,14	0,29	0,73	39,32	43,62	50,13	72,47	73,51	74,26	73,27	74,02	74,56	143,18	144,80	145,51
32	31,75	37,65	42,73	0,93	2,21	5,19	28,09	39,08	45,06	64,52	67,66	69,36	49,45	50,59	51,03	110,52	120,39	126,39
33	19,85	22,89	25,35	3,79	8,72	18,72	20,82	23,70	27,45	38,76	43,48	45,73	74,99	81,51	83,41	90,44	99,33	105,97
34	45,98	47,27	48,65	2,23	4,67	8,66	47,41	50,78	55,66	62,99	63,26	63,55	61,58	62,35	63,02	122,84	123,37	123,70
35	56,10	56,28	56,46	15,60	22,17	28,37	57,21	59,40	62,62	62,53	62,71	62,78	62,10	62,48	62,74	108,68	111,73	113,51
39	32,39	36,78	40,06	0,00	0,00	0,02	31,82	35,73	39,31	59,60	63,73	65,93	11,99	19,75	24,79	68,68	81,16	88,19

Patient Number	EQD_2 Chiasm D2% old	EQD_2 Chiasm D2% new	EQD_2 Chiasm D2% sum	EQD_2 OptiCL D2% old	EQD_2 OptiCL D2% new	EQD_2 OptiCL D2% sum	EQD_2 OptiCR D2% old	EQD_2 OptiCR D2% new	EQD_2 OptiCR D2% sum
7	13,07	45,79	50,14	14,71	14,12	24,70	26,53	56,40	77,13
8	2,85	37,30	41,81	3,05	40,79	48,79	3,38	16,55	20,95
10	53,89	4,63	57,30	58,35	68,65	124,09	33,16	6,83	37,01
11	0,93	50,52	49,50	1,11	48,28	50,08	1,13	71,35	72,17
12	39,93	6,44	46,45	49,41	13,00	63,21	11,83	0,70	12,18
14	47,31	2,48	46,53	29,59	5,08	33,66	66,77	17,14	77,35
15	20,69	277,12	300,66	4,06	76,10	60,32	19,36	565,07	576,59
18	10,91	45,77	53,82	3,66	21,85	27,13	5,15	63,00	66,14
19	1,51	11,91	13,74	2,82	29,51	32,49	1,87	1,60	2,88
20	0,26	42,68	46,35	0,44	17,40	19,81	0,42	47,08	48,34
21	0,00	0,27	0,28	0,11	0,34	0,42	0,00	0,88	1,16
22	0,00	0,00	0,00	0,00	0,01	0,01	0,00	0,05	0,05
26	71,43	30,10	100,11	73,57	7,84	77,57	74,71	73,93	146,10
32	24,67	17,06	41,53	16,52	16,64	33,31	67,37	51,20	163,21
33	10,35	56,25	69,04	7,39	27,14	33,23	0,00	0,00	0,00
34	50,54	9,00	58,65	50,58	8,73	56,25	36,44	9,02	41,40
35	56,78	0,02	56,68	55,78	0,01	58,64	45,34	0,01	53,69
39	47,13	1,10	45,83	31,07	5,07	30,84	48,80	21,63	49,53

Patient Number	BED Brainstem D2.0cc old_2	BED Brainstem D0.7cc old_2	BED Brainstem D0.1cc old_2	BED Brain D5cc old_2	BED Brain D2cc old_2	BED Brain D1cc old_2	BED Chiasm D2% old_2	BED OpticL D2% old_2	BED OpticR D2% old_2	RBE Brainstem D2.0cc old_2	RBE Brainstem D0.7cc old_2	RBE Brainstem D0.1cc old_2	RBE Brain D5cc old_2	RBE Brain D2cc old_2	RBE Brain D1cc old_2
7															
8															
10															
11															
12															
14															
15	0,87	1,02	1,06	45,11	146,34	205,29	1,38	1,08	3,94	0,66	0,74	0,84	8,55	16,14	19,29
18															
19															
20	24,13	29,48	35,24	60,87	76,38	85,63	2,61	2,71	3,18	18,80	22,45	25,69	39,05	46,23	49,99
21															
22															
26															
32	0,64	0,71	0,78	76,47	97,25	105,40	2,16	2,56	112,64	0,63	0,70	0,77	41,80	49,22	52,00
33															
34															
35															
39															

Patient Number	RBE Chiasm D2% old_2	RBE OptiCL D2% old_2	RBE OptiCR D2% old_2	EQD_2 Brainstem D2.0cc old_2	EQD_2 Brainstem D0.7cc old_2	EQD_2 Brainstem D0.1cc old_2	EQD_2 Brain D5cc old_2	EQD_2 Brain D2cc old_2	EQD_2 Brain D1cc old_2	EQD_2 Chiasm D2% old_2	EQD_2 OptiCL D2% old_2	EQD_2 OptiCR D2% old_2
7												
8												
10												
11												
12												
14												
15	0,94	0,78	1,98	0,44	0,51	0,53	22,56	73,17	102,65	0,69	0,54	1,97
18												
19												
20	2,30	2,63	3,07	12,07	14,74	17,62	30,44	38,19	42,82	1,31	1,36	1,59
21												
22												
26												
32	1,96	2,48	53,79	0,32	0,36	0,39	38,24	48,63	52,70	1,08	1,28	56,32
33												
34												
35												
39												

Appendix F.

Database of Summed up Distribution's Data only including Comparisons

Patient Number	Patient Name	First Treatment	Re-irradiation Treatment	Recovery Time [m]	Histology	RBE Brainstem D2.0cc sum	RBE Brainstem D0.7cc sum	RBE Brainstem D0.1cc sum	BED Brainstem D2.0cc sum	BED Brainstem D0.7cc sum	BED Brainstem D0.1cc sum	EQD_2 Brainstem D2.0cc Sum	EQD_2 Brainstem D0.7cc Sum	EQD_2 Brainstem D0.1cc Sum
7		70Gy/35fr	72Gy/36fr/30+6	55	PLECA	38,85	51,10	74,48	62,34	76,73	122,88	31,17	38,37	61,44
8		70Gy/35fr	70Gy/35fr/4+13+13+5	27	PLECA G3	31,59	37,36	48,61	43,50	50,96	67,35	21,75	25,48	33,68
10		69,6Gy/58fr	70Gy/35fr/15+15+3+2	27	PLECA G3	33,38	40,25	52,00	43,13	54,06	74,12	21,57	27,03	37,06
11		60Gy/30fr(25+5)	70Gy/35fr/15+15+3+2	15	PLECA G3	50,52	57,29	62,54	81,53	98,68	111,44	40,77	49,34	55,72
12		54Gy/30fr/30	60Gy/30fr/15+15	80	Benignes Meningeom	15,75	26,26	51,37	18,82	33,50	76,91	9,41	16,75	38,46
14		66Gy/33fr(25+5+3)	70Gy/35fr/15+15+5	42	PLECA G2	27,70	29,47	31,52	40,15	43,83	47,94	20,08	21,92	23,97
15		2xGammaknife 14Gy at edge	36Gy/20fr & 22Gy/11fr/ 10+10 & 9+1+1	57	Benignes Meningeom	23,21	37,16	49,90	245,55	462,94	727,70	122,78	231,47	363,85
18		60Gy/30fr(25+5)	70Gy/35fr/15+15+5	16	PLECA G3	39,12	49,78	62,91	54,51	70,87	94,99	27,26	35,44	47,50
19		59,4Gy/33fr(28+5)	66Gy/33fr/7+14+4+5+3	40	Synovialsarkom	51,11	58,25	66,84	75,36	87,42	102,96	37,68	43,71	51,48
20		50Gy/25fr + 70Gy/35fr	70Gy/35fr/8+8+5+4+10	28	PLECA G2	50,53	61,06	72,92	74,63	94,53	117,14	37,32	47,27	58,57
21		60Gy/30fr	69Gy/30fr/15+15	12	PLECA G3 Undifferenziertes Sarkom	11,14	17,04	24,95	13,25	22,10	35,50	6,63	11,05	17,75
22		50,4Gy/28fr(23+5)	54Gy/18fr/	13		0,46	1,79	6,86	0,47	1,86	7,90	0,24	0,93	3,95
26		70Gy/35fr	67,5Gy/30fr/2+1+13+14	29	Adeno G2	47,16	50,92	56,48	78,64	87,23	100,25	39,32	43,62	50,13
32		60Gy/30fr+ 45Gy/25fr	50Gy/25fr/12+13	27	PLECA	40,53	46,03	53,74	56,17	78,16	90,12	28,09	39,08	45,06
33		60Gy/30fr(25+5)	2,6/11fr/BS1 3/11fr/BS2	14	PLECA G3	27,69	30,46	37,91	41,63	47,40	54,90	20,82	23,70	27,45
34		60Gy/30fr?	60Gy/30fr/7+7+8+8	91	GBM	53,15	57,82	64,13	94,82	101,55	111,31	47,41	50,78	55,66
35		56Gy/28fr	60Gy/30fr/15+15	32	Astro III	60,55	63,96	68,61	114,42	118,80	125,23	57,21	59,40	62,62
39		66Gy/33fr	66Gy/30fr/6+5+5+3+11	29	Adeno G2	39,69	43,16	46,22	63,63	71,45	78,61	31,82	35,73	39,31

Patient Number	RBE Brain D5cc sum	RBE Brain D2cc sum	RBE Brain D1cc sum	BED Brain D5cc sum	BED Brain D2cc sum	BED Brain D1cc sum	EQD_2 Brain D5cc Sum	EQD_2 Brain D2cc Sum	EQD_2 Brain D1cc Sum	RBE Chiasm D2% sum	BED Chiasm D2% sum	EQD_2 Chiasm D2% Sum	RBE OpticL D2% sum	BED OpticL D2% sum	EQD_2 OpticL D2% Sum	RBE OpticR D2% sum	BED OpticR D2% sum	EQD_2 OpticR D2% Sum
7	89,48	98,21	103,40	157,37	175,19	187,57	78,69	87,60	93,79	62,06	100,28	50,14	32,66	49,39	24,70	89,34	154,26	77,13
8	84,35	97,69	103,89	148,71	175,48	189,40	74,36	87,74	94,70	50,03	83,62	41,81	57,70	97,57	48,79	30,71	41,89	20,95
10	119,06	130,52	134,72	200,80	227,46	237,92	100,40	113,73	118,96	74,87	114,60	57,30	138,59	248,17	124,09	53,91	74,02	37,01
11	72,99	74,73	81,47	142,52	144,51	147,18	71,26	72,26	73,59	55,79	98,99	49,50	56,61	100,15	50,08	72,80	144,33	72,17
12	88,82	100,17	105,88	155,85	184,54	199,77	77,93	92,27	99,89	56,78	92,90	46,45	73,49	126,42	63,21	18,87	24,36	12,18
14	103,67	116,66	122,79	186,00	219,32	235,31	93,00	109,66	117,66	53,92	93,06	46,53	45,01	67,32	33,66	85,31	154,70	77,35
15	73,96	82,35	88,26	1195,51	1284,80	1374,14	597,76	642,40	687,07	48,30	601,31	300,66	15,47	120,64	60,32	67,02	1153,17	576,59
18	110,93	120,05	124,62	208,31	232,29	244,48	104,16	116,15	122,24	63,27	107,63	53,82	37,58	54,26	27,13	70,28	132,28	66,14
19	92,93	110,54	117,59	168,63	209,63	225,35	84,32	104,82	112,68	20,84	27,47	13,74	42,07	64,97	32,49	5,43	5,75	2,88
20	87,34	101,12	108,25	150,06	178,86	195,44	75,03	89,43	97,72	54,09	92,69	46,35	27,05	39,62	19,81	56,06	96,67	48,34
21	36,37	45,48	50,35	58,69	79,73	91,17	29,35	39,87	45,59	0,56	0,56	0,28	0,82	0,83	0,42	2,21	2,31	1,16
22	97,73	101,90	103,39	205,98	221,08	226,74	102,99	110,54	113,37	0,00	0,00	0,00	0,01	0,01	0,01	0,09	0,09	0,05
26	138,45	139,49	139,95	286,35	289,60	291,02	143,18	144,80	145,51	106,44	200,21	100,11	81,32	155,13	77,57	140,38	292,20	146,10
32	118,72	128,51	134,09	221,04	240,77	252,78	110,52	120,39	126,39	56,34	83,06	41,53	47,31	66,61	33,31	162,10	326,41	163,21
33	87,14	94,51	98,67	180,88	198,66	211,94	90,44	99,33	105,97	69,22	138,08	69,04	41,93	66,46	33,23	0,00	0,00	0,00
34	121,87	122,21	122,44	245,67	246,73	247,39	122,84	123,37	123,70	66,88	117,30	58,65	64,77	112,50	56,25	50,76	82,79	41,40
35	110,97	113,10	114,35	217,36	223,45	227,01	108,68	111,73	113,51	56,45	113,36	56,68	55,76	117,27	58,64	54,45	107,38	53,69
39	75,77	86,93	93,09	137,36	162,32	176,38	68,68	81,16	88,19	51,59	91,66	45,83	39,80	61,67	30,84	62,55	99,05	49,53

Patient Number	RBE-EQD_2 Brainstem D2.0cc	RBE-EQD_2 Brainstem D0.7cc	RBE-EQD_2 Brainstem D0.1cc	RBE-EQD_2 Brain D5cc	RBE-EQD_2 Brain D2cc	RBE-EQD_2 Brain D1cc	RBE-EQD_2 Chiasm D2cc	RBE-EQD_2 Optic L D2cc	RBE-EQD_2 Optic R D2cc	
7	7,68	12,74	13,04	10,80	10,62	9,62	11,92	7,97	12,21	
8	9,84	11,88	14,94	10,00	9,96	9,19	8,22	8,92	9,77	
10	11,82	13,22	14,94	18,86	16,79	15,76	17,57	14,51	16,90	
11	9,76	7,95	6,82	1,73	2,48	7,88	6,30	6,54	0,63	
12	6,34	9,51	12,92	10,90	7,90	5,99	10,33	10,28	6,69	
14	7,63	7,56	7,56	10,67	7,00	5,14	7,39	11,35	7,98	
15										
18	11,87	14,35	15,42	6,78	3,91	2,38	9,46	10,45	4,14	
19	13,43	14,54	15,37	8,62	5,73	4,92	7,11	9,59	2,56	
20	13,22	13,80	14,35	12,31	11,69	10,53	7,75	7,24	7,73	
21	4,52	5,99	7,20	7,03	5,62	4,77	0,28	0,41	1,08	
22	0,23	0,86	2,91	-5,26	-8,64	-9,98	0,00	0,01	0,05	
26	7,84	7,31	6,36	-4,73	-5,31	-5,56	6,34	3,76	-5,72	
32	12,45	6,95	8,68	8,20	8,12	7,70	14,81	14,01	-1,11	
33	6,88	6,76	10,46	-3,30	-4,82	-7,30	0,18	8,70	0,00	
34	5,74	7,05	8,48	-0,96	-1,16	-1,26	8,23	8,52	9,37	
35	3,34	4,56	6,00	2,29	1,38	0,84	-0,23	-2,88	0,76	
39	7,88	7,44	6,92	7,09	5,77	4,90	5,76	8,97	13,03	
	0,23	0,86	2,91	-5,26	-8,64	-9,98	-0,23	-2,88	-5,72	MIN
	13,43	14,54	15,42	18,86	16,79	15,76	17,57	14,51	16,90	MAX

Appendix G.

Validation Protocol for the BED Script

Dokumententitel / Document Title 000000000			
Script to Calculate the Biologically Equivalent Dose (BED) of a Treatment Plan Voxel by Voxel			MedAustron Ion Therapy Center
Dokumentennummer / Document Number	*DokKlasse / DocClass*	*Inhaltskennz. / Content Code*	*Version*
			1.0
Dokumenteneigner / Document Owner	*gültig ab/ effective from*	*gültig bis / effective until*	*Maintenance*
	= Freigabe / release date	n.a.	

zugrundeliegende Vorlage / underlying template: ZA000_10700_1310011, v18.0

Dokumentenhistorie / Document History		
Version	*Datum / Date*	*Description (of Changes)*

Freigabe / Approval				
	Name + Function / Funktion		*Bemerkung / Remark*	*Date / Datum*
prepared by erstellt von	*Name*	PRO		
	Function	Volunteer		
checked by geprüft von	*Name*			
	Function			
approved by freigegeben von	*Name*			
	Function			

Empfehlung bezügl. Schulung des DokEigners / recommendation regarding training by DocOwner					
Schulungsrelevant subject to training	ja/yes ☐ -->		Selbstschulung ☐ self-instruction		Schulung durch Trainer ☐ instruction by trainer
	nein/no ☐				

Dieses Dokument ersetzt das (die) folgende(n) Dokument(e) This document replaces the following document(s)	-

weitere Anmerkungen further remarks	-

Gender Disclaimer:
For better readability, the remaining text refrains from using gender-specific role designations. Where applicable, both genders are implied.

Wegen der besseren Lesbarkeit wird im weiteren Text zum Teil auf die gleichzeitige Verwendung weiblicher und männlicher Personenbegriffe verzichtet. Gemeint und angesprochen sind – sofern zutreffend – immer beide Geschlechter

Inhalt / Content

1 Purpose

The purpose of this document is to define the software verification and validation tests for the script generated in the scope of the project on the toxicity of re-irradiation in organs at risk of patients with tumors in the head and neck region at MedAustron. The script calculates the biologically effective dose of a treatment plans dose distribution in RayStation v8B_SP1 voxelwise. The document shall be used and filled during the script validation process for the clinical use.

2 Scope

The stipulations within this document are binding for the below specified version of the script ***BED.py*** and its affiliated files ***bed_input_1.xaml*** and ***bed_input_2.xaml***.

For simplification the above specified script name will be called ***BED script*** in the following.

Further, the verification and validation test for the BED script is only valid for the version of RayStation entered below by the tester. The version of RayStation must be clinically accepted.

RayStation _____

If in any case the script and/or the version of RayStation are not specified above, the validation is not valid.

3 References

This document has been developed according to the standard ISO 62304:2006 about the Medical Device Software Lifecycle and to the internal MedAustron Software Validation SOP [1].

4 Abbreviations and Definitions

Refer also to *Glossar, DokNo: ZA000_11100_1505131 and QM Manual TA Division Chapter 3, DocNo: DC011_10500_1302013*

4.1 Abbreviations

Abbr.	Explanation EN
BED	Biologically Equivalent Dose
RS	RayStation
TPS	Treatment Planning System
BS	Beam Set

5 Roles and Responsibilities

Role	responsible for

PRO	Software development and writing verification and validation procedures
PAB	Reviewing software development and approving verification and validation procedures
MP user	Certified MP, Final Software validation and approval

6 Script specifications

6.1 RayStation

In praxis the validated BED script will be called within the TPS RayStation on a clinical TPS workstation. The version shall be specified in section 2.

6.2 IronPython

The programming language used for the script is IronPython. It is Python integrated within the .NET framework. RayStation uses IronPython 2.7.1. The corresponding version of CPython is Python 2.7.

7 Installation verification

The procedures in this section are meant for testing the user requirements, as found in [1]. The tests are valid in the version of RS specified in section 2.

7.1 Workspace preparation

Test procedure

- Start an instance of RayStation on a clinical TPS workstation.
- Open a random patient, case and treatment plan and select the "Scripting" tab.

Check

❒ The script is visible in the list of "Module specific scripts".

❒ The script can be run by clicking the "Run script" button.

❒ Verify that the script can run simultaneously on at least two TPS workstations.

Comments

Date/Signature: _____PRO

Date/Signature: _____MP User

8 Operational verification

The scope of this part of the validation is the principle functioning of the software according to [1]. This part is not covering the technical implementation of the software.

8.1 The BED script shall run on different patients

Test procedure

- Access one TPS and open two different arbitrary patients and select a plan.
- Run the BED script simultaneously for the two patients.

Check

❒ The script is running on two patients simultaneously.

❒ No crashes were observed.

Comments

Date/Signature: _____PRO

Date/Signature: _____MP User

8.2 Output generated

Test description

The output of the script will be a new plan with a name similar to the old plan and a "Calculated BED from plan" in front of the name. The table below is an example to show the plan name labeling used by this script:

Old plan name:	BS#CT#PTV#p###
New plan name:	Calculated BED from plan BS#CT#PTV#p###

The new plan will contain BED distributions which were calculated voxelwise from the original plan's dose distributions. The calculation is done separately for each beamset which makes the evaluation also valid in case the individual beamsets of a plan have different fractionation patterns.

The script will open up a dialog window where it is possible to enter the desired α/β ratio in [Gy] and also a recovery factor in [%].

In case the plan on which the script is used on contains an imported dose distribution where the number of fractions is 1 or undefined, a second dialog window will appear and provide an input for the number of fractions. It should be noted that for imported dose distributions containing multiple already summed up beamsets with varying fractionation schemes, the correct BED distribution can not be calculated by the script.

Additionally to the new plan, an evaluation dose will be created which displays the total BED distribution of the plan with the defined number of fractions.

The present test has the purpose of checking whether the script runs through completely with a standard output.

Test procedure

- Run the script for any selected plan to create a new plan with BED dose values
- When executing the script, click on the tab "Execution details" and follow the progress until the script finishes its execution.

Check

- ❒ The script successfully creates a new plan with the same name as the old plan plus "Calculated BED from plan" at the beginning.
- ❒ Additionally an evaluation dose was created, containing of a sum of the plan's beamsets with their assigned fraction numbers

Comments

Date/Signature: _____PRO

Date/Signature: _____MP User

9 Performance verification

The scope of this part of the validation includes testing expected functionalities and performance, as well as the script usability.

9.1 Output as expected: Case 1

Test description

- Use the script to create a treatment plan containing the BED distribution of a test plan
- Compare new and old dose distributions visually
- Manually calculate the BED of single voxels in the center and on the outskirt of the distribution and compare it to the values provided by the script

Test procedure

Open the dedicated test plan and run the BED script:

- Patient name: "zzz_StudyReIrr_YHA_PAB_Pet35"
- Treatment plan name: "Plan1CT1PTV12pIR2"

Check

- ❒ Verify that a new plan has been created.
- ❒ Verify that the name of the newly created plan follows this labelling format: Calculated BED of plan + old plan name (Calculated BED from plan Plan1CT1PTV12pIR2)
- ❒ Verify that the BS name of the new plan follows this format: BED + beamset number

- ❒ Verify that the number of the beams in the new plan is identical with the old one.
- ❒ Compare one of the BED beamset distributions optically to its accompanying RBE distribution in the evaluation window. It should have the same shape, but the high dose levels should be more centered
- ❒ Write down multiple dose values of both the outskirt and the center of the BED dose distribution and the dose values of the same voxel in the RBE dose distribution
- ❒ Confirm the correctness of the BED in these voxels by calculating it manually from the RBE dose

Comments

Date/Signature: _____PRO

Date/Signature: _____MP User

9.2 Output as expected: Case 2

Test description

- Use the script to create a treatment plan containing the BED distribution of a test plan
- Use the node structure created in MICE Toolkit to evaluate the BED distribution of the beamset
- Verify optically and by comparative measures whether the BED distributions are the same
- Note that the node structure in MICE only works on distributions that are the result of a single fractionation scheme

Test procedure

Open the dedicated test plan and run the BED script:

- Patient name: "zzz_StudyReIrr_YHA_PAB_Pet35"
- Treatment plan name: "Plan1CT1PTV12pIR2"

Check

- ❒ Verify that a new plan has been created.
- ❒ Verify that the name of the newly created plan follows this labelling format: Calculated BED of plan + old plan name (Calculated BED of zzz_StudyReIrr_YHA_PAB_Pet35)
- ❒ Verify that the BS name of the new plan follows this format: BED + beamset number
- ❒ Verify that the number of beams in the new plan is identical with the old one (shall be checked BS wise).
- ❒ Export the original RBE dose of one BS and the accompanying BED distribution and import both of them into MICE Toolkit
- ❒ Load the BED calculating node structure in MICE and perform the calculation on the RBE dose distribution
- ❒ Open the resulting distribution and the imported BED distribution in the visualization window
- ❒ Compare optically whether both distributions have the same shape
- ❒ Take multiple points in the distribution and confirm that the values in the MICE calculated BED distributions match the values in the Raystation script calculated BED distribution

Comments

Date/Signature: _____PRO

Date/Signature: _____MP User

9.3 Output as expected: Case 3

Test description

- Imported plan contains a treatment method and treatment machine that are not existing at this institute and therefore are not in its Raystation's machine database
- Running the script should result in the correct BED distribution but change treatment method and machine to a registered one

Test procedure

Open the dedicated test plan and run the PIP 1b script:

- Patient name: "zzz_StudyReIrr_YHA_PAB_Pet35"
- Treatment plan name: "Plan_Extern"

Check

- ❒ Verify that a new plan has been created.
- ❒ Verify that the name of the newly created plan follows this labelling format: Calculated BED of plan + old plan name (Calculated BED of).
- ❒ Verify that the BS name of the new plan follows this format: BED + beamset number
- ❒ Check whether treatment method and machine were changed
- ❒ Check whether the BED dose distribution was evaluated correctly

Comments

Date/Signature: _____PRO

Date/Signature: _____MP User

10 Overall Validation

10.1 Summary and significant deviations

The compilation involves a summary of the results and insights obtained from the interim reports and a concluding description and evaluation of the significant deviations and their impact on the validated status of the software.

Summary and deviations

Date/Signature: _____PRO

Date/Signature: _____MP User

10.2 Practical testing

The overall validation is a proof of the BED script for fitness to use and that the specifications are able to fulfill practical requirement.

Test procedure

- Start RayStation and load a plan.
- Run the BED script.
- Compare BED distributions of different plan or BS or create evaluation doses to see summed up BED distributions

Comments

Date/Signature: _____PRO

Date/Signature: _____MP User

10.3 Overall validation

- ❒ Accepted
- ❒ Accepted with reservation
- ❒ Partly accepted
- ❒ Rejected

If accepted set the script as *validated script* in RayStation.

Comments

11 References and Attachments

11.1 References

further applicable documents		
RefNo	Title	DocNo
[1]	SOP Software Validierung / SOP Software Validation	DC020_10510_1403101

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Citations proofed in August 2020

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Ich sehe die Möglichkeiten und Privilegien welche sich mir bieten keineswegs als selbstverständlich an und hoffe mir selbst nie untreu zu werden und möchte auch zukünftig alles was ich habe, erreiche oder erlebe wertschätzen.