Evaluation of Relative Biological Effectiveness for Proton Therapy

A Thesis

Presented to

The Faculty of the Department of Industrial Engineering

University of Houston

In Partial Fulfillment

Of the Requirements for the Degree

Master of Science

By

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Abstract

Proton therapy for treating cancer patients has been evolved to become a highly desired choice of radiation therapy due to the physical characteristic of protons. Currently, the biologic effectiveness of protons relative to photons is considered to be a constant ratio of 1.1. However, experiments show that the RBE is higher in different portions in proton ranges. Since the usage of a constant RBE is justified based on experiments conducted using older methods of dose delivery, the re-evaluation of using a constant RBE and proposing models for determining RBE values is necessary now that recent experimental results, using new actively scanned beam delivery method, are available and suggest deviations from conventional data. To suggest a method for calculating RBE values, an experiment by Guan et al. is chosen to derive biologic response results with respect to proton beams. A widely used phenomenological RBE model by Wilkens and Oeflke is chosen for comparison purposes. The proposed RBE model is based on Wilkens and Oeflke model with revisions on tissue parameters behavior vs. LET based on Guan et al results. Three RBE models including the constant RBE, Wilkens' model and the suggested model based on Guan's experiment are compared for three brain cancer patient cases. The comparisons are demonstrated using cumulative RBE weighted dose volume histograms. The sensitivity of models to tissue parameter changes are also analyzed. The suggested model shows escalated variable RBE weighted dose compared to constant RBE weighted dose, and it is sensitive to RBE model parameters in all three patient studies.

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Chapter 1

Introduction

1.1 Background and Motivation

According to a report by Hannah Nichols published in MNT website (medicalnewstoday.com), cancer was the second cause of deaths after heart disease in United States in 2012, with 584,881 deaths (Nichols). There were 14.1 million new cancer cases reported around the world in 2012 and it was estimated to grow to 24 million cases by 2015 (International). Also there were 8.2 million deaths, 32.6 million people around the world living with cancer (GLOBOCAN). Considering present statistics, cancer disease is taking lives of a great number of people worldwide and leaves so many others at the risk of death. In addition to be deadly, the disease has economic impacts on the society worldwide. To more elaborate on the expenses cancer imposes, two viewpoints are presented here. First, the high costs of cancer treatment are considered. According to IMS institute, global spending on cancer treatment drugs has passed 100 billion dollars threshold in 2014 (Constantino). New cancer drugs are introduced every year and the amount spent on cancer drugs are increasing at the same time. That means more funds are being spent on the disease. The costs are putting individuals with cancer, and the governments with public funds allocated for cancer patients in a problematic situation. UK government has recently cut off a part of cancer drug funds as it is no longer able to afford it (Ward). On the other hand, as cancer causes premature death and disability, an economic cost other than direct medical costs of cancer

exists. A report of a research done jointly by American Cancer Society and LIVESTRONG on global economic impact of cancer indicates that an 895 billion dollar in total cost was imposed by premature death and disability caused by cancer in 2008. This accounts for 1.5 percent of gross domestic product worldwide. This is of more importance when the findings show that cancer is growing to become the first cause of death instead of heart disease and stroke (American cancer society). According to the formerly mentioned points, cancer has had to be taken seriously from the beginning and a significant amount of time and resources is devoted to research on the disease and its possible treatments. As a solution to a problem begins with understanding the problem and its characteristics, cancer has been under investigation. Below is a brief description on cancer.

Cancer is a disease in which cells in any organ start to divide abnormally and uncontrollably leading to a whole body malfunction and death if not cured. Different types of cancer treatments have been found trough time, including Surgery, Chemotherapy, Radiation therapy, Immunotherapy, Targeted therapy, Hormone Therapy, Stem Cell Transplant, and Precision Medicine. The methods available for curing cancer, however, depend on the type of cancer (NIH).

One of the cancer treatments is radiation therapy. The method was introduced in 1903, five years after radium was discovered by Curie. Over the recent century radiation therapy has come a long way from being conceptualized to being implemented widely on many cancer patients in cancer treatment institutions (Brady et al.). Radium was used to emit Gamma ray at first, giving its place to Cobalt 60. Generally Gamma rays and X rays were often used before the use of heavy ions in radiotherapy was introduced. Cancer

radiotherapy treatment approach is uncertain in nature and always has been used despite the risks and uncertainties. Earlier methods for radiotherapy of the tumor cells however, had more built-in errors and risks as they were not very precise in defining the target volume and in optimization of the dose function. Later on, the use of heavier ions was taken into consideration and implementation. The rationale for using proton or other heavy ions mostly was the characteristics of its dose distribution and "Bragg peak". Heavy ions provide with a homogenous field in the target. Such ability is known as "spread-out-Bragg peak" which enables the maximum effectivity to include the whole tumor while sparing the normal tissue around it, is the outcome of the spread out Bragg peak. Keeping the healthy tissue around the tumor is important due to the probability of second hand cancers caused by irradiation of normal cells during radiotherapy. Furthermore, the dose distribution characteristics make the treatment process more effective. Proton beams are known to be the most practical of all heavy particles potentially used in radiation therapy.

To create a homogenous field within the target, the intensity of the beams is modulated. Lomax has studied different types of intensity modulation methods for proton therapy to reach the conclusion that only the 3D localization of dose by individual narrow beam creates a Bragg peak in three dimensions to fully cover PTV (Planning Target Volume)(Lomax). Similar methods are also introduced by (Brahme, Källman and Lind) and (Carlsson, Andreo and Brahme). Such methods have made the treatment plans more precise than before, however, the need to further optimize the plans is yet to be met. The reason for such need is expressed in next paragraph; but in addition to the optimization of the plan discussion, the path to more precise and safer treatment plans is considered to

pass through the calculation of the "Relative Biological Effectiveness" (RBE) simultaneous to optimizing the treatment plan. That means considering the nearest to actual values for RBE when optimizing the dose. Such matter is discussed further in the problem statement section of this chapter. But a brief explanation of the motivation on the topic is given below.

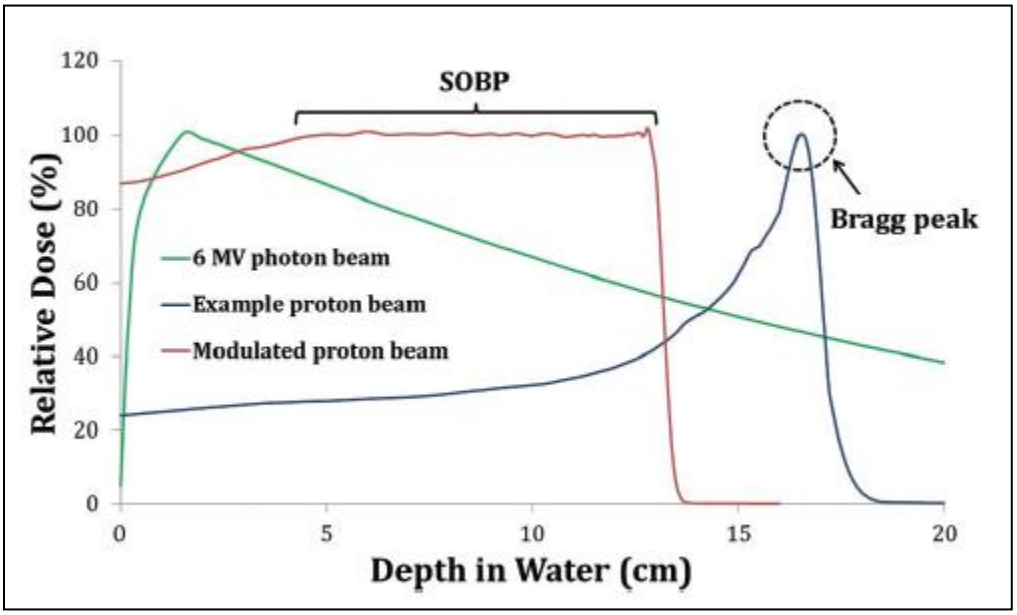

Figure 1 Depth-dose characteristics of proton and photon beams (Skinner and Komaki).

There are many uncertainties in regard to proton therapy approach. One of these uncertainties is caused by the effectiveness of the beam in regard to the target tissue. The effectiveness of the proton beam depends on the dose, the rate at which the energy of the beam is delivered to the tumor mass, and the characteristics of the target tissue.

The effectiveness of a beam is defined by a factor called "Biological Effect". However, the value that is usually used to observe the effectiveness of a particular beam in regard to a tissue is the ratio of absorbed dose of a standard radiation to the beam that

is under study. The reference radiation is usually X-ray produced by Cobalt 60. The reason for this choice is the sufficient amount of available data because of previous high use of the radiation. Basically, the absorbed dose of the new radiation, is the absorbed dose that causes the same amount of biological effect that the reference radiation causes. The discussed ratio is called "Relative Biological Effectiveness".

The clinical implementation of proton therapy considers the RBE of proton beams as a constant value of 1.1. The value of 1.1 is derived from experimental results in *in vivo* and *in vitro* experiments and are justified to be used as a constant value which is also spatially invariant in the target volume. As the results from former experiments haven't shown significant variation in the dose calculation quality when RBE is considered a variable compared to its constant assigned value, with regard to the large amount of uncertainties aligned to the RBE, the continual use of the constant 1.1 is still practiced in current clinical applications (Paganetti et al.).

Despite the mentioned rationale for continual use of constant RBE, with further availability of clinical data for proton therapy results and target response to the treatment, considerable research has been done on relative biological effectiveness as a variable, and its dependence on dose, linear energy transfer, and tissue specific parameters. Also, the use of constant RBE was assumed to be the right choice only considering the older methods of dose delivery including passive scattering proton therapy and high dose per fraction (Guan et al.). Such methods also carried a large amount of uncertainty within the experimental data. With the emergence of newer system for delivering the proton beams to the target tissue the question of either using the same constant RBE or calculating the RBE as a variable rises again. As a result, further investigation on the nature and

characteristics of RBE seems a good start point for the journey. To begin, we can take a look at the former studies on variable RBE.

Based on a report from (IARC), 7,054,446 cases of cancer were documented in the world with 8201 cases of death from cancer in 2012. Noting this and the formerly mentioned statistics, more study on cancer treatment methods seems extremely necessary to achieve better effectiveness. The severity of the issue is the motivation for optimizing the Proton therapy method used currently at the cancer treatment institutions.

1.2 Problem Statement

The purpose of this study is to investigate the impact of the recently developed RBE models on intensity modulated proton therapy (IMPT) treatment plans. A RBE model will be derived using the data from the experiment that is performed by Guan et al. (Guan et al.), and the RBE values from analogous RBE models will be compared. The difference between the variable and constant RBE weighted doses in retrospectively selected proton patient cases will be demonstrated. Finally, we will analyze the uncertainties in RBE model parameters in the same patient cases.

1.2.1 Comparison of Relative Biological Effectiveness for Three RBE Models

To evaluate the variable RBE and its uncertainties in IMPT treatment plans three brain tumor cases from patients who had received IMPT and clinical plans will be selected and exported. The LET and dose data from all beamlet to al voxels will be computed using Monte Carlo simulations. Subsequently, three RBE weighted doses will be compared along with the dose distribution and dose volume histograms. The three RBE weighted doses will be the constant RBE (cRBE), the variable RBE based on

Wilkens' (J. J. Wilkens and U. Oelfke) which will be calculated from fitted LET, α and β data presented in that study (vRBE-Wilkens), and the third RBE will be a RBE based on Guan's (Guan et al.), and presents a formulation for calculating RBE as a function of dose, LET and target tissue parameters (vRBE-Guan).

1.3 Contributions

This dissertation contributes to the literature by further investigating in the question of whether to use variable or constant RBE in dose calculation for IMPT planning. To achieve a better understanding of the influences and advantages that using a variable RBE would cause to the quality of the treatments, this study aims to compare weighted dose calculated based on constant RBE, to weighted dose calculated based on two estimated variable RBE. One of these variable RBEs is derived from Wilkens' model (J. J. Wilkens and U. Oelfke), and the other one is planned to be calculated based on data derived from Guan's experiments to determine LET and its respective tissue parameters (Guan et al.). Subsequently, by comparing worst case doses representing worst case scenarios based on RBE model parameters (variable RBE models), this study will incorporate uncertainties of IMPT treatments within the RBE models that are under study while it tries to determine whether the proposed models are accurate enough to be used in optimization of treatment plans. Moreover, three IMPT plans which are going to be optimized based on the three RBE options are going to be compared to ultimately decide whether the accuracy and improvements in quality of the treatments planned using such approach justifies using a variable RBE, and if the proposed RBE model functions superior to other variable models.

Our study will provide important data for future variable RBE based treatment planning that possibly leads to improved therapeutic ratio for cancer patients. Tools developed in this study will be used to guide and validate novel treatment planning approaches, such as robust optimization toward RBE uncertainty, distal edge avoidance, use of more beams, etc., which ultimately ensure sufficient dose to target while reducing possible toxicities in normal tissue.

1.5 Organization

In the next chapter a comprehensive literature review is presented from emergence of radiation therapy to the most recent RBE calculation methods. The review mostly focuses on the RBE and its long way from the past until today. After the literature review, a description of the procedures and methods that are used during the study is presented in chapter three, as well as the details of the steps mentioned above. The results and conclusions will be presented in chapters 4 and 5, and finally the future work is discussed in chapter 6.

Chapter 2

Literature Review

2.1 Radiation Therapy

One of the approaches to cure cancer tumors is radiation therapy. Traditional methods of radiation therapy use x-rays, gamma rays, and electron beams while newer methods for radiation therapy promotes use of proton particles in radiation of cancer cells. In radiation therapy the goal is to produce maximum damage for tumor cells and spare the healthy tissue around it as much as possible simultaneously (Terasawa et al.).

Charged particle radiotherapy was put into consideration and use since 1954 (Terasawa et al.); and it has come a long way. According to an article on precision of radiotherapy (Dutreix), the start to using photon beams as a new approach of radiotherapy as opposed to conventional X-rays, occurred in early 1950s and it continued to advance in using computers and diagnostic imaging. Also, at the very first years of implications, the target volume was considered a rectangular shape. That means the shape of the tumor was not being considered as it is but as a constant shape that was feasible for the approach. Yet the most important issue according to mentioned publication has always been the difference between the prescribed dose, delivered dose to the tumor, and the effective absorbed dose to the target volume. At that time, the only factors considered in dose effectiveness in regard to absorbed dose were patient positioning, patient immobilization and setting of machine parameters; however, the variations of biological effects are considered in regard to delivered dose uncertainty which is considered to be acceptable if between ± 5%.

Relative biological effectiveness – also known as RBE – is a ratio indicating biological effectiveness of one ionizing particle in regard to another ionizing particle when the same amount of energy is absorbed. Often we need the RBE of a particular charged particle relative to a reference particle for which the biological effects are known better. The above definition is correct, however, it might be over simplified as RBE depends on various factors for different particles. Although all of such factors cannot always be considered while determining RBEs for different particles, depending on the information available, some or most of these factors can be used in calculations. Also, due to complicated calculations needed for determining RBE, sometimes a constant RBE is used. Using constant vs. variable RBE will be discussed further in present review; since one of the major goals of this review is to show the differences between variable and constant RBE and the reasons behind choosing one over another.

RBE is mostly useful for calculating the dose which should be implemented during radiotherapy sessions. Dose has two different meanings in radiotherapy. "Prescribed dose" clearly is the dose that is prescribed to be delivered to the patient, while "absorbed dose" is the dose that is actually being absorbed by the target cells. The latter is the important value for us in order to determine the actual energy that is received by the tissue and the damage that this energy is causing both for tumor and normal tissues. So the absorbed dose is considered to determine biologically effective dose. The biologically effective dose is described as

$$\text{Biologically effective dose} = \text{RBE} \times \text{radiation dose} \quad (1)$$

in equation (1) (Terasawa et al.).

2.2 Proton Therapy

Heavy charged particles can produce a dose distribution throughout the target volume that has a spread Bragg peak meaning the high dose will include all the target volume. This ability also lets the dose to spare the healthy tissue around the tumor which prevents the radiation to harm the normal cells. The radiation will enter the target with a moderate speed and will slowly rise so that the dose delivery will be the maximum near the end of the range. Unlike photon beams which can only optimize two dimensions for different treatment beams, proton beams have the ability to optimize the 3D dose distribution to the tumor (Miller). At the time, the method used for proton therapy was passive beam spreading according to Miller.

According to the study conducted by Miller, since the stopping point of proton beams is important in proton therapy treatment planning, and also because the tissue surrounding the tumor has to be spared precisely, the uncertainties have to be considered and analyzed. The physical characteristics of proton beams in the field of proton radiation therapy is more certain that their radiobiological properties but the researches are on their way to find out more about biological effects of proton beams. According to Miller et al. the optimization of proton therapy treatment plans in four dimensions in the future can elevate the effectiveness of the treatment.

A new method for proton therapy in introduced by (Lomax). In the mentioned study, a 3D localization of dose is suggested. Using an individual Bragg peak pencil beam for each target unit, a homogenous dose distribution can be delivered to the planned target volume. (Brahme, Källman and Lind) presented a procedure to optimize the pattern of scanning for spot scanning beam method to achieve the planned dose distribution

inside the target volume. Additionally, (Carlsson, Andreo and Brahme) has developed a similar method to Lomax, using Mote Carlo simulation calculations. All of mentioned studies presented the Intensity Modulated proton therapy method for proton therapy.

Later in 2001, Oelfke introduced a method for photon and proton radiation treatment planning, called "Inverse Planning". An optimization approach for the mathematical model of the problem (clinical objectives) is discussed (Oelfke and Bortfeld). In 2004, Nill, Bortfeld, and Oelfke compared two techniques of Distal Edge Tracking (DET), and the 3D scanning for dose delivery practicing inverse planning (Nill, Bortfeld and Oelfke). The Bragg peak of is located at the distal edge of the target volume in DET, while the Bragg peak of the dose distribution is positioned inside the target volume as well as the distal edge in the 3D technique. The comparison result was that DET uses less number of spots and therefore less calculation time than 3D scanning technique. However, the beam spots for both delivery systems can be reduced with a slight difference in the dose distribution. The quality of the treatment was measured to be better in 3D spot scanning method, though, as mentioned before DET can be almost as good as the 3D method with less number of beam spots. Although inverse planning for IMPT is believed to be a very fast and optimized algorithm for dose calculation, the journey to the best treatment planning approaches is not finished yet. Since the physical dose calculation still carries a considerable amount of uncertainty and factors that are not considered. Physical dose calculation overlooks the actual effect of the beam to the target. The local energy spectrum should also be considered.

The radiobiological effect caused by proton beams are currently considered to have the constant value of 1.1 relative to Cobalt 60 according to (Paganetti et al.) and

(Gerweck and Kozin). However, in order to achieve treatment plans with more accurate absorbed dose calculations, and with the increase in the available data from proton therapy patients, considering the RBE in optimization process might be reasonable.

2.3 Relative Biological Effectiveness

A constant value of 1.1, expressed in (Paganetti et al.), is used for RBE of proton beams. This was justified based on the fact that the existing uncertainties attached to RBE are large compared to the methods available for determining RBE value. The 1.1 value is derived from experimental data relative to reference radiation of Cobalt 60.

Gueulette et al performed an experiment on thirteen mice to analyze the impact of depth on RBE of 200-MeV proton beams. RBEs were calculated using modulated and unmodulated beams at the beginning, middle and end of the spread out Bragg peak. Cobalt 60 was used as the reference and the RBEs were found to be equal to 1.16 ± 0.04, 1.10 ± 0.03, 1.18 ± 0.04, 1.12 ± 0.03, and 1.23 ± 0.03 which were more that constant RBE of 1.10 at all depths. Also the RBE increased where the dose decreased. In this study, no relationship between depth and RBE values were found. (Gueulette, Böhm, et al.). Later in 1998 however, (Gerweck and Kozin) found that RBE of protons increase with the depth increasing. Moreover, in this study the constancy of RBE around the central axis, RBE as a function of dose, and dependency of RBE to target cell tissue properties (α and β) using modulated proton beams is analyzed. The results showed that RBE increased when dose decreases, which was found before in former studies, and also suggests that the RBE is dependent on α/β ratios of tumor cells, concluding constant RBE of 1.1 especially for tissues with low α/β ratios is too low for those tissues.

In 2001, a study was conducted by (Gueulette, Slabbert, et al.), that evaluated the impact of dose fractionating on biological effectiveness. This study used intestinal crypt regeneration in mice as the experiment tissue, and Cobalt 60 was considered the reference for RBE. The fractions were defined as one, three and ten every 3.5 hours with a 7cm Bragg peak for the proton beams. The results for respective fractions were 1.15 ± 0.04, 1.15 ± 0.05, 1.14 ± 0.07 for corresponding 10.0, 4.8, and 1.7 (Gy). The conclusion was that after 10 fractions, more proton irradiations were more effective. Also, it was found that the RBE was irrelevant to fractionation up to ten fractions. However it is not proven if it goes up or stays unchanged with for higher number of fractions. A sloping depth dose curve is advised to be considered in places nearer to the end points of the target tissue. Also this study mentions the importance of noticing the values for RBE which are more than 1.1 which is being used.

According to Paganetti et al. no need for changing the value of 1.1 for RBE in proton therapy treatment planning is observed (Paganetti et al.). In this study, the results from In vivo and In vitro experiments are evaluated to determine the variations of RBE in regards to LET, dose/fraction, and tissue specific parameters. The average value for RBE for the mid SOBP is reported to be about 1.2 and 1.1 for in vitro and in vivo respectively, ranging from 0.9 to 2.1 and 0.7 to 1.6. An increase in RBE values is reported in relation to decreasing dose per fraction. The most important result however, is noticing a substantial increase in RBE values within 1 -2 mm from end of the range. The results of RBE values are evidently showing a difference with the used value of 1.1, but the study suggests that since the uncertainties regarding RBE calculations are currently high, calculating tissue, dose, or LET specific RBE will not be practical. It is been proposed

that the hot region at the end of the tumor range be considered as a variation region for biological effectiveness in treatment planning.

Although the studies performed on necessity of considering a variable RBE in treatment planning and the factors on which RBE might depend, expressed a highly uncertain environment for determining RBE, newer researches have been done considering RBE as a variable factor. Additionally, efforts began to be done to calculate variable RBE. Considering the fact that former studies on continuing use of constant RBE of 1.1 for proton therapy was performed when passive scattering beam delivery methods were used to deliver the prescribed dose to patients.

The dependence of RBE on LET, dose, and tissue parameters are confirmed according to mentioned studies, and in many research papers including (Jan J. Wilkens and Uwe Oelfke), (Gu et al.), etc. the authors attempted to come up with new methods to calculate dose and LET and gather and use tissue specific parameters to calculate RBE.

Also the difference in application of constant and variable RBE in RBE weighted dose (RWD) is analyzed by Frese et al., using simulation data from four patients (Frese et al.). This study evaluates three treatment plans (physically and biologically optimized considering LET and tissue parameters). The RWD was more sensitive to LET in radio resistant tissues as compared to radiosensitive target.

Wilkens and Oeflke suggested a method to calculate RBE (J. J. Wilkens and U. Oelfke). In this study, RBE is considered to be dependent on dose, target tissue parameters, and linear energy transfer.

Tissue parameters are usually called α and β, and characterize the response to any different radiation that is specifically is the outcome of the combination of the radiation

and the tissue type. In other words, any different cell type (e.g. bacteria cells, eukaryote cells) responds to the radiation differently. This response reflects itself by the means of cell survival fraction.

The LET is calculated based on (Jan J. Wilkens and Uwe Oelfke) ,a previous publication from same authors, which calculates LET using an analytical approach as an alternative to using Monte Carlo simulations to determine the LET. The linear quadratic model is used to characterize the biological effect in order to calculate RBE. Using the evidence on dependence of tissue specific parameters on LET (Tilly), α is indicated as a function of LET. β is defined equal to β_x (β parameter for reference beam). Using LET, α, and β, two RBE functions are introduced, one including proton beam dose as a variable, and the other using SF (survival fraction) and λ (LET coefficient in α function) instead. The RBE values obtained from the proposed method is examined against experimental data. The calculated values are reported to sufficiently match with the experimental data, however, for LETs below 30 KeV/μm (higher SFs), the RBE increases with LET. It should be mentioned that both LET and dose are limited due to use of LQ model. Also cell survival data used in this study is chosen based on availability. This model reflects a basic dependence of RBE on dose, and is able to rapidly reproduce the results, however, it suggest that more information on tissue specific data be sought as different tissue types have different response to radiation.

Later in 2005, Wilkens and Oelfke investigated other models to calculate LET and biological effects (Jan J. Wilkens and Uwe Oelfke). This paper uses the phenomenological model, (J. J. Wilkens and U. Oelfke), and 3D LET calculation method, (Jan J. Wilkens and Uwe Oelfke), to use RBE and LET calculation in the process of

optimizing the treatment plan. New dose and LET functions are introduced and dose per fraction is considered in LQ model rather than total dose. The new objective function biologically optimizes the treatment plan rather than optimizing the physical dose. Since the tissue parameters used in this study are considered not to be absolutely relevant to the ones in in vivo experiment, meaning the values calculated should not be considered as an absolute value for RBE. It is mentioned in the paper that in some cases the values have been over estimated. Also, the LET distributions depend on the scanning techniques and LET distributions affect biological effect. On the other hand, the proposed method provides tools to identify dangerous situations in regard to organs at risk since the biological effect is being optimized and implemented in updating objective function.

Linear Energy Transfer is in fact a way of demonstration of the local energy spectrum of protons within the target tissue. It is also referred to as the radiation quality. LET is calculated using Monte Carlo simulations. Also dose averaged LET which is mostly used to relate cell survival to RBE dependence on depth can be calculated from "the weighted sum of range-shifted Bragg peaks" (Wouters et al.) .

Monte Carlo simulation modeling was used in a study done by Guan et al., to address the biological effects of proton beams delivered by scanning method and decrease the uncertainties (Guan et al.). The surviving fraction was found to be complex and nonlinear and the cell death, dose and LET is found to be related in a non-unique way. This study suggests further implication of this approach to generate data used to optimize treatment plans considering a variable RBE.

Our purpose is to develop an RBE calculating function based on the tissue specific data from Guan et al. study. The approach used in this method is to fit the tissue

parameter with the given LET values and find a sufficiently similar fit for α and β and develop the RBE function using the biological effect function. Then the values will be compared to (J. J. Wilkens and U. Oelfke) and constant RBE to evaluate the method.

Although the current implementation of proton therapy still considers a constant RBE value in treatment planning, and the uncertainties in regard to RBE of target tissues are significant, we aim to evaluate the impact of using variable RBE in treatment planning, using experimental data, phenomenological and analytical models to compare the values. Our goal is to achieve a more relevant, more precise estimating method for RBE to use in optimizing the treatment plans.

Chapter 3

Methods

For a cancer radiation therapy treatment plan, the treatment effectiveness measurement is not reflected in physical prescribed dose, since every tissue with different cell types responds differently to treatment. That means delivered beams do not cause exact same amount of damage to different cell types. This is important when optimization of treatment plans is anticipated by the cancer treatment facilities. However, due to limited available data, presence of inconsistency in available data, and large amount of uncertainties, the response of different cell types to proton beams is rather approximated with a constant 1.1 relative to photon effectiveness. When it comes to use of proton particles in cancer radiotherapy, although the delivered beams are considered to be more effective than previously used beams (like beams produced using photons), there are inherent potentials in proton therapy that are not fully being developed. In IMPT, the treatment has the capability to be optimized incorporating biologic effectiveness of proton beams with respect to specific cell types, Dose, and Linear Energy Transfer. Based on new experiment done by Fada Guan and his team, we introduced a model to estimate RBE values along the beam path for special cell types using the data derived from their experiment results (Guan et al.). The model is compared to Wilkens and Oeflke RBE model (J. J. Wilkens and U. Oelfke), as well as the constant RBE to observe and analyze the results produced using all three models. Several experiments regarding model sensitivity and ability to accurately estimate RBE values for three RBE models are performed. Significantly, the present study provided important information regarding

analytical RBE model and its behavior when constant or linear biologic parameters of the tissue are used. This information can be used to further underscore the importance of using variable RBE instead of the constant 1.1 in cancer proton therapy. The results also provide a rather clear image regarding the possible fluctuations of RBE when LET increases. An analysis is done to evaluate the behavior of the RBE function in response to changes in LET, and tissue parameters.

3.1 Introduction

Interest in using particles in radiation therapy treatments has been increasing in United States over the current decade (Guan et al.). This interest is based on the properties of Protons that allow them to spare the normal tissue from excess radiation to a great extend when used as the radiation beam in treatment. Protons lose their energy when travelling through tissue, and this energy transfers to the cells. The energy transfer rate increases with depth when the speed of the particle decreases. Therefore, the dose is the highest near the end of the range and it is called the Bragg Peak. This characteristic of proton beams is used to produce a conformal and homogenous dose distribution using several beams by modulating the delivered dose of each beam with respect to the preference of the volume shape.

Intensity modulated proton therapy (IMPT) is a powerful tool to deliver homogenous dose distributions to tumor cells while sparing the normal tissue around the tumor by limiting the dose delivery to adjacent organs at risk. While IMPT delivers such goals to a great extent, it does have high sensitivity to range uncertainties and setup variations. In addition to delivery uncertainties, it is discovered that the proton beams

effectiveness is not constant and changes throughout its path into the tumor and OARs. Such variation adds to the uncertainties of IMPT.

Protons have higher RBE than formerly used photons, so they can be more effective in causing tumor cell damage. This would be an important factor when treating radio resistant tumors. Proton RBE is considered spatially invariant and a constant value of 1.1 relative to photons. While as mentioned in Literature Review chapter, it is proved that Proton Relative Biological Effectiveness changes with depth of the beam, dose per fraction, and tissue type, the constant RBE of 1.1 is still justified to be clinically used due to limited available data needed for modeling the RBE function. One important factor to consider as a reason for re-evaluating the usage of spatially invariant and constant RBE, is that although many *in vivo* and *in vitro* experiments have found out that proton RBE is very close to 1.1 relative to reference beam (e.g., X-rays), those experiments have been conducted using older beam delivery methods. Using the new scanning beam delivery method, Guan et al. experiment has shown different results than former studies on proton beam behavior with respect to different tissues. Additionally, even in *in vitro* and *in vivo* experiments, RBE shown an increase at the end of the range which makes further research on proton RBE and delivering models to calculate its values, crucial to IMPT improvement. Therefore, methods for three dimensional RBE calculation is needed to approximate RBE values such that variations of biological effectiveness of proton beams be incorporated in treatment plans. Specifically when optimizing treatment plans with inverse treatment planning, calculating RBE values and then optimizing based on the calculated RBEs for more accurate dose distribution would play an important role.

To be able to model Relative Biological Effectiveness of proton beams, the factors that influence this value have been derived and studied over the years. Researchers found strong dependency of RBE to Dose per fraction, the energy spectrum of the beams which are ultimately characterized by Linear Energy Transfer, and the tissue specific parameters.

In Intensity Modulated Radiation therapy, the main effort is done to place the maximum strength of the beams inside the target volume, when the adjacent organs are safely spared at the same time. Proton beams maximum energy is delivered to the target at the end of their range and this suitably enhances treatment planning to preferably place the maximum energy (Bragg Peak) inside the target. Using this characteristic of proton beams, a highly homogenous dose distribution can be produced to cover all of the target volume range with the maximum effectivity using multiple Bragg Peaks of controlled beams. That means many beams are used to form the dose distribution and the contribution of each beam is modulated using a weight.

In calculating RBE all of influencing factors should be considered. Yet, an approach should be chosen such that the calculation of RBE could be done relatively quickly, since the ultimate purpose of the calculated values are for them to be incorporated in the optimized treatment plans and therefore, the calculation and optimization process should take a reasonable time and effort in order for the physicians to be able to practically implement the method. Accordingly, comprehensive models with relatively short calculation time requirement are in priority to be studied.

On the other hand, if variable RBE is to be used in treatment planning in the future, the significance of the difference caused by implementing the variable RBE in the

treatment effectiveness should be stablished. In other words, the constant RBE implementation in proton therapy treatment planning should be proved inaccurate and therefore not justified as this approach imposes much less expenses to the planning process. That means while the 1.1 value currently used for proton RBE is proved to not be always the case and variability of RBE is established, the effect of considering the biological effectiveness variable when planning proton therapy treatments, should be proved to be significant enough, and the RBE values should be shown to be different enough from 1.1 throughout the beam path, that putting the required resources (time, research resources, computation capacity, etc.) in calculating RBE and optimizing treatment plans with regard to the calculated RBE values, be justified. In order for new models to be developed, as mentioned before, reliable data regarding the relationship of proton beams, their energy, and the behavior of target tissues is needed. However, all of the former available data were inconsistent and included large amount of uncertainties. This was due to limited studies on proton beams, limited access to beam, experimental settings, and equipment calibration differences, as well as difference in reporting the results. Therefore, developing accurate models to calculate RBE while considering all of the influence factors has been challenging. Especially since scanned beams are becoming to be used more and more as the dose delivery methods, and former studies have been based on data which was derived using the passive scattering proton therapy, or high dose per fraction (as examples of older dose delivery techniques), the importance of availability of proton biological effectiveness information, has increased. Fortunately, Fada Guan and his team, have been experimenting on proton radiobiological effectiveness. In their recent paper (Guan et al.), the biologic effectiveness of scanned

proton beams is mapped and the biologic uncertainties are tried to be minimized to accurately reflect the results of the experiment. The details regarding Guan's experiment will be discussed further in next sections. LET vs. tissue parameters' relationship is found to be nonlinear especially toward the end of the range, and higher LETs. Data points for such relationship is delivered as the result of the experiment, approximating the RBE values of proton beams for Lung Cancer cells. With the results from the mentioned experiment, a new window is opened to further investigate in proton beam biologic effectiveness. Delivering and experimenting RBE models based on this newly available data is an interesting way to implement such information with the purpose on improving treatment effectiveness and quality. Accordingly, the purposed of this study, is to choose appropriate variable RBE models to compare with the constant RBE, and to re-evaluate the continued use of 1.1 as the proton RBE. Additionally, the sensitivity of the models is observed with regard to changes in tissue type parameters for both reference radiation and proton beams. For this purpose, Wilkens' phenomenological model for relative biological effectiveness is chosen to be used as an original model that the proposed RBE is compared to. Guan experimental data is used to model the dependency of tissue parameters to LET independently to each other. Using this relationship, an RBE model is suggested and examined against constant and Wilkens' RBE. The differences between the three models are measured based on Cumulative Dose Volume Histograms, which illustrate RBE weighted Doses for all three models.

To calculate RBE values realistically, dose contributions to every voxel of target and organs at risk is needed. For this matter, three brain tumor cases are selected from patients who have received IMPT and clinical treatment. Dose and Linear Energy

Transfer from all beamlets to all voxels are calculated using Monte Carlo Simulation. The RBE values and RBE weighted dose of all three models is calculated for all three patients, and dose volume histograms are used for comparison purposes and results demonstration. The sensitivity of two variable RBE models to tissue specific parameters for reference radiation, and the sensitivity of the RBE model based on Guan et al. experiment data to the tissue parameters fluctuations with regard to proton beams, is observed and analyzed.

The organization of this chapter is as follows: The key information and definitions that are used in this report, are introduced and defined in section 3.2. RBE definition and characteristics is presented, and its role in IMPT plans is discussed. The tools and concepts used to model RBE, calculate the results, and carry out the comparison are introduced and illustrated. In section 3.3 RBE models are discussed in details including the reasons for being chosen and the rationale of developing the models. In the next sections, methods and calculations are demonstrated.

3.2 Preliminaries of Relative Biological Effectiveness

As discussed before, the physical dose is not necessarily an appropriate variable to be optimized during treatment planning as it does not represent the actual effect on the target cells in radio therapy. The reason for this is clearly lays in the variant nature of the target, meaning that a delivered or prescribed dose can evoke different responses from different tissues. The variation in response also can be caused by the linear energy transfer of the delivered dose at different areas in the target. To more elaborate on variable factors that influence on biological effect, which will be discussed mostly under relative biological effectiveness, one can look into mentioned agents in second chapter. It

is mentioned that RBE is dependent on dose, depth, and tissue specific parameters called α and β. It should also be noted that depth alone is not the effective factor and the energy spectrum of the proton beams is the factor. The energy of the proton beams which differ along with their movement into the target volume can be presented by linear energy transfer.

3.2.1 RBE Characteristics and Definitions

Treatment Area

Radiotherapy is a treatment that is localized in patient's body that means the treatment does not affect the whole body of the patient. Therefore, the definition of tumor and target volumes, and correctly locating the treatment is absolutely critical to the success of the treatment.

The patients' cells in treatment planning area are divided into two general categories, which are called "Target Volume" and "Organs at Risk". The area under radiation is also divided into many small areas in the 3D space. The radiation is delivered to the destination volume using a location defining unit called voxel. Voxels are the small three dimensional areas that are considered the unit of volume. Each voxel in treatment planning process is addressed with three indexes, I, J, and K that describe the voxel's location is space. Target volume and Organs at Risk are distinguished in the treatment plans using this voxel information (Burnet et al.).

Three main structures (volumes) that are considered in radiotherapy planning. Gross Tumor Volume (GTV), is the extent of the gross tumor. This is the volume that is observable in imaging and the easiest to define. The second volume is the un-imagable spread of tumor that surrounds the GTV. This sub-clinical disease spread margin around

GTV, is known as the Clinical Target Volume (CTV). CTV is important because it should be considered in treatment planning such that adequate treatment is delivered to the volume for it to be cured. This part is challenging since CTV cannot be adequately defined. In some cases however, CTV is not surrounding a GTV necessarily, as there might be another CTV in another location. This means the density of tumor cells in that area is lower. Accordingly, it is assumed that lower radiation should be delivered to CTV to cure the disease. Planning Target Volume (PTV) is the area that includes CTV and GTV usually with an additional margin to allow for uncertainties in planning or delivering the treatment. PTV is rather a "geometric concept" which is designed to ensure that the treatment is actually delivered to CTV.

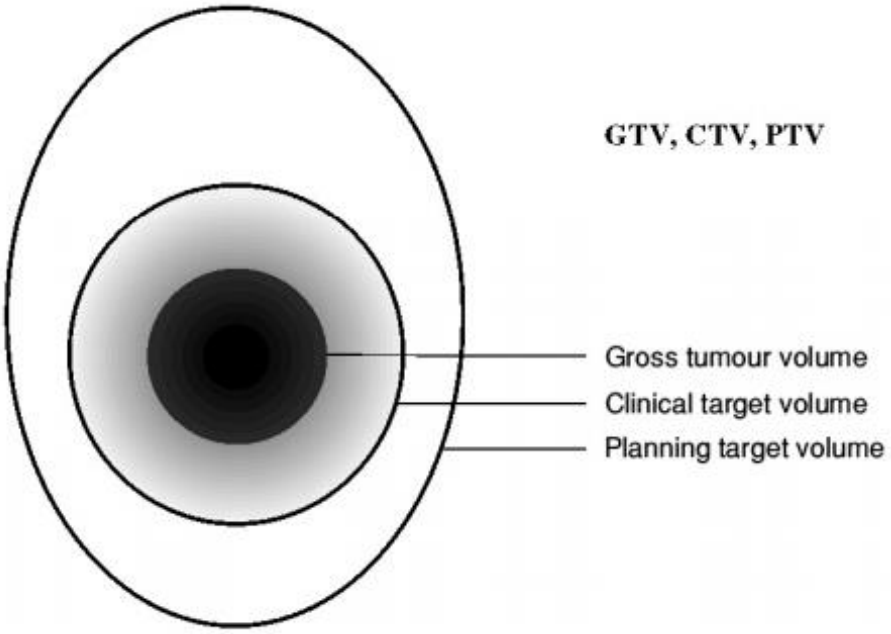

Figure 2 Illustration of the main radiotherapy planning volumes. (Burnet et al.)

When radiation therapy treatment is delivered to the target area, the healthy tissues that surround the tumor are in the danger of tissue damages and depending on the sensitivity of that areas, the treatment plans are adjusted to and influenced by such sensitivities. To spare these normal tissues, a margin is added to OARs. Adding a margin to OARs is sometimes challenging since such margins might ultimately add to the OAR volumes and intervene with the planning target volume.

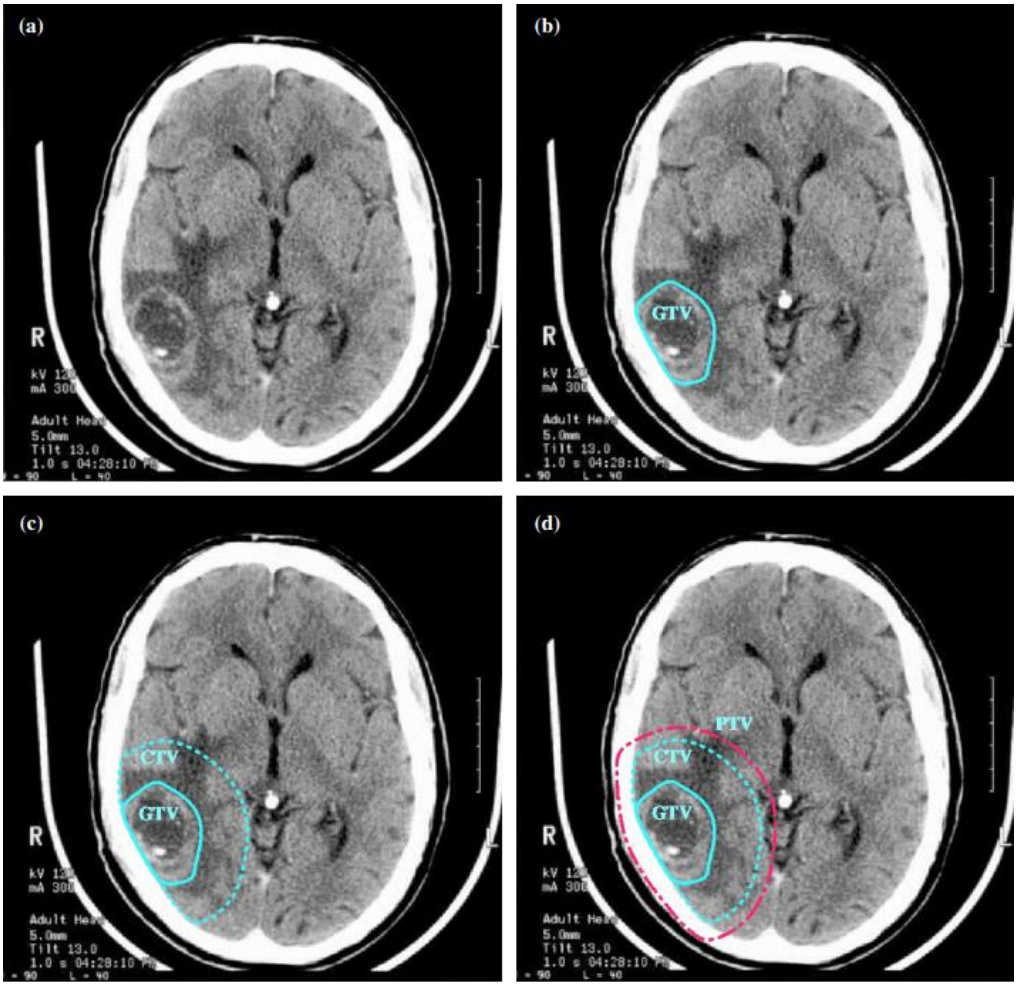

Figure 3 Planning CT showing the visibility of GTV, margin for microscopic spread of the tumor (CTV), and marginal PTV (Burnet et al.).

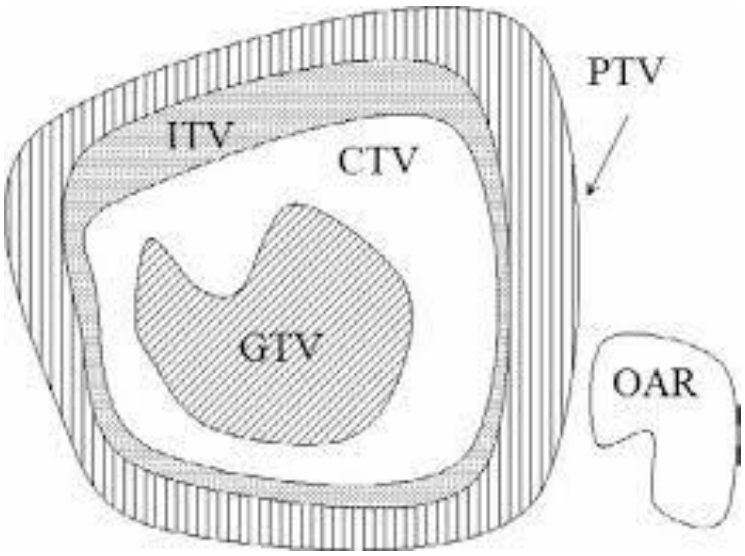

Figure 4 illustrates the structure definitions and their schematic locations inside treatment area.

Absorbed dose effect to the destination tissue is reflected in cells survival fraction. That means the relationship between the fraction of cells that remain reproductive and healthy when radiated, to the total seeded cells with dose. This relationship is illustrated by a most frequently used quadratic model. The cell survival is characterized by two tissue specific parameters that are known to depend on dose of the beams and the biologic properties of the target tissue. Equation (2), illustrated as

$$SF = \exp(-\alpha D - \beta D^2) \quad (2)$$

shows the relation between tissue parameters, dose, and Surviving Fraction (SF), and is called the Linear Quadratic model developed by Kellerer and Rossi. Equation (3), using tissue parameters and dose, characterizes the biologic effect as

$$\varepsilon = \alpha D + \beta D^2. \quad (3)$$

Biologic Quadratic model indicates that the biologic effect of a particular beam depends on the dose and the tissue parameters of the target cells. As a result, it is more desirable to

optimize the biological effect instead of the dose alone when optimizing the treatment plan. Such methodology is important in the sense of effectiveness of the treatment and sparing the organs at risk. Later the biologic effect relationship is used to define the RBE model.

Beam Weights

Intensity of proton beams is modulated to form a homogenous dose distribution throughout the tumor volume in IMPT planning. This is done by multiplying specific optimized weights for every voxels in the corresponding dose for that voxel. These weights are referred to as Wj which denotes the relative fluence weight of beam spot j. That means the contribution weight of the beam spot j to the total dose contribution to the destination voxel.

Dose Dependency

RBE depends on the dose per fraction of the beam. As mentioned before, in several studies, it is observed that RBE changes when dose changes. As a result, dose is a variable factor that effects on RBE value of the beam. To monitor the variabilities of RBE inside the target volume and OARs, RBE for every volume unit should be calculated since the dose distributions are calculated in every voxel, when treatment plans are optimized. In this study, RBE for the target tissue and the organs at risk for the three models is calculated for every voxel. For this matter, the dose contribution of every beam spot to every voxel in IMPT plans should be known when RBE for every voxel under radiation is calculated.

Linear Energy Transfer

The biologic response of the target cells to the radiation depends on the energy spectra of the radiation at the target. Basically, the effect is sensitive to the amount of the energy that the beam is delivering to the target while passing through it. Such effect is characterized by Linear Energy Transfer (LET) also known as Radiation Quality. LET is the amount of energy the beam transfers to voxel of the target volume, per distance unit. LET depends on the entrance energy of the beam, and is related to the type of tissue it is passing through. LET of a particular beam with respect to a cell line, can be determined by experiment. Many experiments are conducted to see the biologic response of specific cells when LET changes. This type of experiments provide important information regarding the behavior of α and β with regard to increase of LET. More on this topic is provided when Guan's experiment is discussed.

After knowing the tissue parameters' relationship with LET, Monte Carlo simulation or analytical approached can be used to determine the LET of the beam under study. Wilkens and Oeflke developed an analytical model for calculation of proton LET distribution, considering the initial beam energy and the initial energy spectrum. This method is a fast method to be used in RBE calculations (Jan J. Wilkens and Uwe Oelfke). Since the target volume is divided by three dimensional unit cubes (voxels), the linear energy transfer of the beam for every volume unit should be known. We used Monte Carlo simulation to spatially determine the LET of each beamlet for each voxel. Then, LET and dose calculation method presented in Wilkens and Oeflke's paper , shown in equations (4) and (5)

$$D_i = \sum_{j=1}^{N} D_{ij} w_j \ . \quad (4)$$

are used to determine the total dose (D_i) in voxel i, and the total dose averaged LET in voxel i from beam spot j (L_i) (Jan J. Wilkens and Uwe Oelfke "Optimization of Radiobiological Effects in Intensity Modulated Proton Therapy"). In the above equation, w_j denotes the "relative fluence weights" of beam spot *j*, when we consider N beam spots, and D_{ij} denotes the dose contribution to voxel *i* per unit fluence of beam spot *j*. D_i then will be the total dose in voxel *i*. The total dose-averaged LET in voxel *i* is given as:

For $D_i > 0$,

$$L_i = \frac{1}{D_i} \sum_{j=1}^{N} L_{ij} D_{ij} w_j . \quad (5)$$

Dose Volume Histogram

In radiation therapy, dose distributions are generated in a computerized treatment planning systems. In such systems, three dimensional dose distributions are the reconstruction of a CT scan from the patient. The dose volume histogram can be used in differential DVH or cumulative DVH types. DVH is generated by determining the size of the dose bins of the histogram, then the cumulative DVH is plotted when dose bins are shown along the horizontal axis, and the high of the bins represent the volume of the structure that is receiving that dose or higher. The volume can be the target volume or normal tissues. In fact DVH relates the radiation dose to tissue volume and summarizes 3D dose distributions in a two dimensional format. Usually a dose volume histogram includes all of the structures in one plot and each structure is shown with a different color than the other ones to demonstrate the shape and the percentage of the volume that is

under the shown dose of radiation (the vertical axis usually shows the fraction of volume rather than the absolute volume).

DVH is a strong tool used to observe and analyze the dose to volume. However, because the purpose of DVH is to show the 3D dose distribution in a 2D histogram, no spatial information is provided in it.

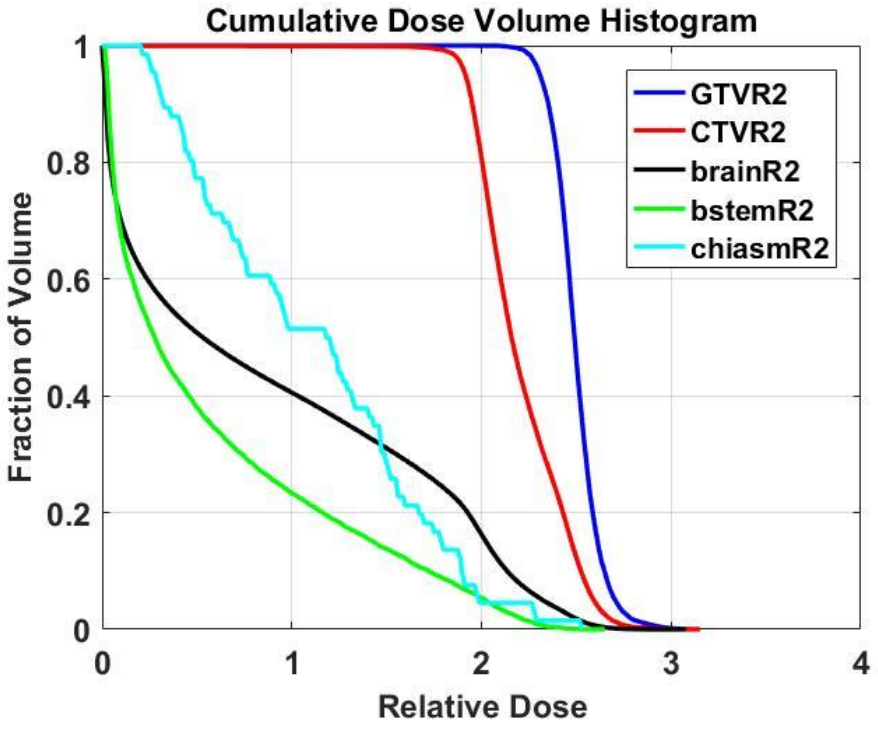

Figure 5 Cumulative Dose Volume Histogram of a radiation for five different structures, representing the RBE*Dose with respect to fraction of volume.

Dose volume histograms are widely used in this study as the measurement tool for determining the differences between every scenario including comparisons between different RBE models for same patient, and between the RBE*Dose values when tissue parameters are changed to observe the sensitivity of a model. The reason for choosing

DVH as our measurement tool is that the data from the calculated values of RBE and Dose*RBE is so large in amount even for one scenario itself, that the comparison between scenarios would be extensively hard if not impossible. On the other hand, DVH provides us with useful illustrations of the driven data and makes comparisons and conclusion significantly easier. Furthermore, it provides the benefit for us to see the meaningful differences and trends quickly.

3.2.2 Study Steps

In this study, we aimed to investigate the impact of recently developed RBE models on intensity modulated proton therapy (IMPT) treatment plans. The difference between variable and constant RBE weighted doses in retrospectively selected proton patient cases is demonstrated. The uncertainties in RBE model parameters in the same patient cases are also analyzed. To deliver the mentioned goals, three brain tumor cases are chosen from the brain cancer patients who have received IMTP and clinical treatments. The tumor volume location information and the prescribed dose information that was calculated based on constant RBE for the three patients is exported. To achieve a treatment plan in which the biological effect is optimized rather than the physical dose alone, three dimensional LET and RBE values should be calculated first, so that the RBE values are determined based on dose and LET values that are specific to each voxel. Using all planning target volume information and OARs definitions, and the dose contribution of each beam spot to each voxel (calculated using Monte Carlo Simulation), the total dose for every voxel and dose averaged LET is calculated. In the next step, RBE and RBE*Dose for both of the variable RBE models for every patient are calculated. The differences are illustrated using cumulative dose volume histograms. The sensitivity of

two variable RBE models to tissue parameters both for reference radiation and proton beams changes is studied and shown in multiple DVHs.

3.3 RBE Models

3.3.1 Choice of RBE Studies

The rationale for anticipating a variable RBE model and making efforts to develop one is based on the presumed practicality of optimization of treatment plans implementing calculated variable RBE. That means when modeling the biological effect, we have in mind that the model should be quick to calculate, and low in uncertainties. However, up to recently, the uncertainties have been an unavoidable part of the journey toward developing accurate RBE models. The limited availability of reliable data is due to limited beam access for researchers, different experiment configurations, machine calibrations, and differences in reporting the results. Moreover, conducting such experiments are time consuming. Although RBE models are being developed even with limited data, delivering accurate models to estimate RBE behavior with lower levels of uncertainties requires that more study be done on the proton beam RBE. As of now, one of the most wide accepted RBE models is suggested by Wilkens and Oeflke which is called the phenomenological model by the authors. This model presents a simple RBE formula based on biologic effect quadratic model. The goal behind delivery of the phenomenological model was to provide a model that can be quickly calculate RBE, while incorporating all of the influential factors on the RBE such as dose, LET, and tissue specific parameters. In the mentioned study (J. J. Wilkens and U. Oelfke), it is discussed that the optimization of treatment plans based on variable RBE should be done within a time that is applicable by clinical frameworks. Since the treatment plans are optimized

right before the treatment delivery, the presence of the patients and their wait time in the facility, as well as time and computational resources can be a concern. Therefore, providing a model that can consider variable agents that affect RBE without over complicating the calculations seems to be the appropriate approach to take. As a result, Wilkens and Oeflke's model that now we call it vRBE-Wilkens, is naturally the often accepted model. However, the data used to model the biological response of tissue to proton beams is not focused entirely on proton beams especially in the ranges of interest. As a result, the model might not reflect the actual values for RBE due to the conclusions made based on that limited data. On the other hand, although vRBE-Wilkens has its own disadvantages that we will discuss further in detail later in this section, it is chosen as a measure that the RBE model based on Guan et al experiment will be compared against. The values and behavior of vRBE-Wilkens when tissue parameters change, or simply the RBE values compared to another RBE is also interesting to assess.

Our other choice of RBE is one delivered based on vRBE-Wilkens model but with a number of modifications. Such modifications are decided to be made, as a result of a recent study done by Fada Guan and his team. Guan et al has experimented proton beams on cancer cells to determine the response of the tissue to known LET. The newly available data provided us with the opportunity to examine new RBE models or extensions of the existing ones.

3.3.2 Wilkens' Method for Calculating the Variable RBE

Wilkens and Oelfke proposed a model for RBE calculation which was designed to calculate RBE values based on Dose, LET, and tissue parameters while keeping the formula simple (J. J. Wilkens and U. Oelfke). This model is defined as a simple and fast

calculation method for RBE. This study is especially conducted to provide a quick approach to estimate RBE in inverse treatment planning for proton therapy when the integration of RBE into the optimization process is desired. It should be noted that α, is defined as a function of LET within the relevant range of 0-30 KeV/μm, while β is considered constant and equal to β_x. This assumption is based on available experimental data, which showed that β is invariant with regard to LET values. The results from calculations based on this model is in good agreement with experimental data, however, as mentioned by the authors, this agreement might be the result of using the same experimental data, both for comparison, and for fitting the tissue parameters. The linear quadratic model of surviving fraction is used to characterize the biological effect based on α and β. The RBE definition is based on the fact that the biological effect of the two radiations, which are proton beams and X radiation here, are the same. That means, both radiation are causing same biologic effect on a same tissue. On the other hand, the biological effect formula proposed in (J. J. Wilkens and U. Oelfke), describes the biological effect as a function of dose and tissue parameters. The phenomenological RBE is derived by considering two survival curves for two different radiation, as a function of dose for the same biological system. Since the definition of proton RBE is the ratio of the reference radiation dose to the proton dose that causes the same biological effect at the reference dose, if the two survival curves with different beams and same tissue type, be put together as equals, then a relationship between proton RBE, dose, and tissue parameters for both radiations is derived.

As the numerical dose values for the reference radiation is unknown when RBE is being calculated, using equation (6),

$$RBE = \frac{D_x}{D_p}. \quad (6)$$

Dx is substituted by RBE*Dp, in equation (7)

$$\alpha_X D_x + \beta_x D_x^2 = \alpha_p D_p + \beta_p D_p^2 . \quad (7)$$

The linear dependence of α on LET, and β value are then used to deliver the equation (8)

$$RBE\left(D_p, L, \alpha_0, \lambda, \alpha_x, \beta_x\right) = \frac{\sqrt{\alpha_x^2 + 4\beta_x D_p\left(\alpha_0 + \lambda L + \beta_x D_p\right)} - \alpha_x}{2\beta_x D_p} \quad (8)$$

to calculate RBE values. The value for $\alpha 0$ had then to be determined. To do so, Wilken et al. approximated $\alpha 0$ with equation (9), as

$$\alpha 0 = \alpha x - 0.5 . \quad (9)$$

The final RBE formula to calculate RBE values based on dose, tissue parameters, and LET is demonstrated by equation (1), as

$$RBE = -\frac{1}{2D_p}\frac{\alpha_x}{\beta_x} + \left[\frac{1}{4D_p^2}\left(\frac{\alpha_x}{\beta_x}\right)^2 + \frac{1+\frac{\lambda}{\alpha_x}(L-0.5)}{D_p}\frac{\alpha_x}{\beta_x} + 1\right]^{\frac{1}{2}} .$$

(10)

Equation (8) shows the developed RBE equation. Since Frese and Wilkens considered the α_0 to be determined using equation (9) in another study(Frese et al.), when implementing this relationship to RBE function, the equation that is used in our study for calculating RBE values is derived.

Wilkens and Oeflke used the results for linear quadratic parameters for the survival of V79 Chinese hamster cells *in vitro*. The experimental data that is used to determine the dependence of β on LET, was inconsistent and included a large amount of uncertainty according to the authors. The relationship could not be determined at some

LET values due to unavailability of information in that areas. Also, since the experiments were conducted using different cell types, and various experimental configurations, and because not all the mentioned experiments used proton beams as the radiation, no meaningful relationship could be developed from experimental data. Besides, results from experiments demonstrated a rather constant value for β which is decided to be assumed equal to reference radiation β_x.

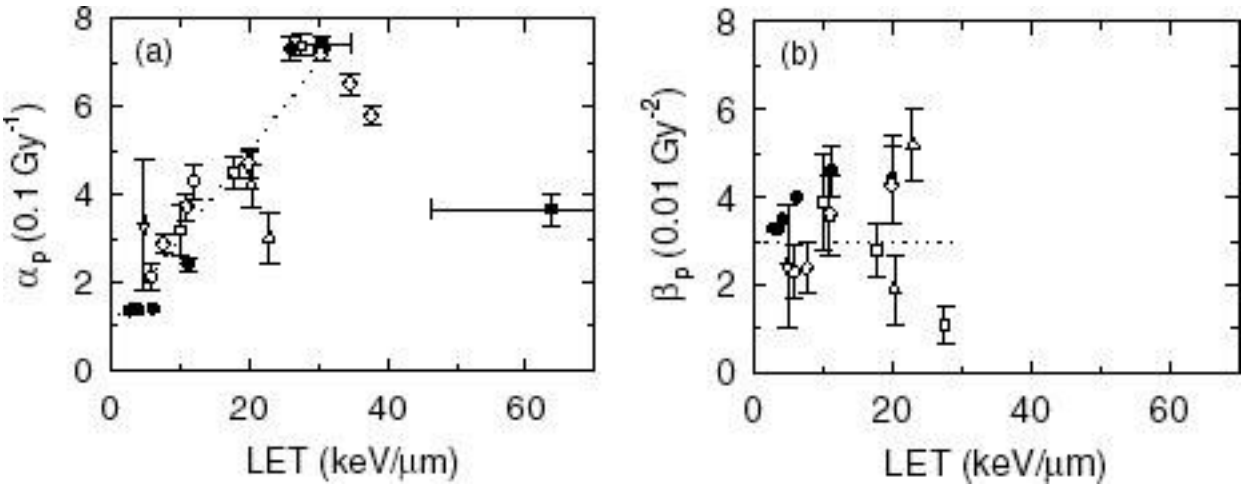

Figure 6 Experimental results for the LQ parameters for survival of V79 Chinese hamster (J. J. Wilkens and U. Oelfke).

For higher LETs (above 10 KeV/μm), α and β behavior is not clearly known, but for lower LETs, the tissue parameters' relation with LET is considered to be accurate in Wilkens and Oeflke's paper, in which it is found that the RBE is higher for lower doses, independent of LET. However, the authors argue that this results pertain to doses above 1 Gy, and below 10 Gy, and for OARs when the dose is very low, the behavior of RBE is not known.

3.3.3 Guan et al. Experiment

Proton relative biological effectiveness is yet to be determined by experiments and as mentioned before, one of the obstacles in the way of developing accurate RBE models, is the lack of accurate experimental data. However, even with high uncertainties in available data, much efforts are being done to model RBE, and while new models are considered every day, radiation technology is improving as well. With newer beam delivery techniques being used more and more every day, radiation therapy becomes more precise and uncertainties are decreasing. The new scanned beam delivery method is used in Guan et al experiment to map the biological effectiveness of protons in space. Guan argues that former methods for mapping variations of biology effectiveness such as high dose per fraction, and passive scattered beams are time consuming and the results driven when using the mentioned methods are inconsistent with large uncertainties tied to them. Therefore, Monte Carlo modeling and clonogenic survival assays are used to determine the biological effectiveness of proton beams with high accuracy and minimized uncertainties.

Guan et al. compared the two delivering methods: passively scanned, and scanned beams at three matched locations along the beam paths and found substantial differences between the two delivery methods. Passively scattered beams introduce significant uncertainty in the relationship between biological effects and LET due to the broad energy spectra of these beams and particularly, the long low-energy tails.

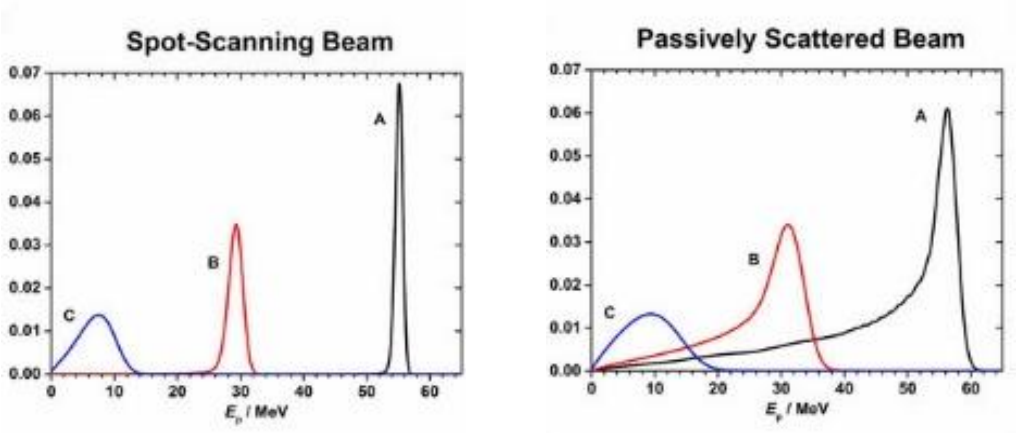

Figure 7 Comparison of passive scattering beams and actively scanned beams energy spectra (Guan et al.).

A customized device based on Monte Carlo models is designed that shifts the range of the radiation in a stepwise manner (consisting of 12 steps), and delivers different combinations of dose and LET to samples. Radiation delivery is done using actively scanned monoenergetic proton beams, and high throughput clonogenic assays of non-small lung cancer cells are used to reduce the uncertainties imposed by beam delivery method, and biological uncertainties caused by counting and plating. Moreover, minimum number of counting steps for a clonogenic assay is used in an attempt to remove complicating biological processes from readout of the colony formation. One radiation is designed to deliver the dose to all of the samples at the same time to reduce the experimental configuration uncertainties and data noises. 96-well plates were used for this experiment.

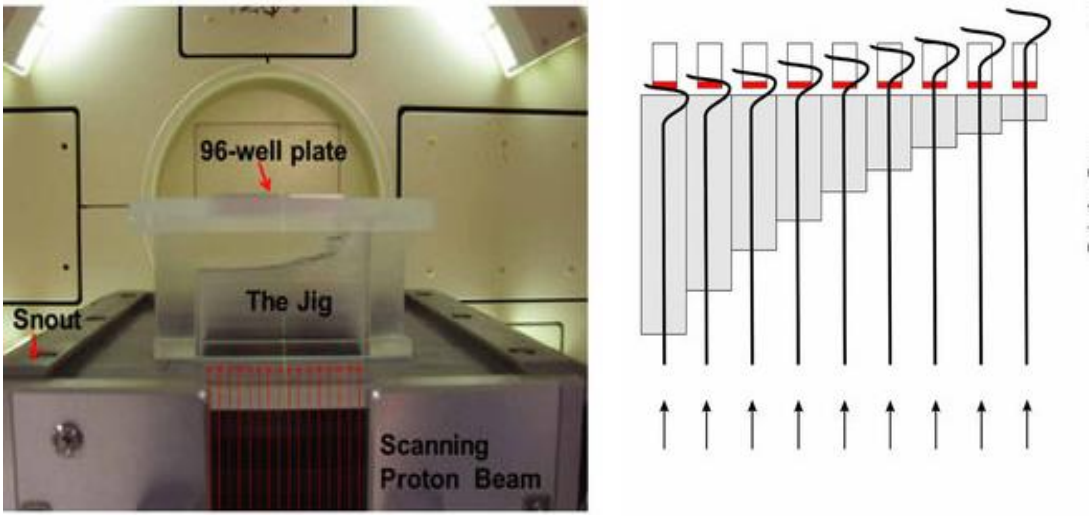

Figure 8 The device (Jig) and a schematic illustration of how the jig reduces the energy in a stepwise manner (Guan et al.)

Although this experiment provides extremely important data regarding proton biologic effectiveness, because the device ended up over sampling the low LET points (5-10 KeV/µm), and under sampling Of higher ones, later when we fitted this data, the distance between data points in higher LETs were rather long. Therefore, tissue parameters' dependence on LET was not shown very precisely by the fitting. However, the information is enough to model the relationship and use the dependence function to calculate RBE values.

One interesting finding from Guan et al. experiment was that a nonlinear increasing trend was observed at points with high LET values. This is new compared to former experimental results which considered α to be linearly dependent to LET, and β to be constant and independent of LET. The fit results shown a linear dependency for β to LET from low LET points up to 10.8 KeV/µm, then the trend shows a nonlinear relationship.

Such differences in experimental data when used to calculate RBE values, would cause significant differences, as the calculations for RBE models done for three patients reflected such differences. Furthermore, not only different relationships are used, but also β is changing with LET. Later in this chapter, the results are discussed with reference to the characteristics of the tissue parameters relationship with LET.

As Guan et al suggested in his paper, direct comparison between studies are difficult and may not be valid due to inherent differences in experiments. However, while other studies reported a linear relationship between LET and RBE, the results from Guan's experiment and his team show a nonlinear relationship. Since previous studies used an average over broad ranges of passively scattered beam for LET values, the derived data can yield the same average spectra with different energy and LET values. The results from our calculations agree with Guan et al. It is not surprising as we used the data from this experiment to model RBE.

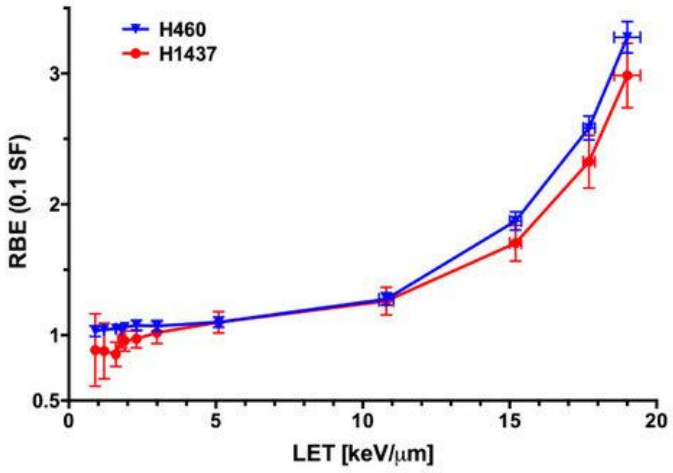

Figure 9 RBE vs. LET plot of the Guan et al experiment results (Guan et al.). Blue and red lines show two similar types of cell lines' results for comparison.

Oversampling in lower LETs and under sampling of higher LET points is clear in the table 1 (Guan et al.). However, even with this data points, the sudden increase of RBE in last three data points is apparent.

Table 1 Alpha, Beta, and LET averages as the ultimate result of Guan et al experiment (Guan et al.).

Table 1 | α and β fit parameters and RBE values at 10% surviving fraction.

Cell line:		H460			H1437	
LET [keV/μm]	α	β	RBE	α	β	RBE
0.9	0.268	0.097	1.03	0.077	0.028	0.89
1.2	0.226	0.112	1.04	0.136	0.020	0.88
1.6	0.151	0.134	1.05	0.067	0.027	0.85
1.8	0.150	0.134	1.05	0.059	0.038	0.98
1.9	0.166	0.134	1.06	0.094	0.031	0.96
2.3	0.137	0.146	1.07	0.096	0.032	0.97
3.0	0.206	0.125	1.07	0.111	0.033	1.02
5.1	0.117	0.159	1.10	0.034	0.052	1.10
10.8	0.318	0.154	1.28	0.119	0.054	1.26
15.2	0.446	0.341	1.87	0.180	0.095	1.70
17.7	0.596	0.662	2.58	0.328	0.149	2.33
19.0	0.883	0.956	3.28	0.360	0.272	2.98
Photons(^{137}Cs)	0.290	0.083	1.00	0.050	0.041	1.00

The trend of α values against LET, fluctuates to higher and lower values when LET is low, and then starts to increase considerably with a steep rate, and finally shows a nonlinear increase when LET increases. On the other hand, β values hardly fluctuate at low LETs, and the sudden change in increase rate and trend occurs after LET = 10.8 KeV/μm.

Delivering The RBE Model Based on Guan et al Study

The radiobiological model suggested by Wilkens and Oelfke (J. J. Wilkens and U. Oelfke) defines the biological effect as function of dose and tissue parameters, which was demonstrated in equation (3). As mentioned before, while calculating RBE, the biological effect for both reference radiation and proton beam are the same for the same tissue. That means α_p, β_p, and D_p will have the same ε as α_x, β_x, and D_x. Knowing this, the right hand sides of both equations can be considered as equal, and we can demonstrate the relation between the reference beam parameters and the proton beam parameters as the equation shown below, with α_x , α_p, β_x, β_p, D_x, D_p as variables. As of the total available data, α_x, β_x,

and D_p are available, and α_p and β_p are derived from the experiment outcomes. We are missing values for D_x, however, since the purpose is to find a formula for RBE, equation (7) is used to replace D_x with RBE*(D_p).

D_X denotes the absorbed dose of the reference radiation (Cobalt 60), and D_P shows the absorbed dose of the proton beam in equation (7). In subsequence, the goal is to propose a function for RBE based on proton dose, LET, α_x and β_x as input; α and β for proton beam are fitted with their corresponding LET values to achieve the relationship between tissue parameters and LET as the variable in the form of quadratic functions. It should be noted that the values seen in table below are the averaged value of minimum and maximum values for the parameters. The average is calculated by the author for ease of use. Although the average values for tissue parameters are used now, later in this study, upper and lower limits of the parameters will be considered and used to examine the sensitivity of RBE when calculated based on the new proposed model.

There is a sufficiently broad range of software that can be used for fitting the data. For now Excel is used to primarily fit the data and see the progress and report primary results. First a quadratic relationship was fitted with the data and the results is shown in figures below. However, after evaluating the results for the first patient using a quadratic relationship for tisuue parameters, we decided to use a linear relationship for the LET values below 10.8, and consider a quadratic fit for the high LET values. Such approach would better reflect the behavior of α vs. LET, and β vs. LET functions. Also, since we are using Wilkens' RBE model for comparison, it would be more reasonable to use a linear relationship for lower LETs where Wilkens has justified data to assume linear relationship for α, then use the quadratic relationship for the rest of the data points where

the difference between Guan et al experiment results and other experiment results is significant and stands out.

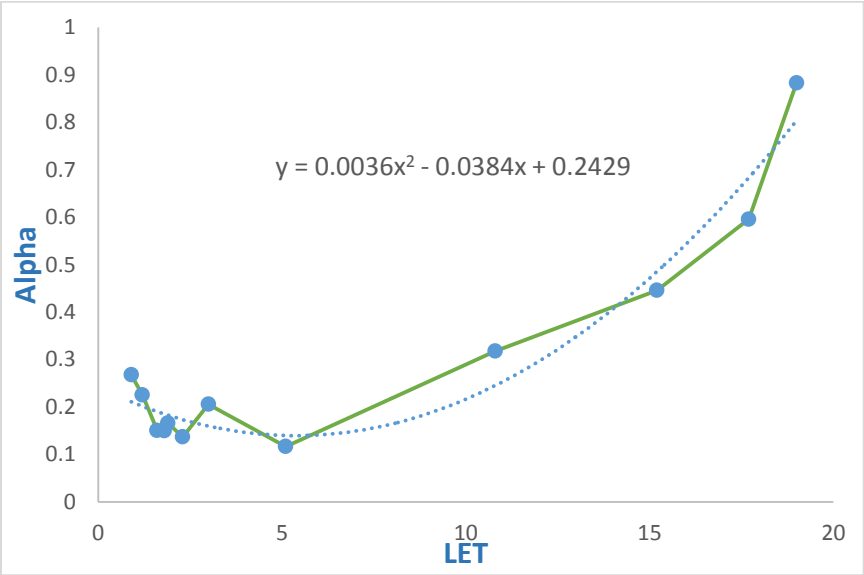

Figure 10 Quadratic fit for the relationship between Alpha tissue parameters and LET.

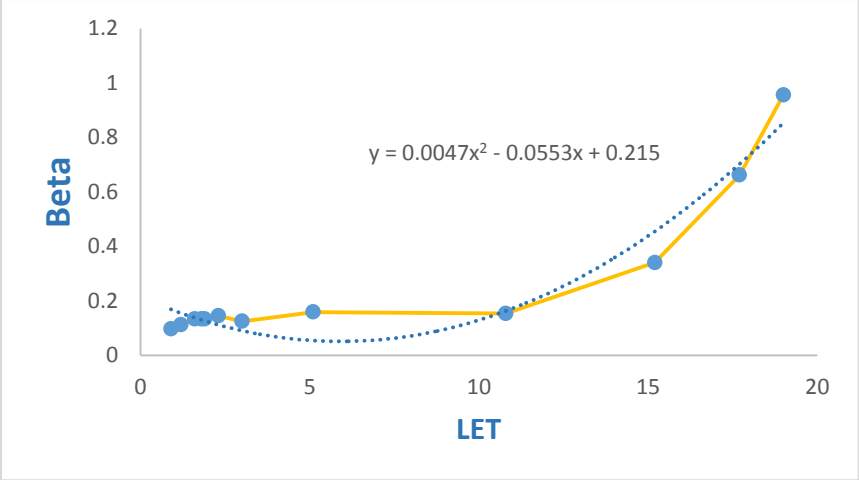

Figure 11 Quadratic fitted relationship to model the relationship between Beta values and LET

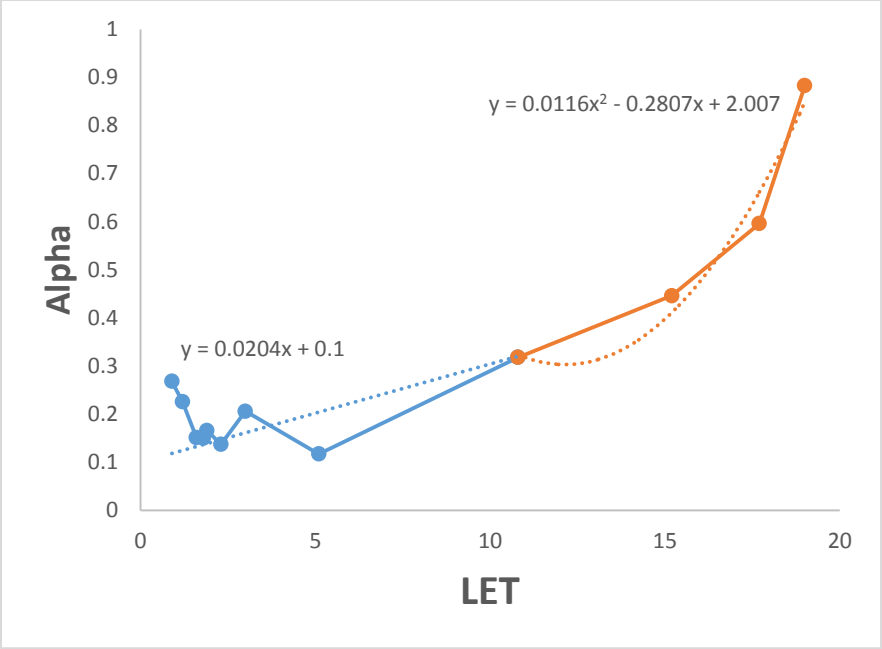

Figure 12 Linear fit of Alpha parameter vs. LET for lower LET values, and quadratic relationship considered for higher LET values

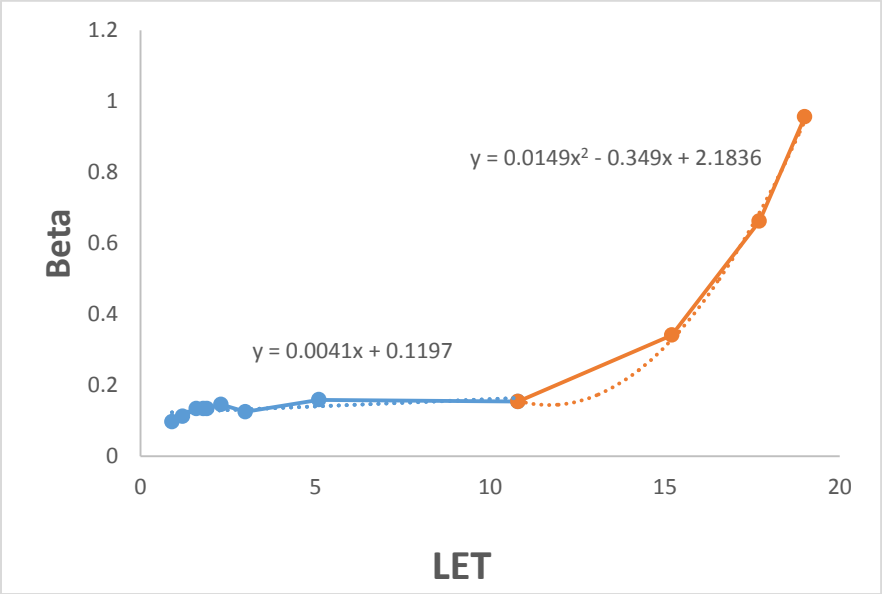

Figure 13 Linear fit of Beta parameter vs. LET for lower LET values, and quadratic relationship considered for higher LET values

The multiplying coefficient is used exactly as calculated in the fitting and as shown in the figure, however, for linear parts of the tissue parameters, the starting points are scaled and moved along the vertical axis to accurately correspond to the organ information that are used to calculate RBE and dose.

For different organs, tissue specific parameters for photons are used to determine the entrance point for the fitted curves. Moreover, since the parameters are different for OARs, using the photon parameters, the parameter for proton is adjusted. Table 2 includes the parameter information of photon beams for structures in this study. The presented table which was derived from Frese et al. paper (Frese et al.), includes accepted values for tissue parameters corresponding to photon beams.

Note that the structures for all three patients that are used for calculating RBE values include, GTV, CTV, brain, brainstem, and chiasm. The later three are the OARs.

Table 2 Tissue parameters for photons and average dose – volume statistics for target volume and organs at risk (Frese et al.)

Tissue	Endpoint	D_{50} (Gy)	γ	Reference	α/β (Gy)	α_x (Gy^{-1})	$\beta_x = \beta_0$ (Gy^{-2})	α_0 (Gy^{-1})
Nasopharyngeal cancer T1 and T2	Tumor control	57.0	2.7	14	10	0.1124	0.0112	0.1084
Nasopharyngeal cancer T3 and T4	Tumor control	70.5	2.5	14	10	0.0854	0.0085	0.0814
Subclinical disease	Tumor control	27.0	0.6	15	10	0.0554	0.0055	0.0514
Brainstem	Necrosis/infarction	65.1	2.4	14	2	0.0532	0.0266	0.0492
Spinal cord	Myelitis/necrosis	68.6	1.9	14	2	0.0407	0.0203	0.0367
Spinal cord (Schultheiss)	Myelopathy (cervical cord)	69.4	4.7	16	0.87	0.0577	0.0663	0.0537
Optic nerves	Blindness	65.0	2.3	14	2	0.0511	0.0256	0.0471
Chiasm	Blindness	65.0	2.3	14	2	0.0511	0.0256	0.0471
Eyes	Blindness	65.0	1.8	14	2	0.0407	0.0203	0.0367
Brain/temporal lobes	Necrosis/infarction	60.0	2.6	14	2	0.0620	0.0310	0.0580
Parotids	Xerostomia	46.0	1.8	14	3	0.0675	0.0225	0.0635
Parotids (Eisbruch)	Flow ratio <25%/1 y	28.4	2.2	17	3	0.1300	0.0433	0.1260
Parotids (Roesink)	Flow ratio <25%/1 y	39.0	0.9	18	3	0.0413	0.0138	0.0373
Inner ears	Sensori-neural hearing loss	50.0	0.7	19	3	0.0265	0.0088	0.0225
Middle-external ears	Chronic serous otitis	65.0	3.5	14	3	0.0915	0.0305	0.0875
Temporomandibular joints	Marked trismus	70.3	3.8	14	3	0.0918	0.0306	0.0878
Larynx	Laryngeal edema	80.0	1.2	14	3	0.0281	0.0094	0.0241
Trachea–esophagus	Clinical stricture	68.0	2.8	14	3	0.0708	0.0236	0.0668

RBE formula is derived by substituting α_p and β_p with the fit from the Guan et al data. Since the relationship is considered to be a two piece function, the calculation for that part of the equation is divided into two parts in the program (one for LET<10.8 KeV/μm, and one for LET ≥ 10.8 KeV/μm). It is important to note that the LET value of 10.8 KeV/μm corresponds to the Bragg Peak of the beam. This provides important information regarding the behavior of tissue parameters before, at, and after the Bragg peak. As we can see, the relationship between LET and tissue parameters at LET = 10.8 KeV/μm changes from almost linear with low steep, to a significantly nonlinear increasing trend. By inserting the fit values to RBE equation we have

For LETs < 10.8 KeV/μm (11)

$$\alpha_x(\mathrm{RBE})(\mathrm{D_p}) + \beta_x[(\mathrm{RBE})(\mathrm{D_p})]^2 = [0.0204(\mathrm{LET}) + 0.1614\,]\mathrm{D_p} + [0.0041(\mathrm{LET}) + 0.1197\,]\mathrm{D_p^2}\,.$$

and for LETs > 10.8 KeV/μm (12)

$$\alpha_x(\mathrm{RBE})(\mathrm{D_p}) + \beta_x[(\mathrm{RBE})(\mathrm{D_p})]^2 = [0.0116(\mathrm{LET}^2) - 0.2807(\mathrm{LET}) + 2.007]\mathrm{D_p} + [0.0149(\mathrm{LET}^2) - 0.0349(\mathrm{LET}) + 2.183]\mathrm{D_p^2}\,.$$

Therefore, RBE is calculated using as

$$RBE = \frac{-(\alpha_x)(D_p) + \sqrt{((\alpha_x)(D_p))^2 - 4((\beta_x)(D_p^2))(-Q)}}{2((\beta_x)(D_p^2))}\,. \quad (13)$$

The values for RBE, dose averaged LET are calculated using GAMS program. RBE*Dose values are calculated and plotted for every organ type in DVHs to be compared. Although the fit presented above is sufficiently accurate to be used in

calculations, more advanced fitting can help the accuracy of the estimations of tissue parameters based on LET. An example of a slightly better fit is shown. Specific software can also be used for this matter.

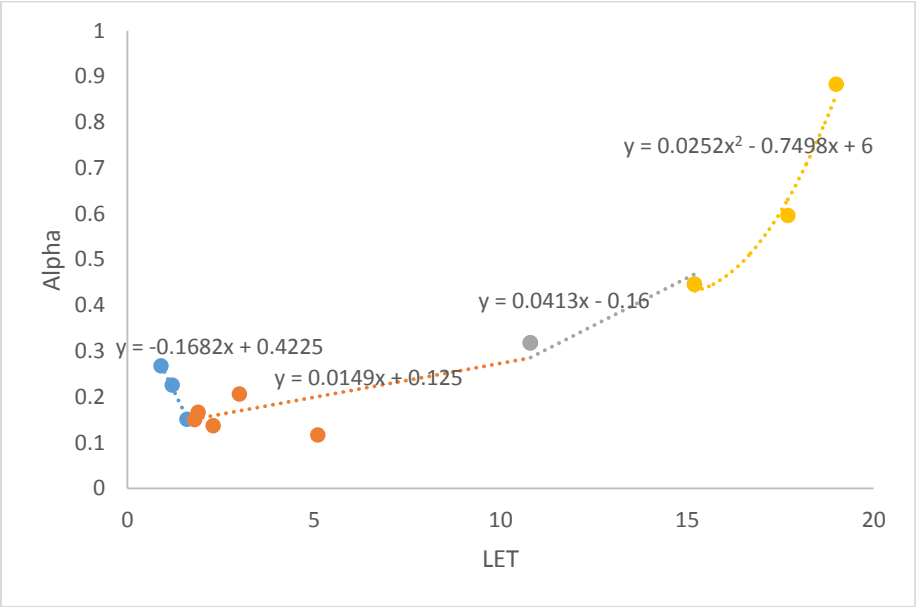

Figure 14 Fitted Guan et al. experiment data for α and LET, to piecewise linear and quadratic functions

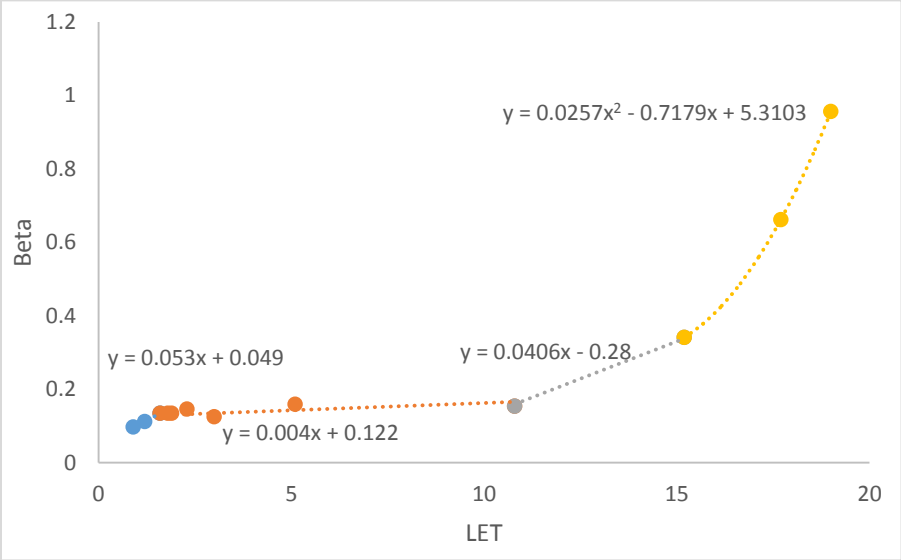

Figure 15 Fitted Guan et al. experiment data for β and LET, to piecewise linear and quadratic functions

The presented fitting method in figures 14 and 15, are not used in calculations in this study, and have the purpose of suggestion for future studies and fitting improvement. The necessity of a precise fitting method, is further underscored and discussed in next chapter, when the sensitivity of vRBE-Guan to fit parameters for α and β dependency on LET is analyzed.

Chapter 4

Results

When comparing RBE*Dose values using vRBE-Wilkens, vRBE-Guan, and constant RBE for the three patients, vRBE-Guan was observed to have significantly higher values than the other two models. Given the large deviation of the Guan et al experiment results from formerly available data on proton RBE, such difference was predictable. That means observing higher values for vRBE-Guan can be possibly due to implementing a variable β instead of a constant, or the increase of RBE vs. LET after Bragg Peak. The role of the β parameter can be significant especially because vRBE-Guan is compared against vRBE-Wilkens which modeled β as a constant value equal to β_x. Furthermore, the nonlinear increase of RBE vs. LET suggests that the calculated values should also be higher than usually observed trends. As discussed later in this chapter, the value of vRBE-Guan is highly sensitive to tissue parameters fluctuations. Please note that same method for developing RBE formula is used for both vRBE-Guan and vRBE-Wilkens, and the two models are only different in modeling the tissue parameters' behavior. Therefore, if the Guan et al experiment data is close to actual behavior of RBE in spite of former experiment data, given that the scanning beam delivery method is used in this experiment, and there are no other reliable data besides Guan et al results that models tissue parameters' relationship with LET, it can be concluded that this relationship may reflect RBE more accurately.

4.1 Calculated RBE Results

The cumulative RBE weighted Dose Volume Histograms of three RBE models for patient 1 are included and are followed by the DVHs for the other two patients. vRBE-Wilkens is referred to as R-Wilkens on the histogram using the dashed lines, and R-Guan shown by solid lines, corresponds to vRBE-Guan. Ultimately, R-constant plotted using dotted lines, demonstrates RBE*Dose for constant RBE. The three models are evaluated in more details as we move forward in this chapter. Colors blue, red, black, green, and cyan reflect the histograms for GTV, CTV, which correspond to PTV (planning target volume), and Brain, Brainstem, and Chiasm contribute to OARs (organs at risk) for all three tumor cases. As observed in the DVHs, the percentage of the target volume that receives the maximum dose, is almost 100% for GTV, and CTV, while this fraction decreases for other organs. The delivered dose to OARs should be the minimum dose possible for the normal tissues to be spared from damaging radiation. Therefore lower fractions of volume against relative dose is preferred.

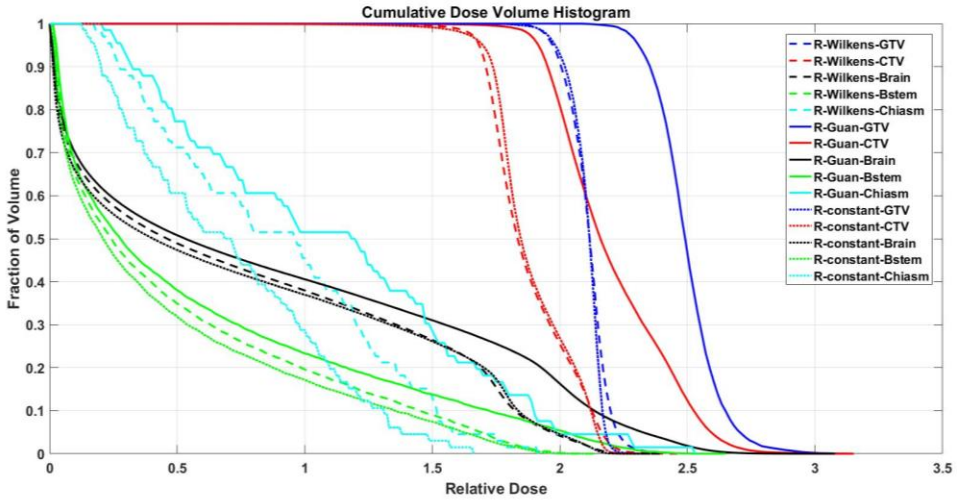

Figure 16 Cumulative RBE weighted dose volume histograms of three RBE model for patient 1. The dashed lines are used to show the vRBE-Wilkens, the dotted lines pertain to constant RBE, and the solid lines are used to demonstrate vRBE-Guan.

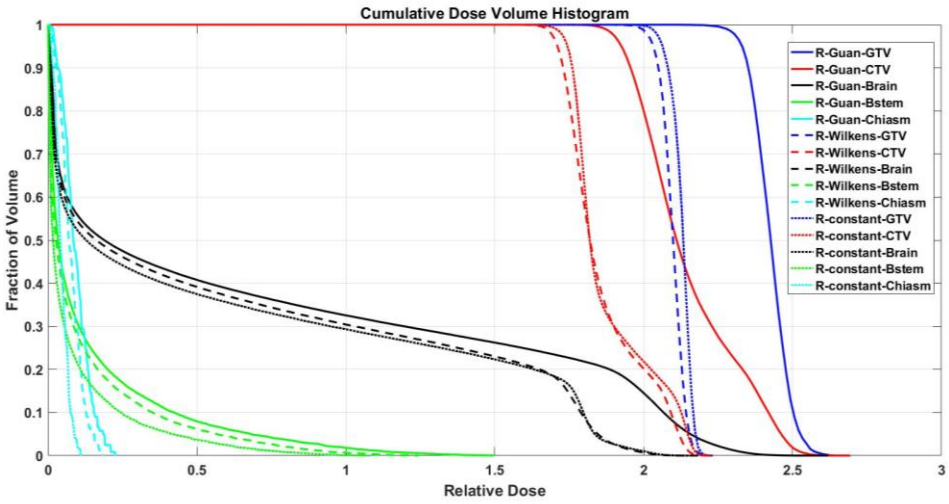

Figure 17 Cumulative RBE weighted dose volume histograms of three RBE model for patient 2. The dashed lines are used to show the vRBE-Wilkens, the dotted lines pertain to constant RBE, and the solid lines are used to demonstrate vRBE-Guan.

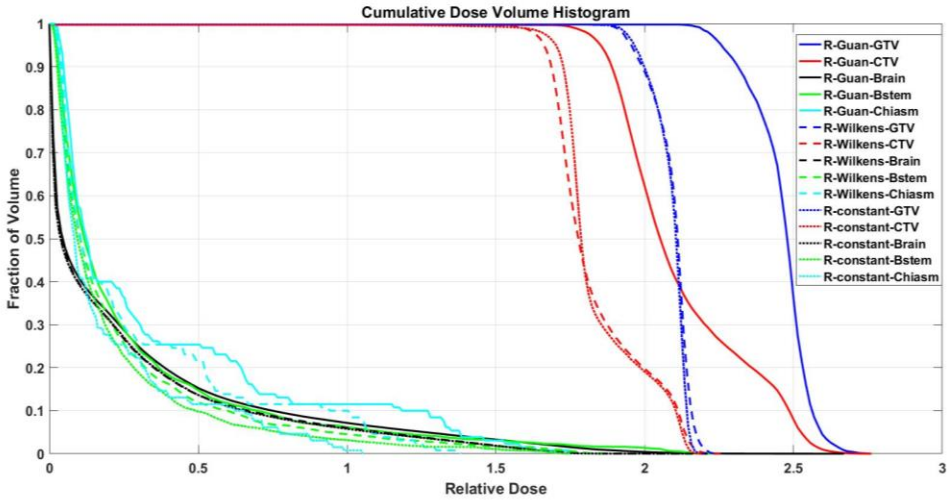

Figure 18 Cumulative RBE weighted dose volume histograms of three RBE model for patient 3. The dashed lines are used to show the vRBE-Wilkens, the dotted lines pertain to constant RBE, and the solid lines are used to demonstrate vRBE-Guan.

It is concluded form the DVHs, the RBE values highly depend on α_x, β_x, and tissue response to proton beams. Although the real RBE values for proton beams might not be as high as the calculated values in this study, the model effectively reflects the

Guan et al experiment results in the calculated RBEs. On the other hand, it should be considered that vRBE-Wilkens might not accurately or completely reflect the biological effectiveness of proton beams effects to the RBE values. Since tissue parameters for proton beam are highly approximated by the tissue parameters for reference radiation in vRBE-Wilkens model, the biological response of radiated tissue by proton beams are not fully present in the formulation, it is not surprising that the RBE values from vRBE-Wilkens are very close to 1.1 which is the assumed value of RBE.

We should also note that even though vRBE-Guan is based on only one study, Wilkens and Oeflke phenomenological model for RBE calculation with linear α and constant β is also a demonstration of the method based on limited data. In addition, similar studies were used to make conclusions regarding biologic response of the tissue as the ones that justified using a constant RBE. Even in those studies, the RBE of protons has an increase towards the end of the range.

4.2 Sensitivity Analysis

4.2.1 Sensitivity to α_x/β_x Fluctuations

α_x/β_x is the ratio of tissue parameters for reference radiation, which are photons in our case. In vRBE-Wilkens model, this ratio is used when calculating the RBE values. In order to observe the behavior of vRBE-Guan compared to vRBE-Wilkens when different cell types are used, the α_x/β_x ratio is increased and decreased by 10%, (also 20%, 30% for patient 1) and the RBE values are calculated based on both variable RBE modes respectively. vRBE-Wilkens is observed to be less sensitive to α_x/β_x changes.

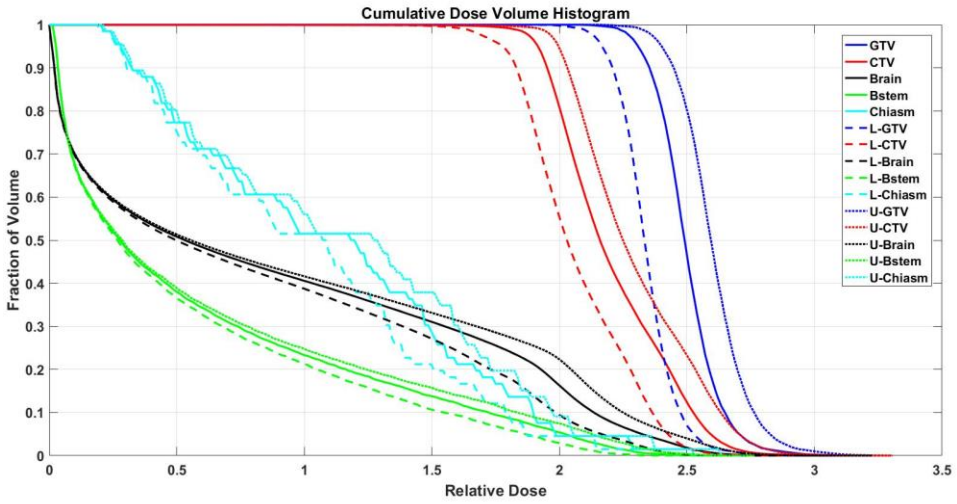

Figure 19 Sensitivity of vRBE-Guan to αx/βx ± 0.3 fluctuations – Patient 1. Dotted line demonstrates the upper 0.3, and dashed lines show the lower 0.3 limits.

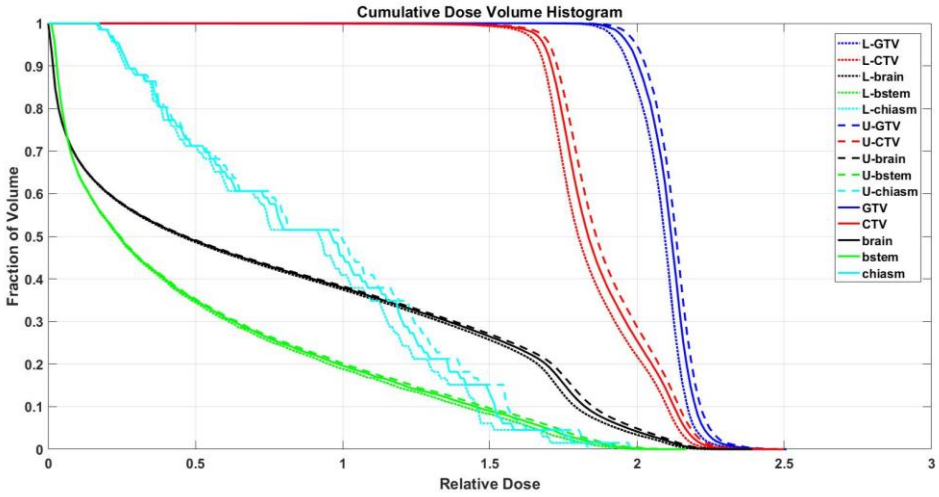

Figure 20 Sensitivity of vRBE-Wilkens' to αx/βx ± 0.3 fluctuations– Patient 1 .Dashed line demonstrates the upper 0.3, and dotted lines show the lower 0.3 limits.

RBE weighted dose volume histograms shown noticeable differences in the extent of the sensitivities of the two variable RBE models. For every patient, vRBE-Wilkens fluctuated less than vRBE-Guan. The underlying reason is related to the formulation of the two models. Considering the equation (10), the formula for calculating vRBE-

Wilkens, we can see that vRBE-Wilkens cannot change much if α_x/β_x changes because the ratio is only multiplied by the inverse of treatment dose, and square of inverse of treatment dose. That means this ratio is multiplied by a small number in the equation and therefore, the changes in tissue parameters for reference radiation (photons) does not cause significant changes to the RBE values. On the other hand, in vRBE-Guan RBE calculation formula, equations (13) and (14), since both tissue parameters for reference radiation are strongly present and are multiplied by dose and the square of the dose, as well as LET, the calculated RBE clearly has a high dependency on the ratio of the tissue parameters of both radiations. That means by looking at the equations for both high and low LET values, a direct relationship can be noted between reference radiation tissue parameters and dose, and proton beam tissue parameters and dose. Thus, the calculated RBE values' sensitivity to tissue parameter fluctuations is significant. This is also true for proton beam corresponding tissue parameters. The sensitivity of the RBE functions is also shown for the other two patients. Same trend is observed for all three patient cases in regard to sensitivity to α_x/β_x ratio. It is notable that calculated values for "Chiasm" show more sensitivity to α_x/β_x changes for patient 1. This might be caused by the location of the tumor volume with regard to Chiasm, but further investigations are anticipated.

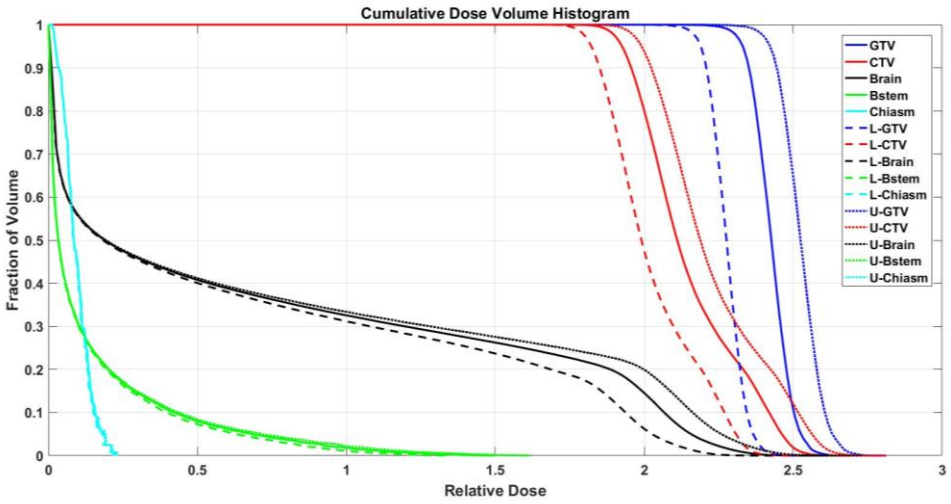

Figure 21 Sensitivity of vRBE-Guan to $\alpha x/\beta x \pm 0.3$ fluctuations patient 2. Dotted line demonstrates the upper 0.3, and dashed lines show the lower 0.3 limits.

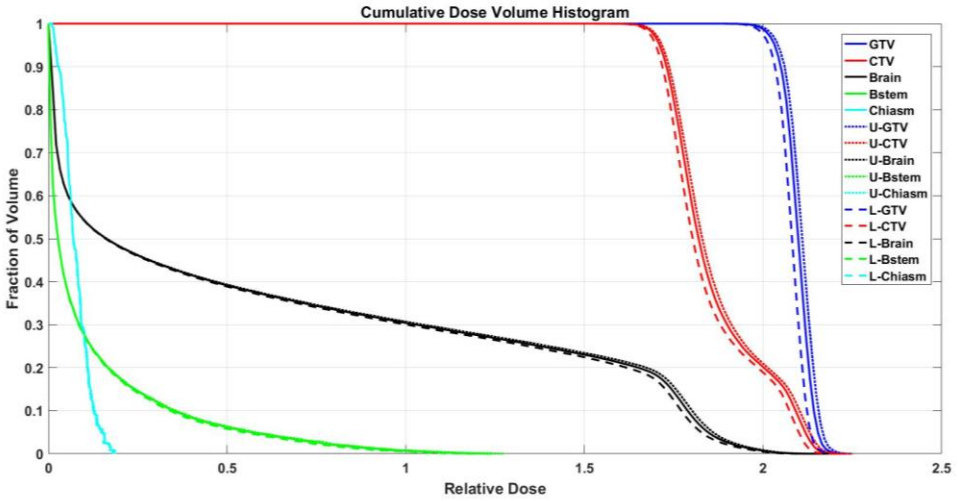

Figure 22 Sensitivity of vRBE-Wilkens to $\alpha x/\beta x \pm 0.3$ fluctuations patient 2. Dotted line demonstrates the upper 0.3, and dashed lines show the lower 0.3 limits.

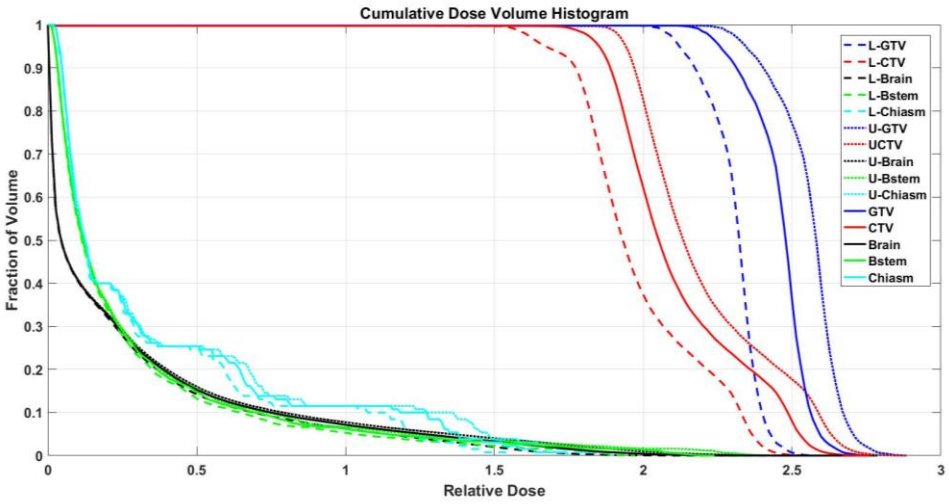

Figure 23 Sensitivity of vRBE-Guan to $\alpha x/\beta x \pm 0.3$ fluctuations vRBE-Guan patient 3. Dotted lines demonstrates the upper 0.3, and dashed lines show the lower 0.3 limits.

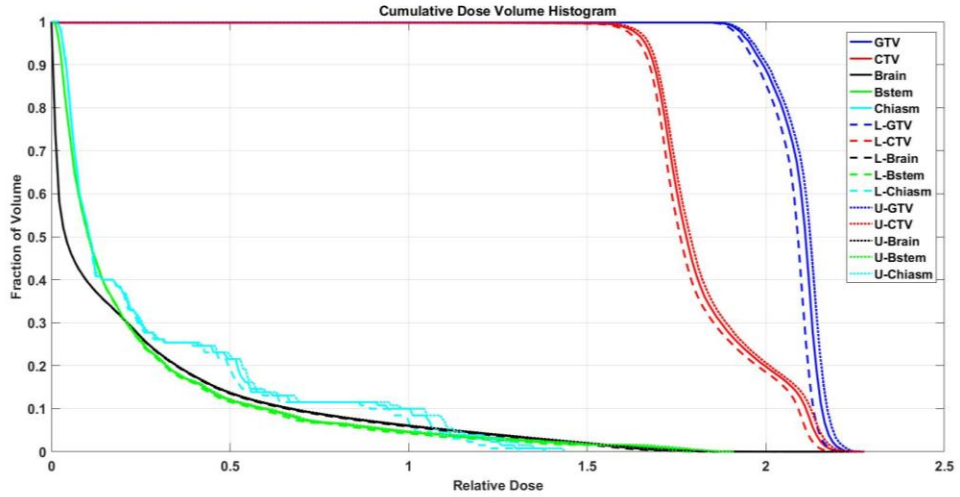

Figure 24 Sensitivity of vRBE-Wilkens' to $\alpha x/\beta x \pm 0.3$ fluctuations patient 3. Dotted line demonstrates the upper 0.3, and dashed lines show the lower 0.3 limits

The low sensitivity of vRBE-Wilkens to photon beam tissue parameters, can be an advantage when compared to vRBE-Guan high sensitivity to tissue parameter values. However, as discussed before, the formula of vRBE-Wilkens might not fully reflect the dependency of RBE values to tissue parameters. Therefore, the usage of vRBE-Wilkens

model should be re-evaluated for precision and accuracy, There might be an argument about the benefits of lower sensitivity vs. the extent of the contribution of the parameters to calculated RBE values. In addition to comparison of two variable RBE models for sensitivity to ± 30% change in α_x/β_x ratio, vRBE-Wilkens and vRBE-Guan are analyzed for the trend of changes if different amount of change occurred. To do so, values for two variable RBE models are calculated considering 20%, and 10% increase and decrease in α_x/β_x.

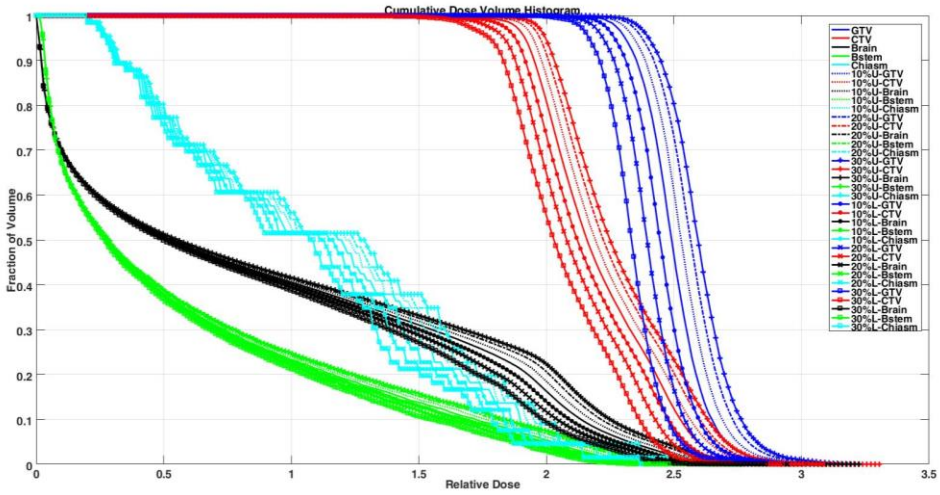

Figure 25 Calculated vRBE-Guan values for α_x/β_x ± 30%, 20%, and 10% for patient 1.

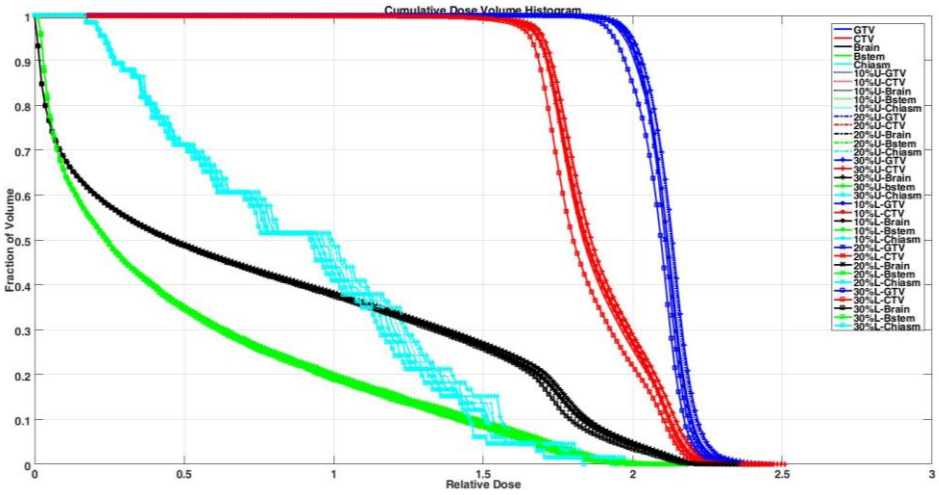

Figure 26 Calculated vRBE-Wilkens values for $\alpha_x/\beta_x \pm 30\%$, 20%, and 10% for patient 1.

A constant and linear trend for vRBE-Guan is observable when 30%, 20%, and 10% fluctuations in α_x/β_x are compared. On the other hand the corresponding fluctuations of vRBE-Wilkens are observed to be very little but nonlinear to the changes especially for PTV.

4.2.2 Sensitivity of vRBE-Guan to Fit Parameters

To observe and analyzed the sensitivity of the proposed model to proton beam tissue parameters, the fitting values (fit parameters) of α and β of proton are changed by 0.3 to monitor the behavior of the RBE function. The results and analysis for sensitivity are presented in following sections.

α Fit Parameters

α parameter of the proton beam demonstrated rather noticeable variability in lower LET values, and a nonlinear relationship with LET based on Guan et al experiment. Therefore, the fluctuations of α with regard to LET changes are important in

the sense of estimating the RBE values especially with expectation of high sensitivity to tissue parameters. Another reason to assess the sensitivity of RBE to α parameters is that since limited amount of data is available regarding proton biological effectiveness to different tissues, the tissue parameters are usually approximated by scaling and/or changing the starting point of the fitted function. Such methods for approximating tissue parameters include in evitable errors and uncertainties. Therefore, the sensitivity and tolerance of the RBE function should be analyzed to observe the effect of such probable errors. To monitor the variability of RBE when α changes, the values from fitting the tissue parameters are changed by 0.3.

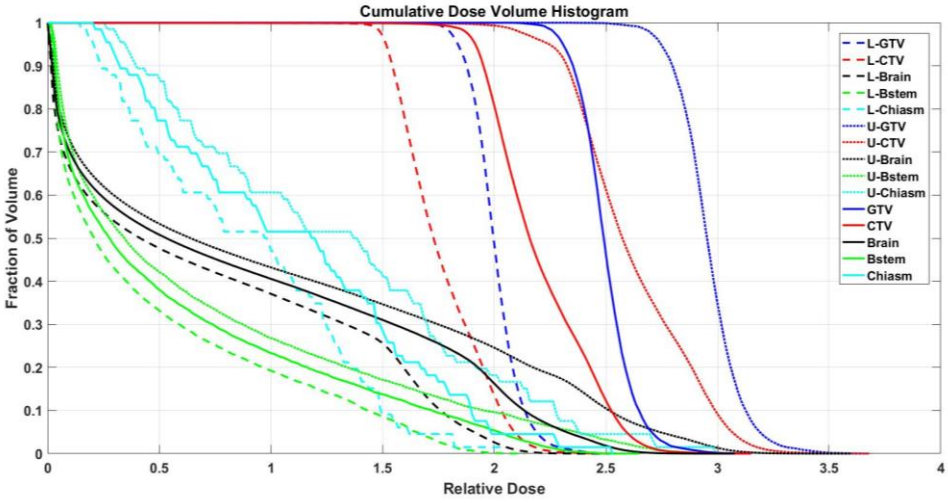

Figure 27 Sensitivity of vRBE-Guan to α ± 0.3 Vs. LET fit parameter 0.3 changes – Patient 1. Dotted lines correspond to increased alpha parameters, dashed lines show the effect of decreasing the alpha fit parameters, and the solid line shows the originally calculated RBE

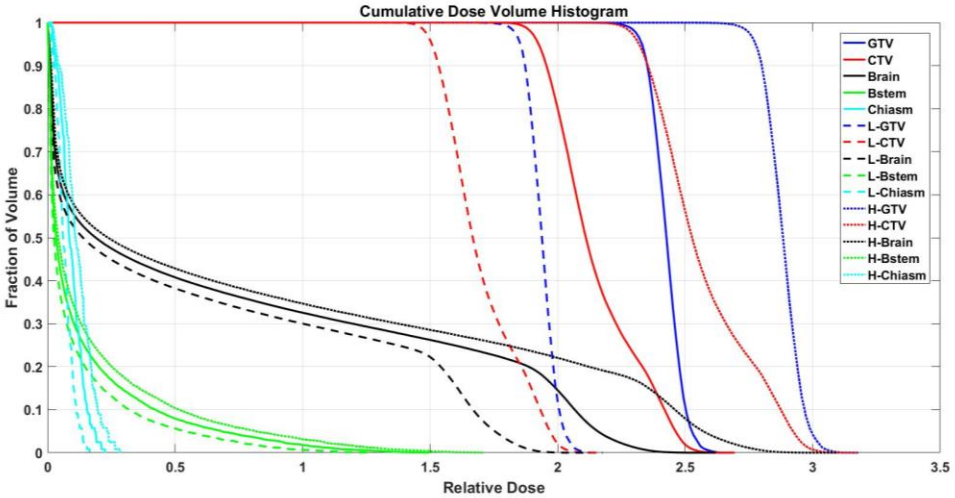

Figure 28 Sensitivity of vRBE-Guan to $\alpha \pm 0.3$ Vs. LET fit parameter 0.3 changes – Patient 1. Dotted lines correspond to increased alpha parameters, dashed lines show the effect of decreasing the alpha fit parameters, and the solid line shows the originally calculated RBE

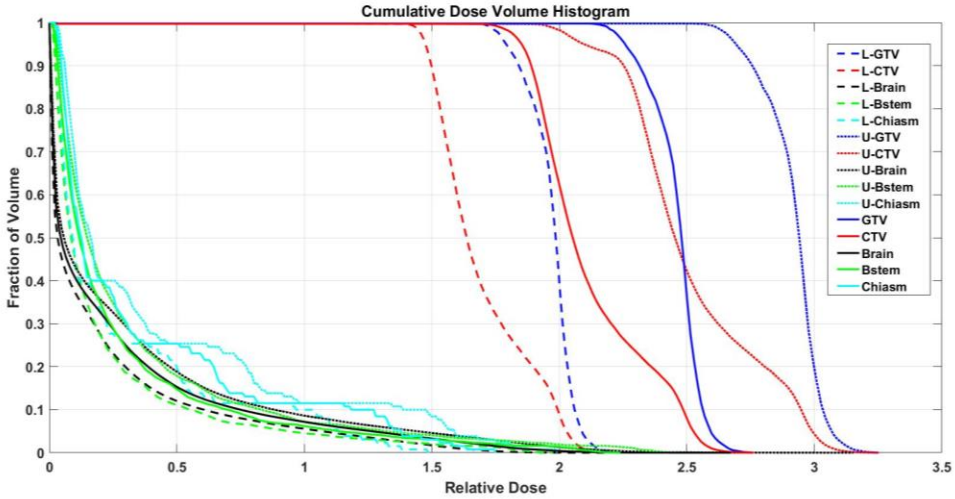

Figure 29 Sensitivity of vRBE-Guan to $\alpha \pm 0.3$ Vs. LET fit parameter 0.3 changes – Patient 3. Dotted lines correspond to increased alpha parameters, dashed lines show the effect of decreasing the alpha fit parameters, and the solid line shows the originally calculated RBE

The response of the vRBE-Guan to a 30% increase and decrease in α fir parameters is demonstrated in Dose Volume Histograms shown in figures 27, 28, and 29. vRBE-Guan shows a significant sensitivity toward α fit parameters fluctuations. The reason of such sensitivity is the linear and nonlinear relationship of α and LET. LET ranges from small values such as 1.5 KeV/μm to significantly higher values. When fit parameters for α are changed, the amount of change is multiplied by LET and D_p. Therefore the amount of change that is reflected in calculated RBE values are significantly high compared to the total absolute value of RBE. As LET increases, the deviation of the calculated α based on changed fit values from the original α and accordingly the deviation of RBE from its originally calculated values increases. As a result, the RBE shows a high level of sensitivity to α fit parameters. Also for Higher LETs (LET> 10.8 KeV/μm) the fit parameters contribute to exponential-shaped increase of α values. Moreover, a relatively constant rate of change in RBE weighted dose is observed when the change of the fit parameter is reduced by 10% and 20%.

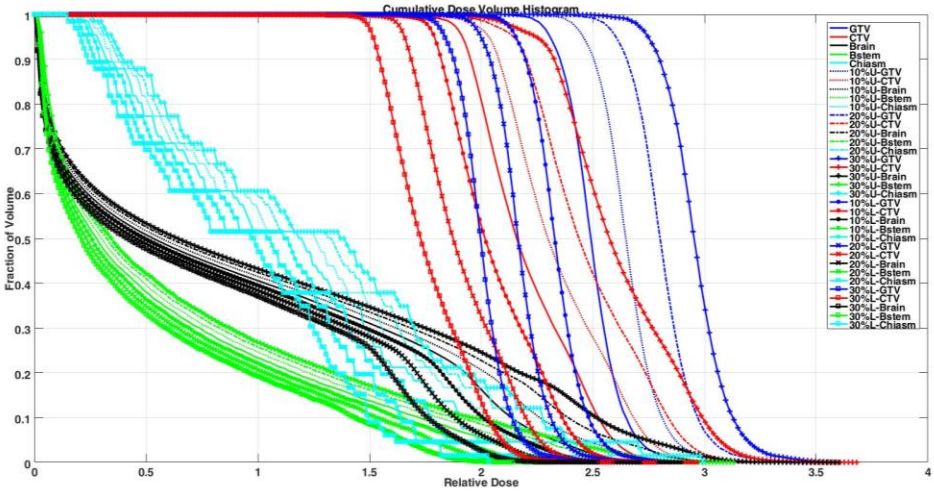

Figure 30 Sensitivity of vRBE-Guan to α ± 0.3, 0.2, and 0.1 Vs. LET fit parameter 0.3 changes – Patient 1. Dotted lines correspond to increased alpha parameters, dashed lines show the effect of decreasing the alpha fit parameters, and the solid line shows the originally calculated RBE values.

Sensitivity of vRBE-Guan to β Fit Parameters

To analyze the RBE model for sensitivity to tissue parameters, α and β should be studied. The sensitivity of vRBE-Guan to β fit parameter changes is of interest since although β is multiplied by square of the dose, the β values are relatively small compared to α.

β was observed to have a linear relationship with slow increase rate with LET when LET is low, but it nonlinearly increases with regard to LET increase. Below are the cumulative RBE weighted dose volume histograms for 30% increase and decrease in β fit parameters.

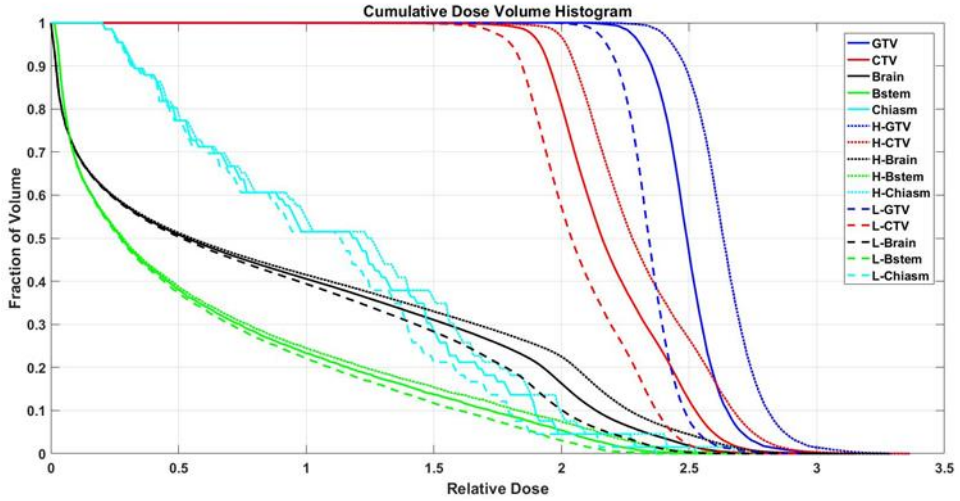

Figure 31 Sensitivity of vRBE-Guan RBE model to β ± 0.3 Vs. LET fit parameter with 30% changes for patient 1

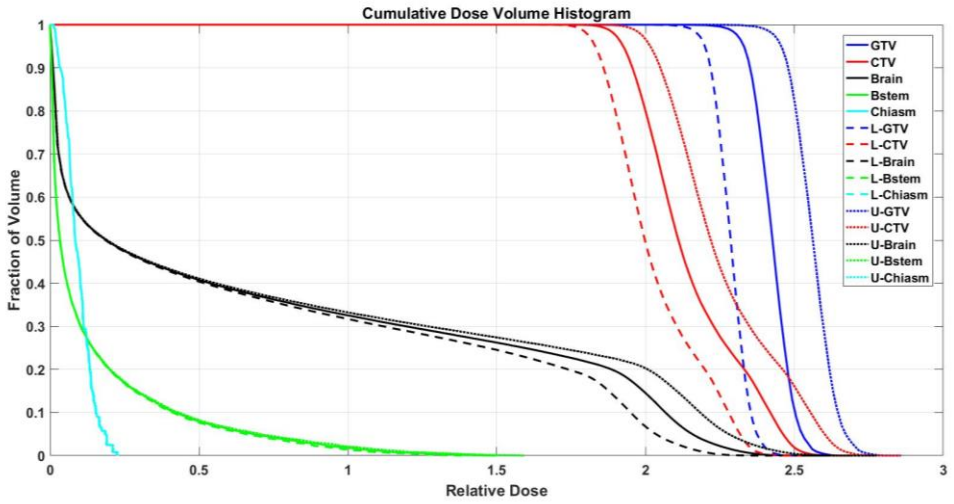

Figure 32 Sensitivity of vRBE-Guan RBE model to β ± 0.3 Vs. LET fit parameter changes for patient 2

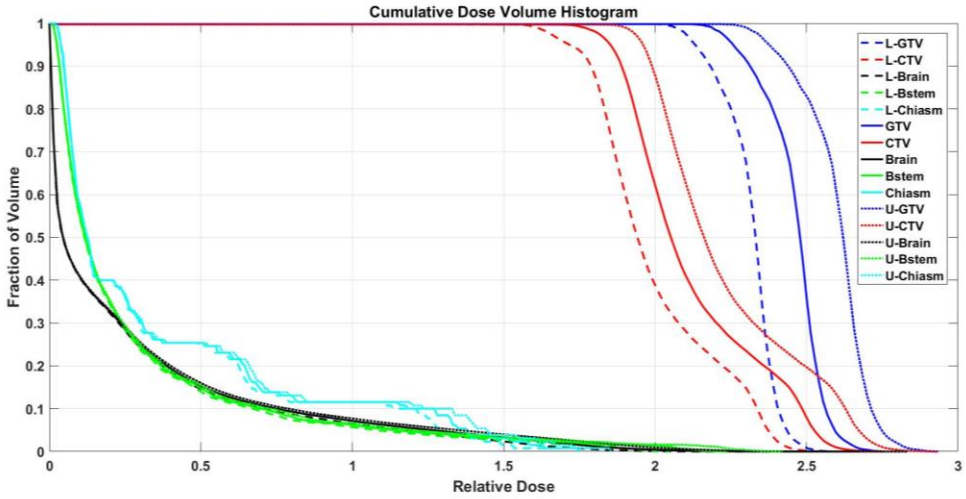

Figure 33 Sensitivity of vRBE-Guan RBE model to β Vs. LET fit parameter changes for patient 3

Although sensitivity of vRBE-Guan to β is less than its sensitivity to α, the amount of measured differences are still significant. On the other hand, as mentioned before, this model incorporates the relationship of β for proton beams and LET in calculating RBE, while vRBE-Wilkens does not. So vRBE-Guan does have the advantage of modeling the β parameter behavior with respect to LET based on an

agreeable experimental results, but the level of tolerated sensitivity should be analyzed in order to reach a decision whether or not to use such a sensitive approach.

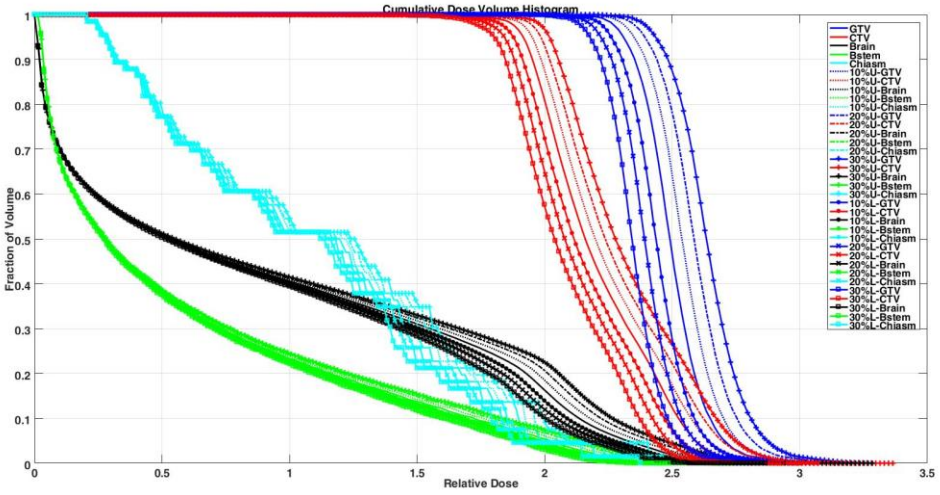

Figure 34 Sensitivity of vRBE-Guan to β ± 0.3, 0.2, and 0.1 Vs. LET fit parameter 0.3 changes – Patient 1. Dotted lines correspond to increased beta parameters, dashed lines show the effect of decreasing the beta fit parameters, and the solid line shows the originally calculated RBE.

The trend of calculated RBE changes when β fit parameters are decreased and increased by 30%, 20%, and 10% is also analyzed and demonstrated in figure below. Again, a relatively uniform change of variable RBE weighted doses corresponding to fit parameter fluctuations is observable. Such fluctuations can be observed to be more signified in PTV.

Conclusions

In this chapter two models for calculating relative biological effectiveness are analyzed and both are compared to the clinically used constant RBE.

Three brain tumor cases were selected and patient anatomical information as well as clinical treatment plans for those patients were obtained from MD Anderson Cancer Center. To compare the three RBE models, RBE and RBE weighted dose for each models are calculated. Dose volume histograms are used to measure and illustrate the differences between designed scenarios.

The model of vRBE-Guan yields distinctively higher results than vRBE-Wilkens and cRBE and is more sensitive to parameter changes than the other two. However, it accounts for the relationship between tissue parameters and LET that are observed to be nonlinear based on recent studies, while vRBE-Wilkens considers a linear α, and a constant $\beta = \beta_x$ for proton beams. Therefore, neither can it be stated that vRBE-Wilkens is the accurate dependable RBE model to calculate RBE values with, since it is based on limited and older experimental data; nor it can be concluded that vRBE-Guan is the preferable model because it shows high sensitivity to tissue parameter changes. This is a problem since there still is not enough experimental data for proton biological effectiveness for various tissues. As a result, for RBE to be calculated based on this model, the behavior of tissue vs. LET should be approximated to scale the existing function to the parameters of each particular tissue that is under radiation. This scaling also should be done for all of the treatment area including organs at risk. Scaling and approximating the tissue fit parameters can bring uncertainties and errors into the calculations. This means more experiments on proton biological effectiveness can help in

reducing the risk of calculating inaccurate RBE values due to inaccurate approximation of tissue parameters in RBE formula.

In regard to continued use of constant RBE, this study found that the proton RBE can vary throughout the range and with high dependency to tissue parameters such that using 1.1 for proton RBE will underestimate the real value of RBE and therefore, underestimate the ability of the beam to damage and kill tumor cells. This is more important in regard to sparing the OARs from the damage caused by excess radiation.

The argument here is that to what extent the sensitivity of the vRBE-Guan can be tolerated in order for the variable RBEs to include the response level of particular biologic systems to proton beams. Also, this means that the value of considering variable biological effectiveness to IMPT planning should be determined to assess the justifiability of considering a rather uncertain RBE which in response can model the biological response of target tissue against the changes in LET, when it comes to unknown tissue parameters. In that sense, robust optimization can be used to take into account the uncertainties of this model. Biologically optimized IMPT plans based on variable RBE values can be generated to address the effect of variable RBE on treatment plans and assess the quality of such plans compared to currently delivered plans based on the constant RBE.

Future Work

As mentioned before, biologically optimized IMPT plans based on variable RBE evaluated in this study will play an important role in decision making regarding the use of variable RBE as opposed to the continued use of constant RBE. Worst case scenarios based on RBE model parameters (e.g., slope coefficient in alpha LET dependence and beta LET dependence) will be used to compare worst case doses for vRBE-Wilkens and vRBE-Guan. Furthermore, three IMPT plans optimized based on cRBE, vRBE-Wilkens and vRBE-Guan will be compared by distributions of dose-averaged LET for those three plans as the extension of this study.

A considerable sensitivity to tissue parameter fluctuations was observed in the sensitivity analysis section for vRBE-Guan. As a solution to the sensitivities observed for the vRBE-Guan, robust optimization can be used to address the high sensitivity of the model, so that variable RBE can benefit from the RBE formula as accurate as possible based on newly derived experimental data.

Optimization of IMPT plans based on calculated RBE values for both variable RBE models will provide comparative material to evaluate the usage of variable RBE, and the effects both RBE models on worst case calculated doses for every patient. However, to fully evaluate the implementation of variable RBE, calculated based on vRBE-Guan model, information on how the optimized plans influence the treatment effectiveness is needed. That means such effect has to be observed with regard to treatment outcomes. Less damage to organs at risk is expected to be observed when IMPT plans are optimized based on variable RBE values for every patient. Which is

rather an important improvement in proton therapy treatment planning especially for patients with brain tumor cases with sensitive organs at risk.

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