T.R.
VAN YUZUNCU YIL UNIVERSITY
INSTITUTE OF NATURAL AND APPLIED SCIENCES
DEPARTMENT OF PHYSICS

THEORETICAL INVESTIGATION OF RELATIVE BIOLOGICAL EFFECTIVENESS OF HEAVY IONS ON SOME BIOLOGICAL TARGETS

M.Sc. THESIS

PREPARED BY: Abdulbasit Faiq MOHAMMED
SUPERVISOR: Assist. Prof. Dr. Ömer Faruk ÖZDEMİR

VAN-2021

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ACCEPTANCE and APPROVAL PAGE

This thesis entitled "***Theoretical Investigation of Relative Biological Effectiveness of Heavy Ions on Some Biological Targets***" presented by ***Abdulbasit Faiq MOHAMMED*** under supervision of assist. Prof. Dr. ***Ömer Faruk ÖZDEMİR*** in the department of Physics has been accepted as a M. Sc. thesis according to Legislations of Graduate Higher Education on …...../...../..... with unanimity / majority of votes members of jury.

Chair:..... Signature:

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This thesis has been approved by the committee of The Institute of Natural and Applied Science on ..……./...../…..….... with decision number .....

Signature
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Director of Institute

THESIS STATEMENT

All information presented in the thesis obtained in the frame of ethical behavior and academic rules. In addition all kinds of information that does not belong to me have been cited appropriately in the thesis prepared by the thesis writing rules.

Abdulbasit Faiq MOHAMMED

ABSTRACT

THEORETICAL INVESTIGATION OF RELATIVE BIOLOGICAL EFFECTIVENESS OF HEAVY IONS ON SOME BIOLOGICAL TARGETS

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M.Sc. Thesis, Department of Physics
Supervisor: Assist. Prof. Dr. Ömer Faruk ÖZDEMİR
February 2021, 69 pages

Since a precise mathematical theory of the change of RBE with LET has not been revealed yet, the developed programs produce quasi-experimental results for RBE with different approaches and models. Testing the applied models with different physical parameters (energy, dose, etc.) at different target depths is important for the optimization and development of the programs. PHITS program used in this study uses the microdosimetric kinetic model (MKM) for the relationship between RBE and LET.

In this study, for the selected energy values of proton and carbon used in hadron therapy, the physical quantities and relative biological activities (RBE) of the effects on biological targets determined as soft tissue and A150 tissue equivalent plastic were examined. Within the scope of the study, LET and specific energy were obtained by using MC simulation method and RBE calculations were made with three different methods given in MKM.

Keywords: LET, MKM, Monte Carlo, PHITS, RBE.

ÖZET

AĞIR İYONLARIN BAZI BİYOLOJİK HEDEFLER ÜZERİNDEKİ BAĞIL BİYOLOJİK ETKİNLİĞİNİN TEORİK İNCELENMESİ

MOHAMMED, Abdulbasit Faiq
Yüksek Lisans Tezi, Fizik Anabilim Dalı
Tez Danışmanı: Dr. Ögr. Üyesi Ömer Faruk ÖZDEMİR
Şubat 2021, 69 sayfa

RBE'nin LET ile değişimine ait kesin bir matematiksel teori henüz ortaya konulamadığından geliştirilen programlar farklı yaklaşımlar ve modellerle RBE için yarı deneysel sonuçlar üretmektedir. Uygulanan modellerin farklı fiziksel parametrelerle (enerji, doz vb.) farklı hedef derinliklerinde test edilmesi programların optimizasyonu ve geliştirilmesi için önemlidir. Bu çalışmada kullanılan PHITS programı RBE ve LET arasındaki ilişkinin çözümü için mikrodozimetrik kinetik modeli (MKM) kullanmaktadır.

Bu tez çalışmasında, hadron terapide kullanılan proton ve karbonun seçilen enerji değerleri için, yumuşak doku ve A150 doku eşdeğer plastik olarak belirlenen biyolojik hedeflerdeki etkilerinin bağlı olduğu fiziksel büyüklükler ile bağıl biyolojik etkinlikleri (RBE) incelendi. Çalışma kapsamında fiziksel büyüklüklerden LET ve spesifik enerji MC simülasyon yöntemi kullanılarak elde edildi ve RBE hesaplamaları MKM içerisinde verilen üç farklı yöntem ile yapıldı.

Anahtar kelimeler: LET, Monte Carlo**,** MKM, PHITS, RBE.

ACKNOWLEDGMENT

In the name of Allah, the Most Gracious and the Most Merciful.

All praises to Allah and His blessing for the completion of this thesis. I thank God for all the opportunities, trials and strength that have been showered on me to finish writing the thesis.

First and foremost, I would like to sincerely thank my supervisor Assit. Prof. Dr. Ömer Faruk ÖZDEMIR for his guidance, understanding, patience and most importantly, he has provided positive encouragement and a warm spirit to finish this thesis. It has been a great pleasure and honour to have him as my supervisor.

My deepest gratitude goes to all of my family members. It would not be possible to write this thesis without their supporting. I would like to thank my father, mother, brothers, and sisters. Also, i would like to thank to my friends Kurdawan, Osman, Rawa, and Chnar.

2021

Abdulbasit faiq MOHAMMED

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SYMBOLS AND ABBREVIATIONS

Some symbols and abbreviations used in this study are presented below, along with descriptions.

Abbrevations	Description
BNCT	Boron Neutron Capture Therapy
CT	Computer Tomography
HCP	Heavy Charged Particles
HIMAC	Heavy Ion Medical Accelerator
ICRU	International Commission on Radiation Units and Measurements
LBL	Lawrence Berkeley Laboratory
LET	Linear Energy Transfer
MKM	Microdosimetric Kinetic Model
MC	Monte Carlo
PT	Proton Therapy
RBE	Relative Biological Effectiveness

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1. INTRODUCTION

The main purpose of radiation therapy (Radiotherapy) is to eliminate unwanted tissues, especially malignant tumors. If appropriate doses can be given, it is possible to control cancerous cells with applications such as x-rays, heavy charged particles (hadron therapy) or boron neutron capture therapy (BNCT). In order to give the patient, the appropriate dose, dose distribution planning is made before radiotherapy applications (Martin, 2006).

The main goal in dose distribution planning is to leave the maximum of the radiation energy on the tumor, in order to cause the least damage to the healthy tissue. While it is inevitable for healthy tissues to receive doses in common x-ray radiotherapy, it is possible to protect healthy tissues by using high linear energy transfer (LET) radiation in applications performed with heavy ions (Krane and Halliday, 1987).

Therapeutic ion beams generally offer the advantage of a deep dose distribution with a pronounced Bragg maximum compared to photon beams and a sharp dose reduction at large depth of penetration. This method is called hadron therapy and it is a type of outer beam radiotherapy. Beam of particles such as protons or carbon obtained with Linac are sent to the tissue. The scattering of heavily loaded ($A \geq 1$) particles used in hadron treatment in the tissue is low. Since the scattering of the particle beam is less, it can leave most of its energy on the targeted tumor, so the healthy tissue is not damaged much (Martin, 2006).

Therefore, heavily loaded particles provide an advantage in radiotherapy in terms of accumulating the dose in the targeted volume and minimizing the dose in the surrounding healthy tissues (Khan and Gibbons, 2014). The rationale for the clinical use of proton and carbon therapy is that higher doses can be given to the tumor and better preservation of healthy tissue than photon-using radiotherapy (Martin, 2006).

When heavily charged ions enter the medium, it transfers its energy approximately inversely to the square of its velocity, and as it moves through the tissue, it slows down until it stops and gradually loses its energy. Therefore, as the particle slows down, the possibility of ionization of the atoms in the environment increases and the maximum dose

is transferred to the depth where the ionization events are maximum. All this energy loss is shown by the Bragg curve (Bragg and Kleeman, 1905; Lomax, 2009).

The main advantage of Hadron therapy over photon radiotherapy is that the ions stopped at a target depth in the matter and a maximum energy storage at the Bragg peak. This effect is characterized by the stopping power of the particle, which is defined as the average energy loss per unit length of the medium, resulting from Coulomb interactions with electrons and atomic nuclei (ICRU, 1993).

In photon radiotherapy, the doses given to the patient are generally at limited energies in order to protect healthy tissues. Whereas, higher doses with ions enable better tumor control (Niemierko et al., 1992).

Advantages obtained with Hadron therapy have provided better results in the treatment of tumors in critical locations (Dowdell, 2011).

Heavier ions, such as carbon, provide more advantages over protons or other lighter ions: the first is less lateral scattering in the tissue, and the second, a high relative biological activity (RBE) at the Bragg peak (Kramer et al., 2000).

The scarcity of experimental data and the high cost of hadron therapy require solving a multivariate and unpredictable problem for appropriate dose planning. The use of Monte Carlo (MC) simulation method for the determination of the dose-dependent LET and RBE values is an appropriate approach and has led medical physicists to simulation programs. Some of the programs developed using MC simulation method to examine the distribution of LET values of heavy ions in tissue are Geant4, MCNPX, FLUKA and PHITS (Granville and Sawakuchi, 2015).

Thanks to these programs, difficult and complex calculations of particle interactions can be made. Thus, possible results and probabilities can be calculated before the application is made and realistic results can be realized with less cost and less time. Therefore, simulation programs have an important place in nuclear and medical physics applications (Khan et al., 2005).

Although it is known that RBE depends on the LET value, mathematical models that give exact results have not been revealed yet. For this reason, the programs developed produce quasi-experimental results for RBE with different approaches and models. Testing the applied models with different physical parameters (energy, dose, etc.) at different target depths is important for the optimization and development of the programs.

The PHITS program used in this study uses the microdosimetric kinetic model (MKM) for the relationship between RBE and LET (Sato et al., 2018).

In this thesis, the physical parameters and relative biological activities (RBE) of proton and carbon used in hadron therapy on biological targets determined as soft tissue and A150 tissue equivelant plastic were examined. Within the scope of the study, LET, lineal energy distribution and specific energies was obtained using the MC simulation method and these physical parameters used to obtain RBE values. In the calculations, two different MKM approaches were used in addition to the analytical approach. We created our script to calculate RBE values directly from the output data files produced by PHITS. The results compared with experimental data found in literature. For obtaining experimental data we searched articles and thesis which published experimental data as open source. For further readings we also gave all data we found the papers which are not related to our calculations.

2. LITERATURE REVIEW

The use of protons in therapy was first suggested by Robert Wilson (Wilson, 1946). Due to technological deficiencies, applications were limited only in certain parts of the body because proton beams could not reach the specific energies that could reach every desired depth (Liu and Chang, 2011).

In 2001 MGH and in 2006 Monroe Dunaway Anderson (MDA) proton therapy centers became operational. Proton therapy centers increased in facilities such as research institutes and hospitals from the 1980s to the 2000s (ICRU, 1993).

The use of carbon in therapy began in 1975, when Bevalac was established at the Lawrence Berkeley Laboratory (LBL), with more extensive research on the clinical potential of heavy ions (Castro et al., 1980).

The Heavy Ion Medical Accelerator (HIMAC) in Chiba was completed in 1993 and clinical trials on carbon therapy began in June 1994. In 1997, the GSI (Gesellschaft für Schwerionenforschung mbH) carbon ion therapy facility in Germany became operational (Ebner and Kamada, 2016).

RBE values of heavy ions vary with physical quantities such as given dose and LET. Therefore, determining the relationship between RBE and LET is very important in optimization of hadron therapy. For this purpose, the LET - RBE relationship was experimentally demonstrated by Barendsen in 1994 (Barendsen, 1994).

The microdosimetric kinetic model that establishes the relationship between LET and RBE through surviving fraction was introduced and developed by Hawkins (Hawkins, 1994; 1996; 1998; 2003).

The relationship between LET and RBE has been examined for different textures and particles (Joiner, 2009). Using the microdosimetric kinetic model, the relationship between linear energy transfer and relative biological activity was calculated for different tissues and different ions (Kase et.al., 2006; Abolfath et.al., 2017; Carante and Ballarini, 2017, Grzanka et.al., 2018). MKM calculations were made with the PHITS program (Horiguchi et.al., 2015; Chen et.al., 2017; Takada et.al., 2018; Kobayashi et.al., 2019).

Bragg curves are calculated in water for protons with 50-250 MeV energy using MC PTRAN program and analytical calculation method and found Bragg peak positions

(Carlsson, 1997). Then, Bragg peaks are obtained in water using the Harvard cyclotron accelerator to obtain Bragg curves for protons with an energy of 160 MeV (Hall et al., 1978). Besides, Bragg peaks was founded by calculating the Bragg curves of protons with 120-250 MeV energy with the help of the MC coded Geant3 simulation program (Li et al., 2005). In addition, they found Bragg curves of protons with 90-200 MeV energies in water phantom with MC coded FLUKA, GATE, MCNPX and PHITS simulation programs and Bragg peaks (Seravalli et al., 2012). Moreover, Schwarz (2011) found Bragg peaks by calculating the Bragg curves of protons with 70-200 MeV energies in water with the MC simulation program and optimizing them with density-modulated proton therapy results. Additionally, it is calculated Bragg curves and peaks for protons of 50-350 MeV and carbon ions of 1.2 - 7.2 TeV by experimental and MC method (Grimes et al., 2017). Using Fluka, Geant4, MCNP and PHITS simulation programs, found Bragg curves for protons of 100 and 226 MeV in water (Yang et al., 2017).

3. THEORETICAL BACKGRAOUND

3.1. Interactions of Particles with Matter

Throughout our lives, we are constantly exposed to radiation both naturally and as a cost of technological developments. While the interaction of radiation with matter has visible results in some cases, sometimes we are not even aware of it. Although we are not aware of it, our organs and tissues interact with radiation in some way.

Radiation is energy emitted by packets of energy called particles or photons. Radio-waves, X-rays used in medicine and industry, bremsstrahlung rays, γ-rays are the types of radiation we are exposed to throughout our lives.

When evaluating the interaction of radiation with matter, it is necessary to evaluate the interaction of light particles and heavily charged particles differently. For example, if we compare the Coulomb scattering of electrons or positrons in matter with heavy particles, we see significant differences.

i. The velocities of electrons emitted from decay are relative velocities.

ii. The electron (or positron) undergoes great deviations during their movement in matter. For this reason, the distance it travels and the linear distance it can travel in the substance will be different.

iii. The electron collides with another electron in the matter, centrally elastic, and transfers most of its initial energy to the other electron.

iv. Electrons can be exposed to great acceleration with changes in their velocity and direction. It emits electromagnetic radiation as a result of this accelerated motion. This emitted radiation is called Bremsstrahlung radiation (Krane, 2001).

Protons, alpha or other nuclei with a mass number greater than or equal to one ($A \geq 1$) are called heavy charged particles (HCP), (Syed, 2007). These heavy charged particles can also react with the nucleus, which is referred to as Rudherford scattering. But the nucleus, with a tiny fraction of the atomic volume ($\sim 10^{-15}$), the particle is 10^{15} times more likely to react with an orbiting electron. For this reason, the biggest factor in the loss of the charged particle's energy is the Coulomb scattering of the atomic electrons (Krane, 2001).

Heavy charged particles lose their energy in matter by the above-mentioned excitation and ionization. Since the Coulomb force has an infinite range, it can be assumed that the charged particle interacts with many electrons at the same time and thus loses its energy gradually but continuously. After traveling a certain distance, it loses all of its energy. This distance is called the range of the particle.

A heavy particle is deflected at a negligible angle in collision with the electrons on its path, so it can be assumed that the heavy particle travels almost in one straight line. The range depends on the type of particle, the nature of the material and the energy of the particle.

Charged particles are ionizing radiation, and the generated primary electrons themselves can generate ions and form secondary electrons through collisions. To measure the linear energy transfer (LET) as an indicator of the energy lost by the particle, it is necessary to consider primary and secondary electrons as well as atomic excitations (Krane, 2001). Heavy ions such as carbon have a lower range in matter compared to protons due to their mass, and they have less lateral scattering, so their LETs are higher (Jäkel, 2010).

3.2. Radiation Dose

In radiotherapy, appropriate radiation doses must be transported precisely to the treatment point. Today, with the reliable information that can be obtained with advanced imaging methods, the data needed to determine the place where the dose will be given and the dose that can be given to the patient can be obtained. Success in radiation therapy depends on the sensitivity of the dose to be given to the tumor. The process of determining the radiation beam used in cancer therapy is based on complex processes and the application of a number of transformation factors. In order to facilitate this process, IAEA published a code named "Absorbed Dose Data admonition in photon and electron beams" (IAEA, 1987).

Dose protocols have also been published in this resource (IAEA, 1987), where current and optimized values of physical interaction coefficients and correction factors are given. Dose units are defined as follows:

The total electric charge Q of ions formed per a certain mass of air is called exposure (irradiation dose), (Eq.2.1).

$$X_p = Q/m \tag{3.1}$$

The unit of the pose is C/kg in the SI unit system, but in practice röntgen (R) is used. Röntgen is a unit used only for air. Röntgen is defined as the irradiation dose that generates an ionization charge of 1 esu in dry air under normal conditions. (Eq.2.2).

$$1\ R = \frac{1\ esu}{0.001293\ g} = 2.58\ .\frac{10^{-4}C}{kg} \tag{3.2}$$

The energy transferred to the environment by ionizing radiation per unit mass of medium is defined as the absorbed dose (D). The most commonly used unit of absorption dose, rad (radiation absorbed dose), is equal to 100 erg energy absorption by 1 g of substance. Gray (Gy) is the SI unit of absorbed dose, and 1 Gy is 100 rad. (Eq.2.3)

$$1\ rad = 100\frac{erg}{g} \tag{3.3}$$

In order to determine the biological effects of radiation, it is necessary to measure the biological effects of different types of radiation. Radiation such as beta and gamma transfer very little energy in a small range of tissue, as they transmit their energy over a long way. Heavily charged radions, like alpha particles, transmit all their energy over a very short distance. The biological damage caused by α radiation of 1 rad is much more than that of-ray of 1 rad.

In order to determine the different rates of damage caused by different types of radiation, the concept of relative biological activity (RBE), defined as the ratio of a given radiation dose to the X-ray dose that produces the same biological effect, has been defined (Hawkins, 1994).

Since RBE is difficult to determine experimentally, the quality factor (QF) calculated for a certain energy type of radiation according to the energy transmitted per unit length is used (ICRU, 1986).

The QF values are 1 as radiations such as beta and gamma transfer relatively less energy per unit length. QF values of radiations such as alpha that transfer more energy per unit length vary up to 20 (ICRU, 1986).

The effect of radiation on biological tissue depends on the absorbed dose (D) and quality factor (QF) values of the radiation. The dose equivalent (H) of the biological effect is called the biological dose or equivalent dose and is obtained by multiplying this dose and the quality factor:

$$H = D \times QF \tag{3.4}$$

When D is taken in units of rad, the equivalent dose is obtained as rem (roentgen equivalent man). If the unit of D in SI unit system Gy is used, the unit of equivalent dose in SI unit system is sievert (Sv). Since 1 Gy = 100 rad, 1 Sv = 100 rem. Brief descriptions and units of radiation dose units are given in Table 1.1 (Martin, 2006).

Table 3.1. Dose definitions and units

	Definition	cgs units	SI units
Radiation Exposure	is a measure of the ionization of air due to ionizing radiation from photons.	R	C/kg
Absorbed Dose	is the measure of energy per unit mass deposited by ionizing radiation.	rad	Gy
Dose Equivalent	is a dose quantity H representing the stochastic health effects of low levels of ionizing radiation on the human body which represents.	rem	sievert

Standards for the maximum irradiation dose that the public and those working in radiated environments can receive are expressed in units of mSv or rem over a certain period of time (usually 1 year). Approximately 1–2 mSv is taken each year from cosmic rays and natural isotopes, which we call natural background. The International Commission on Radiation Protection (ICRP) has determined the annual whole-body absorption dose limits as 5 mSv / year for the public and 50 mSv / year for those working with radiation. The dose absorbed by a sensitive area of the body such as bone marrow is

0.5 mSv for a typical chest X-ray (X-ray) film and 0.02 mSv for a dental X-ray (Krane 2001).

3.3. Lineer Energy Transfer (LET)

There are electronic and nuclear interactions between the charged particle and the target material. Charged particles passing through the material lose energy depending on the particle they interact with and the target. This property is expressed in the literature as the stopping power of the material and denoted by SP. Stopping power is related to the property of the medium in which the particle releases its energy and is defined as the amount of energy the particle loses over a length dx :(Eq.2.5).

$$SP = -dE/dx \tag{3.5}$$

Stopping power is a function of the mass, charge and velocity of the incoming ion and the atomic number and density of the absorbent material. It consists of two components, electronic and nuclear stopping power. (Eq.2.6)

$$SP = -dE/dx = SP_{electronic} + SP_{nuclear} \tag{3.6}$$

The nuclear stopping power arising from the interaction of the medium with the incoming heavily charged particle is much smaller than the electronic stopping power resulting from interactions with electrons (Berger et al., 2000). Hence, the electronic stopping power is:

$$SP = SP_{electronic} \tag{3.7}$$

Tsoulfanidis gives the stopping power equations for heavy charged particles (proton, deuteron and alpha) as follows (Tsoulfanidis, 1995): (Eq.2.8)

$$-\frac{dE}{dx} = 4\pi r_0^2 z^2 \frac{mc^2}{\beta^2} NZ \left[ln\left(\frac{2mc^2}{I}\beta^2\gamma^2\right) - \beta^2 \right] \tag{3.8}$$

Linear Energy Transfer (LET) is the amount of energy that a particle transfers to the medium over a length dx (ICRU, 1970). LET has units of keV / μm and is defined as follows: (Eq.2.9)

$$LET = dE/dx \tag{3.9}$$

LET is numerically the same as the stopping power and increases with decreasing particle velocity and increasing load (ICRU, 1970; Berger, 1993). Therefore, the average LET of each heavily charged particle is different (Belli, 1989). LET values of protons and carbon also change depending on the energy. As the mass number of charged particles increases, the LET values also increase. For this reason, the LET values of protons and carbon are higher than photons. Heavy charged particles with the lowest LET value are protons.

Although LET seems to be similar to the stopping power, the stopping power is the energy lost by the beam, while LET is the energy transferred to the environment at or near the place of the collision (Belli, 1989). Unlike stopping power, LET may not include Bremsstrahlung or delta rays because these beams can go off target without releasing energy to the environment (Martin, 2006).

The damage caused by different types of radiation to the environment is different, even in equal doses, and this effect is defined as the Radiation Biological Effect (RBE). In other words, considering the proton and gamma that give the same dose to the environment, it can be said that they have more LET and RBE compared to gamma rays, considering that protons create more intense ionization. LET, to which RBE is strongly bound, is a useful quantity in radiobiology. LET is approximately proportional to ion charge and velocity so that as ions lose energy, their velocity decreases, resulting in an increased ionization density, especially at the Bragg peak. Moreover, heavier ions, such as ^{12}C, have higher LETs since z is larger than protons (Berger, 1993; Martin, 2006).

3.3.1. Heavy Charged Particles (HCP)

Heavy charged particle are described as charged particle, which is taking loads same or more to the proton’s mass. They engage with rely on the whole via coulomb

forces among their effective fee and the poor rate of the orbital electrons in the medium, which the particle goes through. When the interfaces with nuclei are seldom, the heavy charged particle reduce their strength normally by ionization, excitation, relying on the nearness of the coulomb interplay. By the common connections, so the HCP step by step misses its strength leaving a dose alongside its route till the particle is not moving (Brown and Suit, 2004; Lomax, 2009). Close the give up of the HCP variety, a reported height withinside the power damage delivery, called Bragg-Pick, and seems right away earlier than the particle involves rest. The Bragg-height is a function representative of HCP dose distribution. The top takes place due to the fact the interplay go segment will increase because the power charged particle losses. As proven in Fig. 1, supplied through the Japanese National Institute of Radiological Sciences, the power damage modality of HCPs is distinct than the power of photons because of the feature Bragg-pick. Furthermore, most doses of HCPs arise five at big depths, when the depth-dose delivery of the uncharged radiations has a most close to the floor of the body. So, this fashion of depth-dose delivery of HCP and its excessive organic impact on specific dose localization in radiotherapy (Durante, 2018).

Furthermore, charged radiations communicate a fantastically little dose on healthful tissues, however a better dose at the tumorous tissues. Then uncharged radiations communicate an incredibly excessive dose close to floor of the frame and exponentially lower as they skip through. Exterior beam radiotherapy, which makes use of charged particle is known as CPT and is jumped into subsets: heavy charged particle therapy (HCPT) and proton therapy (PT) (Khan and Gibbons, 2014).

The healing usage of protons turned into main advised via way of means of Robert R. Wilson in 1946 and the primary beam through PT became achieved on the Berkeley Radiation Laboratory in 1954. Afterward editing and linking the small strength heavy ion accelerator, to the excessive strength proton accelerator, the aggregate now called the BEVALAC, HCPT in addition started at Berkeley in 1974 (Wilson, 1946; Liu and Chang, 2011).

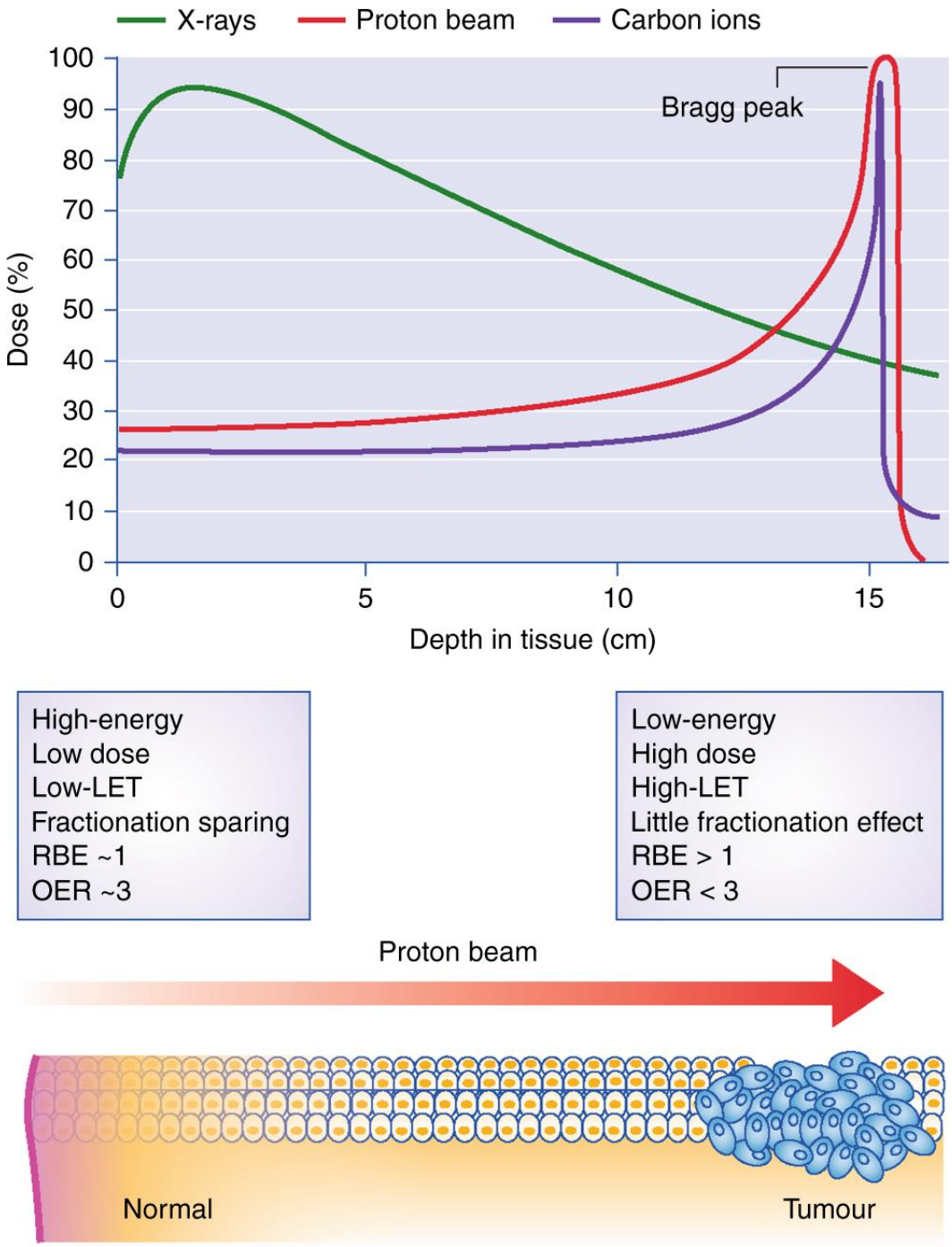


Figure 3.1. In Hadron therapy, a suitable depth-dose curve is used. While the charged particles transfer most of their energy near the region where they slow down at the end of the tumor target (Bragg peak), the X-ray energy decreases exponentially with the dose. For high energetic particles, LET rises around the Bragg peak. This provides radiobiological advantages such as state biological efficacy (RBE) and reduced oxygen enhancement rate (OER) (Durante, 2018).

The NIRS in Chiba, Japan started the usage of HCP for most cancers beam in June 1994, with carbon ions, which have been produced through the Heavy Ion Medical Accelerator (HIMAC). At the parent bellow, which indicates the variations withinside the dose scatterings among the proton and X-rays whilst utilized for radiotherapy. As proven on this determine, the traditional radiotherapy the use of the X-rays has a tendency to have an effect on extra of the encompassing healthful tissues because of the wide dose delivery. As for the Charge Particle Therapy, on the other hand, the dose may be limited to a small area within side the tumorous place minimalizing bad results to the wholesome tissues. Dose can be localized in the cancerous area minimizing negative effects to the healthy tissues (Dowdell, 2011).

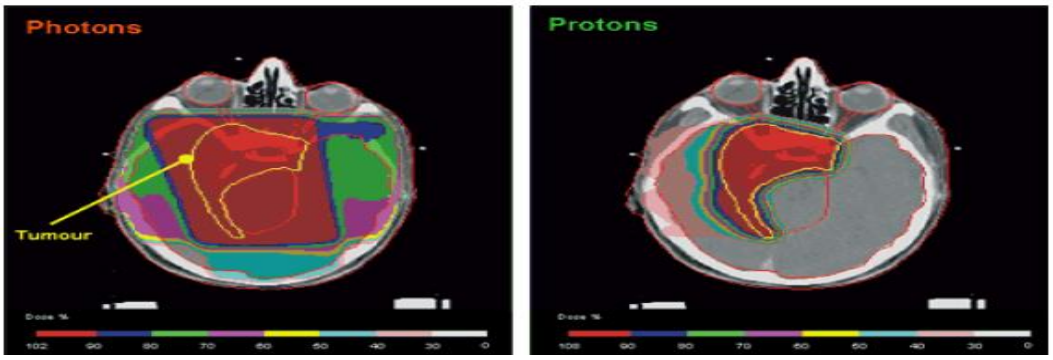


Figure 3.2. Dose scattering assessment among the photon beam (left) and the proton beam. Internal segment of the yellow line shows a meningioma. The photon beam offers an excessive dose all through a huge area (purple segment), however the proton beam limits the dose close to the tumor segment. HCPs are fine for tumor switch; yet, they're disadvantageous if the Bragg-peaks are out of place on regular tissues because of issues in variety devotion from the use of tissue replacements evolved for photon communication. Consequently, cautious putting at the tumorous cells is required (Oliveira and Hormaza, 2009).

While ionization radiation loss huge amount of energy per definite distance consider as high LET. Otherwise, if ionization radiation spend small quantity of energy in long distance trace or exhibit Abnormal or widely distributed ionizing processes. Both types of LET, could be benefited in cancer treatments and radiotherapy as well as could be dangerous by destroyed cells in body and side effect will be appear. Which can also reduce the dose of treatment and thus reduce the chance of tumor control. Since the probability of normal tissue problems rely on the amount of normal tissue expose to

radiation and the dosage. As result of many years of investigations, it concludes that enhancements of linear energy transfer LET caused to decrease the probability of infected by radiation of ionization (ICRU, 1993). However, high LET is more complicate and higher cost compare with classical radiotherapy. Additionally, Processes rely on localized tumors near vital organs or tumors that are resistant to traditional therapy. Currently there are many kinds of treatments are available in clinics which are efficient in limited cancer such as uveal melanoma, pediatric tumors, skull base tumors, and head-and-neck tumors. The possibility of introduction of late standard tissue injury and second malignancies with particle therapy cannot yet be reliably estimated considering the small quantity of applicants to date (Dowdell, 2011).

In the case of particle irradiation, both protons and subatomic particles have a benefit in the application of physical doses, enabling the transmission of a more consistent dosage to the tumor than radiation of ordinarily utilized photons. The concentration of ionization cases, or LET, is greater for radiation with large ions than for photons and protons, giving heavy ions an extra possible biological benefit since cell damage raises with LET. After all, natural tissue results are not induced simply by cell damage, but are induced by a mixture of cell death or other mechanisms such as cell division, epithelial to mesenchymal transformation, cell proliferation, extracellular matrix deposition, and several other processes (Khan et al., 2005).

The objective of this research was to evaluate whether, during high and low LET exposure, a differential in the induction of two entirely distinct processes, associated with natural tissue destruction, p53-induced apoptosis, and the profibrotic expression of the PAI-1 gene, could be detected We illustrate that these two acts are caused differently by high and low LET radiation. This result reveals that biological processes can have different profiles, thereby leading to different manifestations and production of natural cell death caused by high and low LET exposure. Furthermore, LET is determined by (Zapp et al., 2002):

i. Quality of Radiation

ii. Quantity of Radiation

Physical portions are used to explain and signify bodily phenomena in a quantitative way. For the motive of radiation protection, bodily portions are needed: To describe reassets and fields of radiation in addition to the interplay of radiation with

matter. Then, a few portions have a unique importance due to the fact they'll be needed. Moreover, to explain the publicity of the human frame to non-ionizing radiation (dosimetric portions); a critical software of dosimetric portions is in placing publicity limits (Shapiro, 1972).

3.4. Relative Biological Effectiveness (RBE)

The relative biological effectiveness (RBE) is the ratio of biological effectiveness of one type of ionizing radiation relative to another, given the same amount of absorbed energy (Eq.2.4.1) (Neshasteh et. al., 2013).

$$RBE = \frac{\text{Dose of Standard Radiation (250 kV X−rays or 60Co g rays)}}{\text{Dose of Test Radiation}} \quad (3.4.1)$$

The relative biological effectiveness (RBE) is outlined because the magnitude relation of the doses needed by 2 radiations to cause a similar level of effect. Thus, the RBE depends on the dose and therefore the biological termination. Nucleon medical aid has been supported the employment of a generic RBE of one.1, which is applied to all or any treatments freelance of dose/fraction, position within the irradiated volume, initial beam energy or the actual tissue. The variability of RBE in clinical things is believed to be at intervals 100 percent however quantitative dependencies of the RBE on varied physical and biological properties are unnoticed. The magnitude of RBE values and their variations is considerably larger for Carbon particle medical aid.

Studies have incontestable important RBE values of quite three in clinically relevant eventualities for Carbon ions. Further, there can be significant variations in RBE within the irradiated volume that are being thought-about in treatment designing Associate in Nursing delivery serious ions have a possible advantage compared to protons once it involves their therapeutic magnitude relation because of an elevated RBE within the neoplasm (based on the improvement magnitude relation and better average LET values) compared to the encircling tissue (Kramer et. al., 2000). However, on the opposite hand, at the moment there are still significant uncertainties in serious particle RBE values. Elevated RBE values (even for protons) can be expected significantly close to the perimeters of the high-dose volume as a result of doses could also be deposited by high-

LET particles. The rise in RBE as a performance of depth within the patient leads to associate in nursing extension of the bio-effective vary of the beam. Further, as a result of RBE values could increase with deceasing dose inflicting elevated RBE values for organs in danger compared to the place. So as to include careful RBE modeling in treatment designing as a performance of LET, dose and termination, 2 aspects have to be compelled to be thought-about. Firstly, the on the market info from experimental studies and second, our ability to calculate RBE values for a given treatment arrange supported parameters extracted from such experiments. RBE values are typically supported cell survival knowledge as a result of this can be the most termination of interest in irradiation. However, one might expect variations in RBE for cell survival compared to cell mutation, the latter being a very important termination for late effects. This academic session can specialize in summarizing the mechanisms behind RBE variations among treatment modalities. Further, RBE variations as a performance of LET, tissue and dose are given supported experimental and simulated knowledge for nucleon and Carbon particle beams. Finally, completely different approaches for theoretical modeling of RBE values for treatment designing functions are mentioned concisely (Castro ve ark., 1980; Kramer ve ark., 2000; Paganetti, 2003; Verkhoutsev et. al., 2019). Academic Objectives:

1. Comprehend the devicesafter heavy charged particle RBE values.
2. Comprehend the variations of RBE as a role of physical and biological parameters.
3. Comprehend the medicalconsequence of RBE values in proton and Carbon ion therapy.

Biological consequences of radiation on residing cells may also bring about 3 results: 1. Those cells, which are broken or injured recover themselvesresulting in no residual harm. 2. Cells die, just like hundreds of thousands of frame cells do each day, being changed via everyday organic processes. 3. Cells incorrectly restore themselves ensuing in a biophysical change. How should radiation have an effect on cells? Biological impact starts using the ionization of atoms. 4- The mechanism through that radiation causes damage to human tissue and some other material, is with the aid of using ionization of atoms withinside the material. Ionizing radiation absorbed with the aid of using human tissue has sufficient power to cast off electrons from the atoms that make up molecules of the tissue. 5- Kinds of RBE Effects of Radiation may be damaged into businesses in step by way of how replies (signs or results) share to dose or quantity of radiation received.

3.5. Hadron Therapy

Hadron therapy, is a general statement that covers all types of particle therapywhich is a collective word used to describe the treatment of tumors by means of accelerated hadronic particles. Such as neutrons, protons, pawns, antiprotons, alpha, lithium ions, boron ions, carbon ions, oxygen ions, etc. Have been the subject of intense clinical and radiobiological studies. Low energy neutrons were the first hadrons used in radiotherapy. Neutrons move through scattering and rebound ions, and these ions are mostly low energy protons in biological tissues and produce a greater Relative Biological Activity (RBE). However, due to the poor dose distribution, the biologically high effective dose is also large in normal tissues and causes serious side effects in the target volume. Therefore, neutron therapies have been discontinued in most countries (Amaldi, 2015).

Among all these possibilities, proton and carbon ions are at the center of scientific and technological development today. Protons and carbon ions are more advantageous in cancer radiation therapy than X-rays, mainly for three reasons (Braccini, 2010).

The energy release along its path in the target tissue is carried out within the last few millimeters of their range, in the so-called Bragg peak region, where the greatest damage is inflicted to the cells along their path. Moreover, they penetrate the patient with minimal diffusion, and using their electrical charge several "pencil beams" with variable penetration depth can be precisely directed towards any part of the tumor. The third reason is related to carbon ions and light ions in general and is based on radiation biology. For the same range, the ionization column produced is dense enough to directly induce multi-strand brakes in DNA, as carbon ions accumulate about 24 factors more energy in the Bragg peak region than protons. This effect is measured by enhancing Radio Biological Efficacy (RBE) and paves the way for the treatment of X-ray and proton-resistant tumors at the doses prescribed by standard medical protocols.

In order to treat deep-seated tumors, depths of 25 cm are required in soft tissues. This translates directly into the maximum energies of proton and carbon ion beams, which should be 200 MeV and 375 MeV respectively. In the case of beam currents, it is determined by the amount of dose to be delivered to the border tissues, typically 2 Gy per liter per minute (Braccini, 2010).

The physics of proton beam has superior drastically because it turned into proposed in 1946. The records of proton beam commenced in 1946 whilst Robert Wilson posted aninfluential paper wherein he suggested to apply acceleration proton beams to deal with deep-seated tumors in beings. In the research, he defined the bio-physical reason for the beams of proton in addition to the important thing engineering strategies of beam transport. In 1954, the primary human became handled with proton beams on the Lawrence Berkeley Laboratory ((Liu and Chang, 2011).

In 1962, specialized radio-surgical proton remedies began on the Harvard Cyclotron Laboratory, observed within side the mi-Nineteen Seventies through remedies for ocular cancers and large tumors. At Harvard university, some physicists were taking part with medical classmates at general hospital of the massachusetts, the massachusetts eye and ear infirmary, and somewhere else, advanced a great deal of the physics and generation had to deal with sufferers with proton beams properly and effectively. In addition, physicists somewhere else have been growing different key technologies, which includes accelerators, magnetically scanned beams, beams making plans structures (Castro et al., 1980).

The big approval of proton beam has been gradual in evaluation to, for instance, intensity-modulated photon beam. Including a number of motives for this sluggish acceptance of proton beam, which includes practicaltrouble, price, and shortage of proof of fee-competitiveness. Commercial proton shipping structures were pondered for many years earlier than they subsequently seemed in 2001 after overpowering full-size problems. The price of proton beam device stays a whole lot better than that of similar photon beam gadget. Even in instances of relative prosperity, the distribution of threatened assets to proton beam has been limited via way of means of especially sparse proof of its fee-competitiveness and fee-effectiveness. Despite those obstacles, a lot development has been prepared. Nowadays America has sixteen proton beam facilities in operation withinside and forty six facilities international. The Particle Therapy Cooperative Group (PTCOG) pronounced that as a minimum 105,743 sufferers were handled international through the quit of 2013 (IAEA, 2008).

The proton beam network has paced up efforts to behavior medical tests, which examine effects after proton beam with the ones after different superior generation radiation therapies. The relevant reason for proton beam, its advanced spatial dose delivery withinside the patient. In these years, the benefit of protons over photons in offering a notably adapted

and unchanging dose to a tumor has been in large part dwindled through improvements in photon treatments, consisting of intensity moderated photon beam and volumetric curvetreatments. Yet, the qualifiedprofit of proton beam in sparing everyday tissues has in no way been greater obvious or significant; withinAmerica, about 65% of grown person and 80% of children live on five years after their most cancers diagnosis. About 1/2 of most cancers sufferers obtain radio-therapy as a share of their beam. Current research pronounced, which the occurrence of beam-associated morbidity, consisting of 2nd cancers, cardiovascular disease, fertility complications, and different past due results, is alarmingly excessive in lengthy-time period survivors of most cancers. Presently, approximately three% of the United States populace are most cancers survivors. An information of the physics and biology of radiogenic past due consequences from proton beam has began out to emerge withinside the literature withinside the ultimate decade. Proton beam beam, is cutting-edge exercise withinside the majority of facilities to anticipate an RBE fee of 1.1 for protons, relative to photons, for all medical situations. A 'standard' RBE price of 1.1 is endorsed.2 Due to the modest LET (therefore RBE) variant involved, advice of a common RBE weighting element W (RBE) of 1.1 for protons appears logical for maximum medical situations. However, withinside the distal a part of the SOBP, a small boom of RBE has regularly been found due to the LET boom in that region. One outcome of LET growing wherein dose is lowering at the distal fringe of the SOBP is the extension of the biologically powerful variety of the proton beam through ~2 mm for 160–250 MeV and ~1mm for 60–eighty five MeV proton beams. The 'widespread' RBE price of 1.1 is the RBE weighting element, WRBE or W(RBE), and its product with the absorbed dose is the RBE weighted dose, DRBE or D(RBE). This weighting thing of 1.1 might be same to the 'is effective dose weighting element' WIsoE and (1.1 × D) might be identical to the 'is effective dose' DIsoE best if fractionation, universal beam time and all different situations might be the ones described for the reference beam situations (IAEA, 2008).

In the Darmstadt–Heidelberg programed the use of carbon ion beams, the RBE is computed deliberating the radiation pleasant (LET) and dose in line with fraction at any factor of interest, relative to photons brought at three Gy according to fraction, three fractions according to week. It must, of course, be talked about that, with inside the case of carbon ions, the RBE values are a lot better and showcase extra version during the goal quantity than the ones assumed for protons. The Chiba method in carbon ion beam. The weighting

issue, WI, for carbon ion beam followed in Chiba is primarily based totally on a mixture of radiobiological experimentation and a big quantity of medical revel in with neutron beam. The medical revel in with neutron beam indicated that a ‘medical RBE’ price of three changed into suitable while scientific consequences received with neutrons have been as compared with the ones received with photons. Based on a chain of radiobiological experiments in diverse mobile structures and determinations of LET in each the neutron and carbon ion beam (IAEA, 2008).

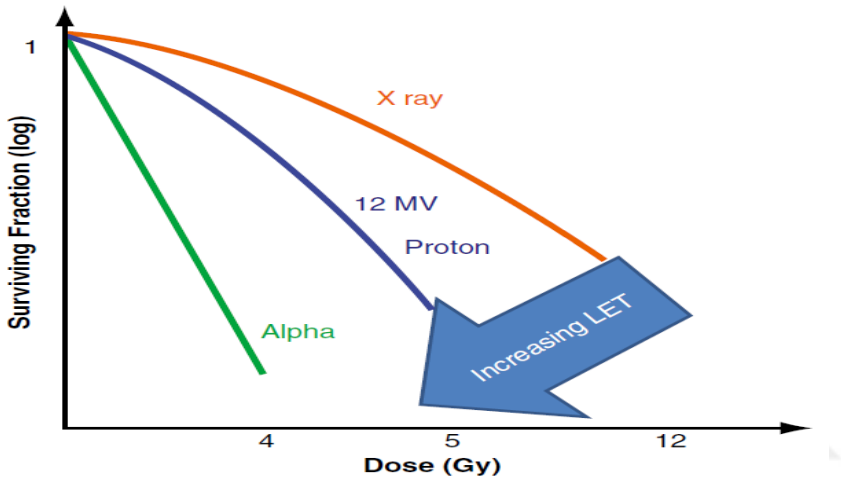


Figure 3.3. Liner energy transfer and survival fraction (Beyzadeoğlu et. al., 2010).

4. MATERIALS AND METHODS

4.1. Microdosymetric Kinetic Model (MKM)

The nucleus of a cellular in the MKM, is split into several domain names, and the ionizing radiation is thought to purpose sorts of number one DNA lesions withinside the domain. A kind I lesion is constantly deadly to the cellullar, and the kind II lesion is probably to be DSB that is probably deadly and may be effectively restored. The range of number one kind I and sort II lesions in a site are each relative to the particular strength z absorbed with the aid of using the domain, with the proportionality regular as λd and kd unbiased of the radiation quality (Hawkins, 1996).

A kind II lesion may also go through one of the 4 assumed alterations, after which the quantity of deadly lesions within side the domain, L is derivative to have a linear-quadratic dating with z, through fixing kinetic equations (Chen et. al., 2017). In the principle of the MKM, the yield okay of kind II DNA lesion, that's probably to be DSB, is unbiased of radiation quality (Hawkins, 2003; Hawkins and Inaniwa, 2013). To the experimental evidences of the DSB vintage of the cells of mammalian, the DSB profitlittle by little will increase with LET, while the LET is beneath 10th of keV μm^{-1}, because of the boom of the electricity statement density (Barendsen, 1994; Goodhead, 1994). In addition, when LET will increase with inside the better range, chemical unfastened radicals produced with the aid of using the radiation may also have greater chance to react with every different due to the excessive nearby density and feature much less chance to react with DNA, and the saturation impact might also additionally seem because the excessive ionization density may also result in a waste of strength, as a consequence the DSB yield will lower. Therefore, the parameter okay and have to range with LET. Also, the RBE of the cell survival fraction will increase with LET after which goes to lower at approximately a hundred keV μm−1, that is brought on via way of means of several causes (Heilmann et al., 1995, Hawkins, 1998; Hoglund et al., 2000).

The specially one is probably the parting from a Poisson scattering of deadly lesions of the various cells that has already saturation-corrected with inside the present MKM (Kase et al., 2006). Additionally, there is aninvolvement from the version of DSB income with

Linear Energy Transfer, however the conforming correction has now no longer been taken into consideration with inside the MKM. In brief, the existing MKM gets the unique strength z scattering amongst domain names under consideration for specific radiation qualities, however the extrade of the number one lesion yield with one of kind radiations isn't always taken into consideration and assumed because the steady, because of this, that β in equation is a consistent various with LET because the experimental value. By the way, the connection among the income of number one lesion and Linear Energy Transfer changed into taken into consideration, and a changed MKM become constructed primarily based totally at the modern MKM (Kase et al., 2006; Inaniwa et al., 2010, 2015).

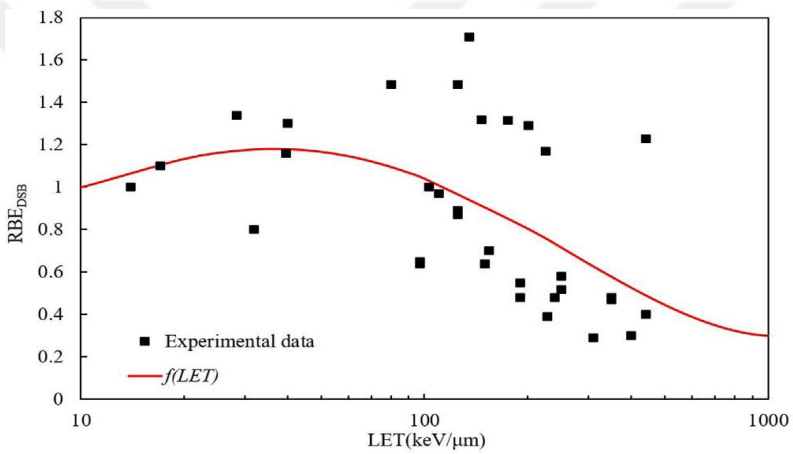


Figure 4.1. RBE DSB of the cells of the mammalian for particles with dissimilar Linear Energy Transfers (Chen et. al., 2017).

MKM derived from linear-quadratic relation of the Survival Fraction (SF) on the absorbed dose D (Sato et al., 2011): (Eq.3.1)

$$S = \exp [- (\alpha D + \beta D^2)] \quad (4.1)$$

Six basic assumption in MKM:

i. A nucleus of a cell may be separated into several domains;
ii. Radiation generates two kinds of DNA harm(lethal and sub-lethal lesions in cell nuclei)
iii. The number of lethal and sub-lethal lesions is proportional to the particular energy, z_n, in the domain;

iv. A sub-lethal lesion is to be fixed, or changed into a lethal lesion throughimpulsive transformation or interface with another sub-lethal lesion produced in the similar domain;

v. A domain is to be measured inactivated when an intra-domain lethal lesion is formed;

vi. A cell is to be measured inactivated when an intranuclear domain is inactivated (Sato and Furusawa, 2012).

The quadratic coefficients in Eq. (3.1) given as

$$\alpha_p = \alpha_0 + z_D\beta_0 \tag{4.2}$$

$$\beta = \beta_0 \tag{4.3}$$

Ronald B. Hawkins developed the model of The Microdosimetric Kinetic (KM), who used benefits from the philosophy of dual radiation action (TDRA), the lethal-potentially lethal (LPL) model the repair-misrepair form and. with the compare and contrast of the model, a brief explanation of historic sources of the form and the full description of its fundamental will be illuminated.

Presently, it describes a summary of the theoretical formulation in which forms are built on. The theory accepts that after taking place of the cell irradiation, in a small range of the cell nucleus the number of lethal lesions defined place is relational to the four-sided of the particular energy z placed in that place (Bellinzona et. al., 2020): (Eq.3.6)

$$\varepsilon(z) = Kz^2 \tag{4.4}$$

Here, the rate of the mixture of sub-lesion and modeling of lesion is expressed by K factor. This hypothesis is generalized in the improvement of the MKM. Putting more quadratic proportionality to the lethal injuries and then assuming a linear-quadratic reliance on z.

MKM gets the conception of impairment time development for the repair or conversion into a lethal unreparable lesion (chromosome aberration) of the main hypothetically lethal radiation encouraged lesions in DNA from the repair-misrepair (RMR)

form, established by Tobias. To understand radiobiological experimentations with heavy ions.

This form, RMR, which considers the sum of DSBs in the DNA, U (t) is relational to the radiation dose rate; an amount of DSBs grow in lethal lesions, L (t), while mostly disruptions are positively repaired with a primery order development. Also there is a possibility of misrepair as second order development in the model, since it contains 2 broken DNA elements to shape a chromosomal aberration. The concept of misrepair was primarily developed by Lea and Catcheside in 1942, to define the development of chromosome aberrations in tradescantia.

Obtaining the direct link of the form to the cell survival phenomenological LQ formulation is possible. Therefore, the α coefficient apparently reliant on the radiation quality with a single term, the dose average particular energy for each single event z_D, which may be associated to microdosimetric measurements. In this formulation of the MK form, it has to be considered that it has no apparent reliance to the radiation quality in the quadratic coefficient $\beta 0$, which is considered constant analogously to the consequence of the TDRA. Lately, there is an approximation of the model, which is difference with trial observations, even though in several ways, particularly noting the investigational suspicions related to the $\beta 0$ determination, wich is considered to be realistic, this calculation will be peaceful and the β coefficient will be noticed reliance on the radiation quality (Bellinzona et. al., 2020).

From the information of the LQ parameters is probable to derive the dose (D) and the quality of radiation (z_D) in need of RBE (Dale and Jones, 1999; Carabe-Fernandez et al., 2007): (Eq.3.5)

$$\text{RBE}\,(D,z_D) = \frac{1}{2D}\{-1+\sqrt{1+\frac{4}{R}(RBE\alpha(z_D)D+\frac{(RBE_\beta\, D)^2}{R})}\} \qquad (4.5)$$

Where $R = \alpha x / \beta x$, $RBE_\alpha(z_D) = \alpha(z_D) / \alpha X$, $RBE_\beta = \sqrt{\beta/\beta_x}$ and αx and βx are the phenomenological LQ coe_cient for the photon reference radiation. Since the parameters α_0 and β_0 are considered to be liberated on the quality of radiation, and $\beta = \beta_0$, it is logical to define $a0 = \alpha$ (LET $\rightarrow$ 0) and $\beta_0 \sim \beta_x$($RBE_\beta \sim 1$). In high-LET calculations, meanwhile the

one dose particle be an average of a particular energy z_D for photons may be noticed slightly minor relation to that of high-LET radiation, $\alpha_0 \sim \alpha_x$ and from now is probable to compose;

$$RBE_\alpha = \frac{\alpha 0}{\alpha x} + \frac{\beta 0}{\alpha x} \times z_D^{(c,d)} \approx 1 + \frac{1}{R} \times z_D \quad (4.6)$$

Wherever ratio R may can be produced from a non-linear reversion examination of measured data of the survival cell for a low Linear Energy Transfer position radiation. So the equation may be formed as:

$$RBE_\alpha = k_1 + \frac{k_2}{R} \times y_D \quad (4.7)$$

Anywhere k1 and k2 are phenomenological parameters. Since z_D is relational to the average dose lineal energy yd, is similar to the linear simulations built on the averaged dose LET, which was used for protons (Carabe et al., 2012; Wedenberg and Toma-Dasu, 2014; Jones, 2015; McNamara et al., 2015).

Non-Poisson correction

It is expected, which the variance of the particular energy z_n between cells is totally small. So, in each cells, the number of lethal events accompanies the similar Piossion scattering, with average χ_n,I . Though, generally the received energy in the cell, which is called a stochastic quantity, which differs from one cell to another, while noticing entire population of the cells of irradiation, it brings also a deviation from the Poisson distribution. It is be commented that the devitation is essence even if the radiation is totally monoenergetic. By the way, the variance of the specific energy z_n rises from the uctuation of the particle numbers, whichare beating the cells. Moreover, the uctuations are mostly related, since giving a macroscope dose D, the the Liner Energy Transfer of the particle is comparatively high, interacting of the averaged amount of particles of the high liner energy transfer with the cell is lower than the amount of the particles of low linear energy trasfer. The development to the MK model has been presented by Hawkin (2003), to explanation for the non-Poisson scattering of the lethal events. Transporting a nonconformity from the linear behaviour of the RBE vs. LET, in the high LET region (Bellinzona et. al., 2020).

The effect of the non-Poisson distribution of lethal lesions is considered by explicitly evaluating the fraction of hit and non-hit cell nuclei. Considering a very low dose high-LET irradiation, D << 1, the probability for a cell to interact with more than one particle is negligible. In this case the population 13 of cells can be subdivided in a fraction Φ of cells that su_er a single particle interaction and a fraction 1 - Φ of cell with zero interactions. We denote with χ_I,n (z_n,D) the average number of type I lethal lesions in the fraction Φ of cells whose sensitive nucleus has been hit by a single particle imparting exactly a specifc energy z_n;D in the nucleus then, we obtain (Eq.3.8)

$$\chi_I,\text{n}\ (z_n,\text{D}) = -\log \text{S}(z_n,\text{D}) = (\ \alpha 0 + z_D \beta 0)\ z_n,\text{D} + \beta 0 z_n^2, D. \tag{4.8}$$

It is possible to explicitly write the global surviving fraction of cells (including both hit and non-hit nuclei) as (Bellinzona et. al., 2020): (Eq.3.9)

$$\text{S(D)} = (1 - \Phi\ ) + \Phi e^{-\chi_I,\text{n}\ (z_n,\text{D})} \tag{4.9}$$

This corresponds to consider a probability density function fn (z_n,D) = (1 - Φ) δ(z_n) + Φδ (z_n-z_n,D) . Since the number of lethal lesions per cell averaged over the whole cell population (including both hit and non-hit nuclei) exposed to the macroscopic dose D can be directly evaluated as (Eq.3.10)

$$\langle \chi_I, n\ (z_n, D) \rangle_c = \Phi \chi_I,\text{n}\ (z_n,\text{D}), \tag{4.10}$$

equation 3.9 can be rewritten as :

$$\text{S(D)} = 1 + \frac{\langle \chi_I, n\ (z_n,D) \rangle_c}{\chi_I,\text{n}\ (z_n,\text{D})} (e^{-\chi_I,\text{n}\ (z_n,\text{D})}) - 1$$

$$= 1 + [\frac{e^{-(\alpha 0 + z_D \beta 0) z_n,\text{D} - \beta 0 z_n^2, D} - 1}{(\ \alpha 0 + z_D \beta 0)\ z_n,\text{D} + \beta 0 z_n^2, D}]((\alpha 0 + \beta o z_D)\text{D} + \beta 0 D^2 \tag{3.11}$$

Taking the log of S, expanding around D = 0 and dropping terms in D^2 or higher powers, the linear term of log S(D) can be written as

$$- \text{Log } S(D)|_{D\to 0} \approx (\alpha 0 + \beta o z_D) \times \left(\frac{1-e^{-(\alpha 0 + z_D \beta 0) z_{n,D} - \beta 0 z_{n,D}}}{(\alpha 0 + z_D \beta 0)\, z_{n,D} + \beta 0 z_{n,D}^2} \right) \times D$$

$$\approx \alpha p \times \left(\frac{1- e^{-\alpha p z_{n,D}}}{\alpha p z_{n,D}} \right) \times D \qquad (4.12)$$

$$= \alpha_{NP} \times D$$

Where αp is the Poisson α coefficient, while the subscript NP signify the Non-Poisson modified α coefficient. Resulting also the unique preparation of Hawkins, the quadratic term $z_n^2, D << z_n, D$ was similarly ignored. It is considered that in the above equations a indirect calculation is expected to tie the request of having a Poisson scattering in the lethal procedures, by one well-defined value of $z_n = z_n, D$ when the cells are hitted by particle. Mostly, it is the way and the particular energy may similarly differ as a function of the influence parameter of the particle with respect the nucleus of the cell. Still, $\chi_I, n\ (z_n, D)$ is utilized as an estimate of the middling amount of lethal lesions in those cells, which suffered an event after exposure to a dose D. This statement may be practical when small energy particles with high LET are measured. The Non-Poisson correction to the RBE in the limit of zero dose (RBE_) is given by (Bellinzona et. al., 2020)

$$RBE_{\alpha,NP} = \frac{\alpha_{NP}}{\alpha_X} = \left(\frac{1- e^{-\alpha p z_{n,D}}}{\alpha p z_{n,D}} \right) RBE_{\alpha,P} \qquad (4.13)$$

With $RBE_{\alpha,P}$. no alterations are given to theRBE_β, which is still expected unbroken ($RBE_\beta \sim 1$) and free on radiation quality. The alteration reasons the RBE_α to be fewer than specified by the extrapolation of the linear relationship to higher LET, and to go through a extreme in the range of LET of 50 to 150 keV/_m. such an action is well-matched with some scientific studies the literature and it demonstrates similarliy a sensitivity of the maximum of the RBE to the reply of the cell at low-LET, linked to the parameter $R = \alpha_X / \beta_X$. An exemplification of the RBE behaviour and the calculation of the model. So, several qualitative suggestions of the non-Poisson regime in high-LET ion beam therapy are portrayed (Bellinzona, 2020).

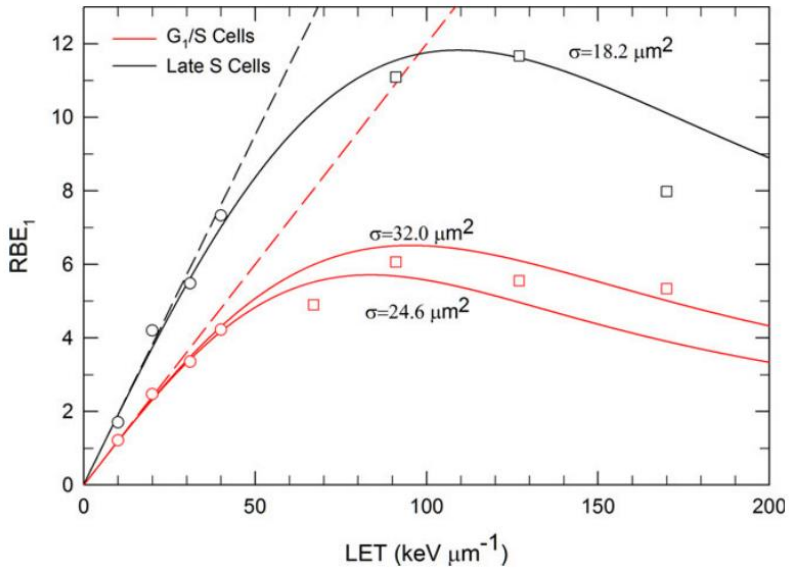


Figure 4.2. Comparison of MKM estimates of particle RBEα to experimental, values for V79 cells (Bellinzona et. al., 2020).

4.2. Monte Carlo Simulations

Any technique which solves a hassle with the aid of using producing appropriate random numbers and staring at that fraction of the numbers obeying a few assets or properties (Staporve et. al., 1988).

Monte Carlo simulation: is an automatic mathematical method that lets in humans to account choice making. Moreover, entire proton dose willpower in presenting a position beam generally needs perturbation corrections primarily based totally at the Monte Carlo approach to decide the aids from number one and secondmechanisms, for the photon number one average. Moreover, Monte Carlo primarily based totally beam making plans structures may be utilized to decide the arrangement, and checking out information for affected person dose prediction is predicated on correct models. Additionally, a medical necessity is to apply an unbiased device to confirm the rightness of the beam plan. Consequently, a demonstrated Monte Carlo device for the radiation simulation delivery will be a beneficial device for pre-medical and medical studies (Foster Jr and Arthur, 1982; Sato et. al., 2013, Yang et. al., 2017).

There are three MCCs. Which are FLUKA, GEANT4 and MCNP6, with inside the standard authentication for the appropriate valuation of influence and dose, as features of

role and area. For the total simulated proton shipping become followed with brought on neutrons, generating a negligible dose. The proton antiquities of various runs controlled as a minimum 1×107 occurrence particles in an effort to lessen the statistic variations.

4.3. PHITS Program

In current years, carbon beam has attracted tons hobby because of its capacity to supply a more dose attention on tumors and better beam effectiveness relative to different radiation beam techniques. In beam planning, it's miles critical, which the dose delivery in sufferers is envisioned correctly. Though one dimensional heavy ion distributionprogram were evolved and utilized at medical establishments or utilized to version area radiation arenas, the impact of beam unfold due to distribution or deflection isn't always engaged into account. Pay no attention to beam distributiondrops calculation accuracy of dose distribution, particularly whilst the projectile beam is distributed or is deflected at a big direction. A 3-dimensional delivery code is needed which will estimate the dose distribution in a carbon bam gadget generally. Lately, hasdeveloped for the primary period a popular reason heavy ion delivery, Monte Carlo codes, PHITS. PHITS is primarily built totally at the NMTC/JAM program and consists of Shen’s components for calculating overall response go units of heavy ions, the code of SPAR, for the common strength lack of heavy ions, and the code of JQMD, for the evaluation of heavy ion responses. PHITS is the primary three-dimensional Monte Carlo code, which may put on the shattering in heavy ion crashes, and nicely copiesinvestigationalfacts in heavy ion variety and manufacturing go phase of second particle. For the reason, PHITS may be implemented to dose scattering evaluation for carbon beam withinside the close to upcoming. Though, PHITS offered demanding situations, which had to be triumph over previous to its software for carbon beam systems. Primarily, most effective shipping in a DC magnetic subject turned into to be had withinside the unique PHITS code, aleven though AC magnetic arenas are hired in carbon beam aperture. Secondly, PHITS did now no longer consist of a version to calculate the electricity dispersion across the common power loss, which can save you a correct estimation of dose distribution.

Improvement of three dimensional Monte Carlo code, PHITS for heavy ion beam, PHITS is a multi-purposeheavy ion and particle shipping Monte Carlo code machine that turned into specifically evolved and continued throughKEK, RIST and JAEA, in Japan. It offers beside the transportations of all hadron styles and heavy ions with energies as much as two hundred GeV, and atomicresponses of low strength neutrons right all the way down to current energies. Due to this, PHITS program employs 3 response fashions: a molecular dynamics version JQMD, a hadron cascade version JAM, Moreover, for nucleus–nucleus crashes, and a response version primarily based totally at the estimatedatomic facts along with the ENDF-B/VI, JENDL-three. Three and JENDL-HE, for low power neutrons and photons withinside the identical way as in MCNPX. Neutrons, Protons, electrons, photons different slightpaticle and additionally heavy ions may be tracked through PHITS. In 2007, PHITS changed into evolved an occasion generator mode withinside the MCNP component for low power neutron shipping that mixes the nuclear records and the response fashions to hold the power and energyprotection in a crash. Thus you'll gain now no longer most effective the suggest price which includes track, flux and electricity statement, however additionally the variations across the suggest price, which elements the opportunity for the calculation of credit power scattering in Pb spallation goal.

Heavy Ion Transport code System andParticle, PHITS, which is a popular reason three dimensional Monte Carlo particle delivery simulation code evolved via collaboration with numerous institutes in Japan and Europe. To observe PHITS to scientific physics, unique features have been applied withinside the code: an occasion generator mode and a microdosimetric tally function. Utilizing those features, a brand new relative-biological-effectiveness -weighted dose estimation technique for charged-particle beam become installed on the idea of the double-stochastic micro-dosimetric kinetic version. Owing to those features, PHITS has been used for numerous scientific packages, inclusive of affected person dose estimation for radiotherapy and computed tomography exam code is an crucial put in force withinside the layout examine of accelerator centers in addition to for different diverse packages including radiotherapy 1 BNCT is a binary radiation beam modality that brings collectively additives that once stored separate have simplest minor results on cells. The first factor is a solid isotope of boron (10B) that may be focused in tumor cells through attaching it to tumor looking for compounds. The 2d is a beam of low-strength neutrons.

10B in or adjoining to the tumor cells disintegrates after shooting a neutron and the excessive strength heavy charged particle produced break best the cells in near proximity to it, ordinarily most cancers cells, leaving adjoining regular cells in large part unaffected.

5. RESULTS AND DISCUSSION

Hadron therapy is done with high energy heavy ions. Ion energies are determined by the depth of the target, the amount of dose required for the target, and the clinically accepted dose of the surrounding tissues. Incorrect energy selection may cause some of the delivered dose to damage surrounding tissues outside the target. The sharp Bragg peak of protons and heavy ions provides an advantage in choosing the right energy and dose for treatment and plays a decisive role in the correct RBE calculation. For RBE calculations linear energy transfer is one of the fundamental parameter for transferring the desired energy to a specific area for tumor control and preservation of healthy tissue.

In this study, relative biological effectiveness (RBE) calculations were made for the targets determined for proton and carbon used in hadron therapy with taking account the LET and lineal energy values. Hadron energies were determined as 160 MeV/u and 200 MeV/u for proton, 135 MeV/u and 290 MeV/u for carbon considering the energy range used in clinical studies. Soft tissue and A-150 (tissue-equivalent plastic) were selected as biological targets and their chemical weights were taken from the NIST database.

In RBE calculations, results obtained from PHITS program were used in analytical, poisson (Eq. 3.5) and nonpoisson (Eq. 3.13) equations obtained from basic linear quadratic equations of MKM (Eq. 3.2 and 3.3). In the calculations, 200 kVp X-rays (α value: 0.19 Gy^{-1}, β value: 0.05 Gy^{-2}) values and domain radius r_d: 0.282 μm were accepted as input parameters for the reference radiation.

The geometry used in the program was selected in thicknesses that would absorb the entire dose, considering the values given in the literature (Fig. 4.1.a, 4.1.b). Survival fraction and RBE values obtained by making calculations for the depth (Bragg peak) at which the dose distribution (energy transfer) occurs most in the selected geometry were compared with the literature.

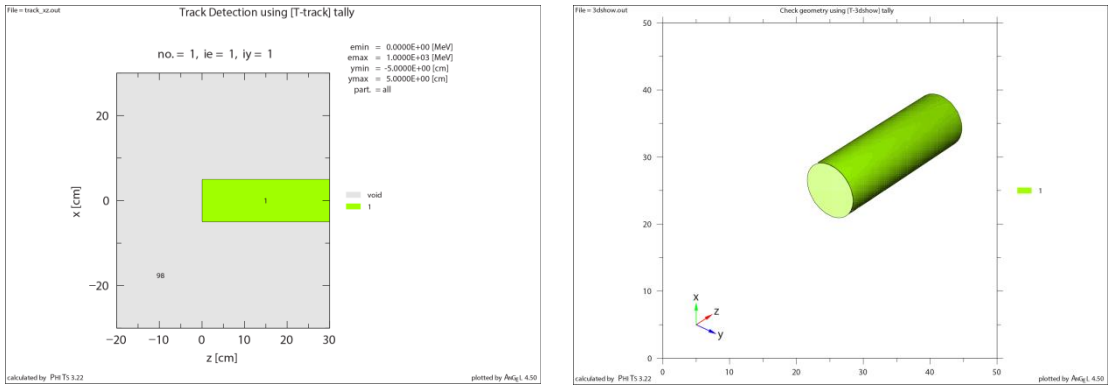
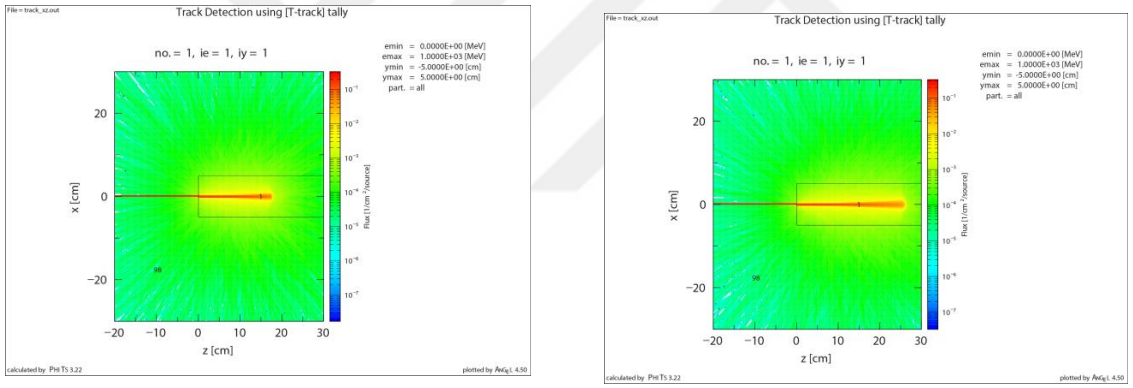


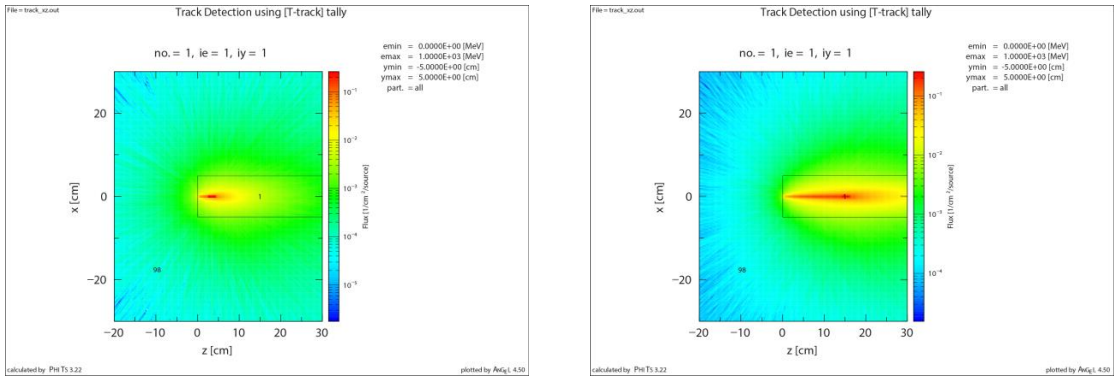
Figure 5.1. 2D and 3D geometries of target area.

5.1. Soft Tissue

The maximum dose depths for the projectiles and energies used for soft tissue were



a) b)



c) d)

Figure 5.2. Track tallies of projectiles in soft tissue a) 160 MeV/u proton beam b) 200 MeV/u proton beam c) 135 MeV/u carbon beam d) 290 MeV/u carbon beam.

determined from the track files (Fig. 4.2). The maximum depths of dose distributions were verified with dose distribution values. When the track graphs given in Fig. 4.2 are examined, it is seen that the maximum dose distribution are around 17 cm and 26 cm for protons with 160 MeV and 200 MeV energies, respectively. Similarly, it is seen that these values are 5 cm and 16 cm for 135 MeV and 290 MeV energy carbons, respectively.

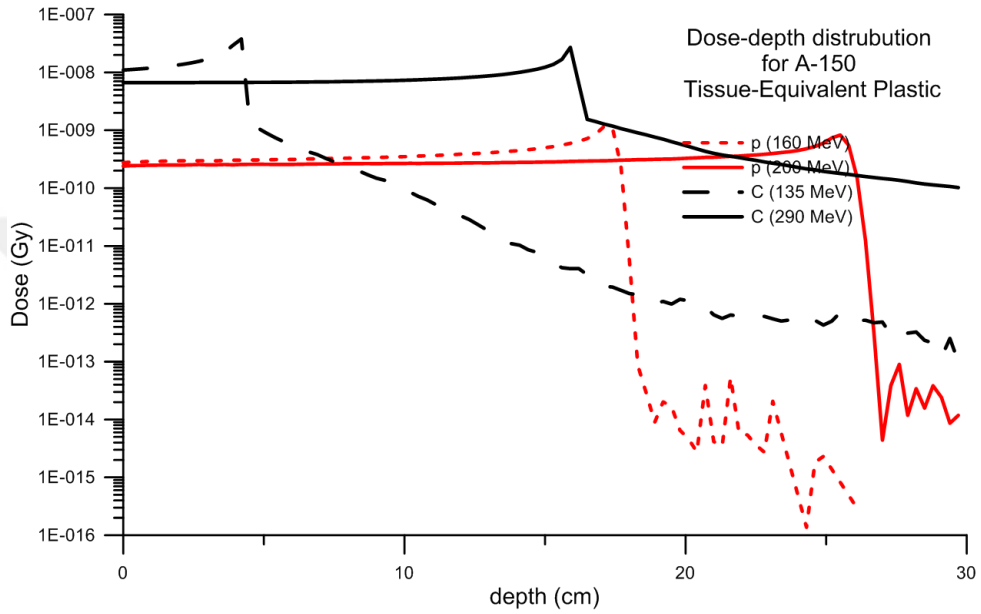


Figure 5.3. Dose distributions of 160 MeV/u proton beam, 200 MeV/u proton beam 135 MeV/u carbon beam, 290 MeV/u carbon beam in soft tissue.

When the dose values given in Fig. 4.3 are examined, it is seen that the dose distribution obtained is at the expected values. Another detail seen in the dose distribution graph is that carbon peaks are sharper than proton peaks.

When survival fraction calculations were made using the dose values obtained from the lineal energy distribution, the graph given in Fig. 4.4 was obtained for soft tissue. As can be seen from the graph, the highest cell death at the same dose value belongs to carbon beams with 135 MeV energy. This is because low energy carbon has a higher LET compared to high energy carbon. It is possible to establish a similar relationship between protons.

When the relative biological activity values for protons with 160 MeV energy given in Figure 4.5 are examined, it is seen that analytical calculations and poisson's calculations are similar, but translation is required for similar values. Although all three models give similar results in the low LET region, it is seen that especially analytical calculations give

discordant results in the high LET region. Only calculations with non-poisson correction give the result compatible with the Bragg peak area. The Poisson calculation did not give the expected bending in the Bragg peak area.

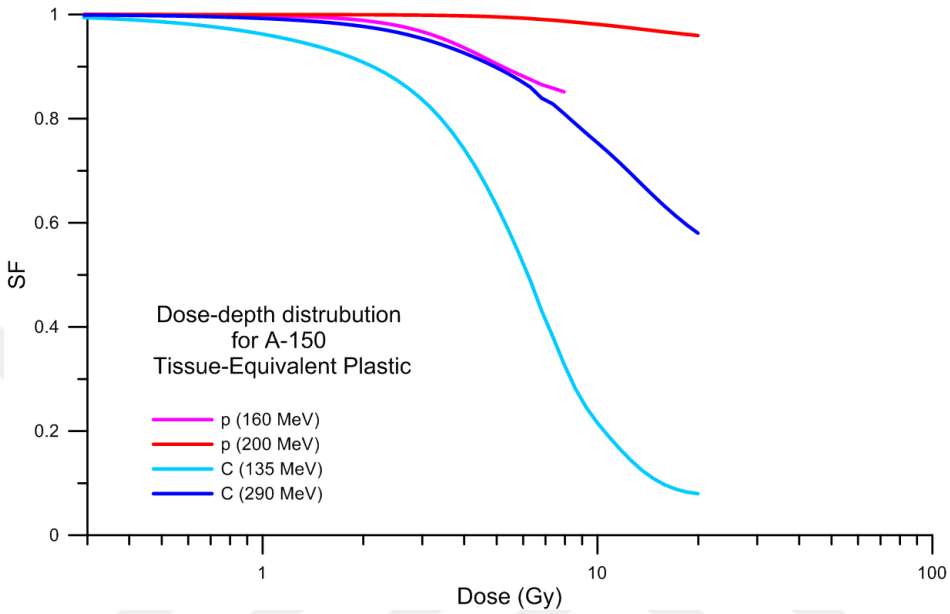


Figure 5.4. Survival fraction calculations of projectiles in soft tissue.

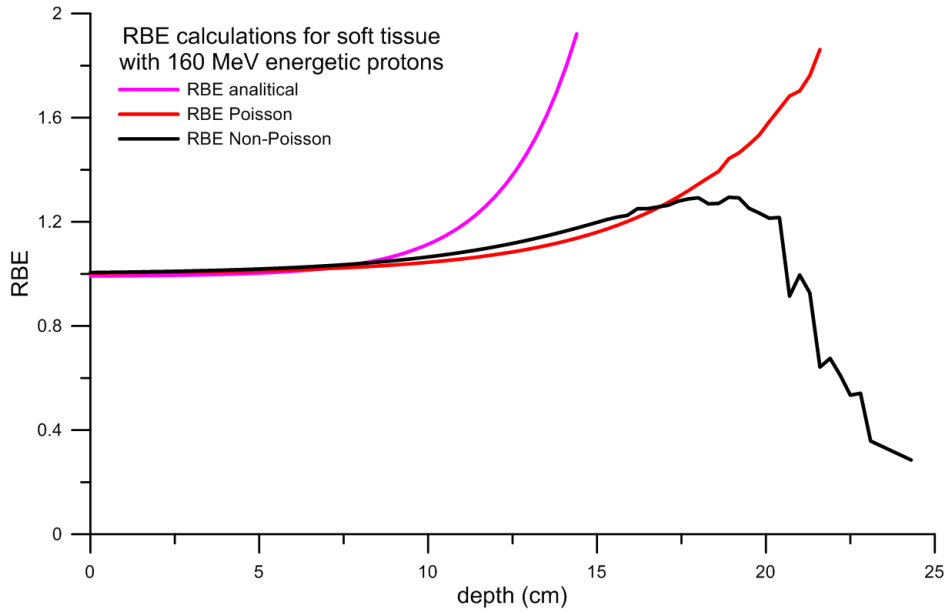


Figure 5.5. RBE results of 160 MeV/u protons in soft tissue.

When the relative biological activity values for the 135 MeV energy carbon beam given in Fig. 4.6 are examined, it is seen that analytical calculations and poisson calculations are similar, but translating will disrupt the correlation. Since the Brag peak is close to the point where the beam enters the surface, the peak in the non-poisson correction was observed close to the surface. However, the peak expected to be sharp has a wide distribution. The other two models, on the other hand, failed because the Bragg peak area was observed close to the surface and they were not capable of bending.

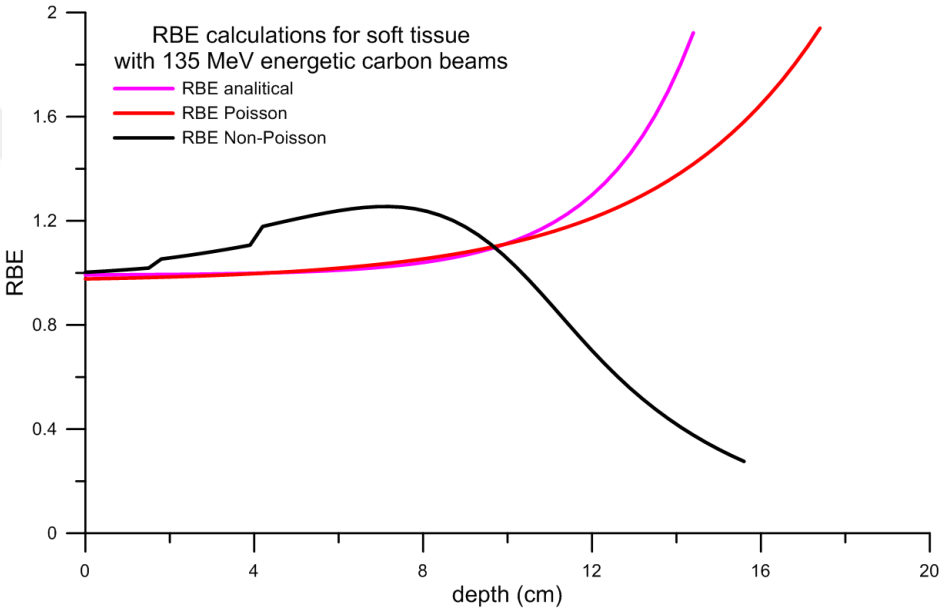


Figure 5.6. RBE results of 135 MeV/u carbons in soft tissue.

In Fig. 4.7 for given results for analitycal, poisson and nonpoisson calculations of RBE gives expected shapes. For low energetic protons it can be seen that the results are not agreement with the experimental results. But higher LET protons give results with good agreement with experimental measurement. As expected analitical and poisson calculations give the same shape on the graphic but poisson results are multiplied with 2.7 to gain good agreement. Both analitical and poisson results are not able to get curve with higher LET values. In our calculationswe obtained same non poison results for two different energy values for protons and unfortunateley our calculation results are not acceptable limits compared to experimental data.

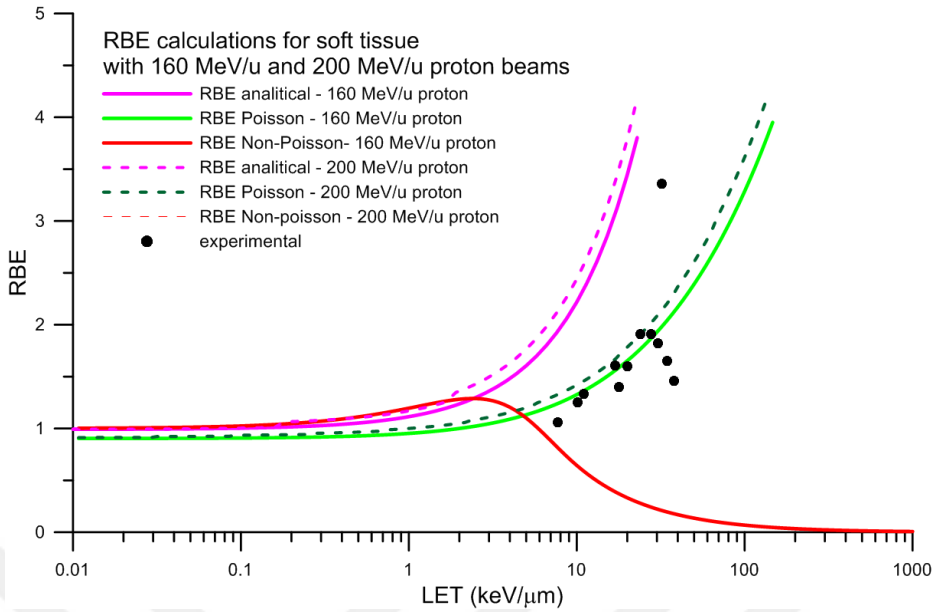


Figure 5.7. Analitycal, poisson and nonpoisson RBE results of 160 MeV/u and 200 MeV/u proton beams in soft tissue.

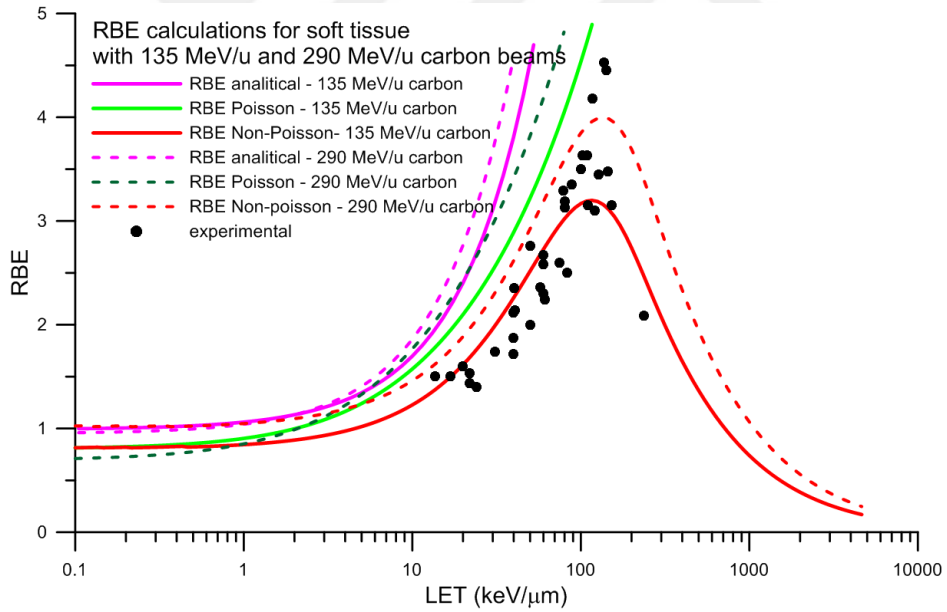


Figure 5.8. Analitycal, poisson and nonpoisson RBE results of 135 MeV/u and 290 MeV/u carbon beams in soft tissue.

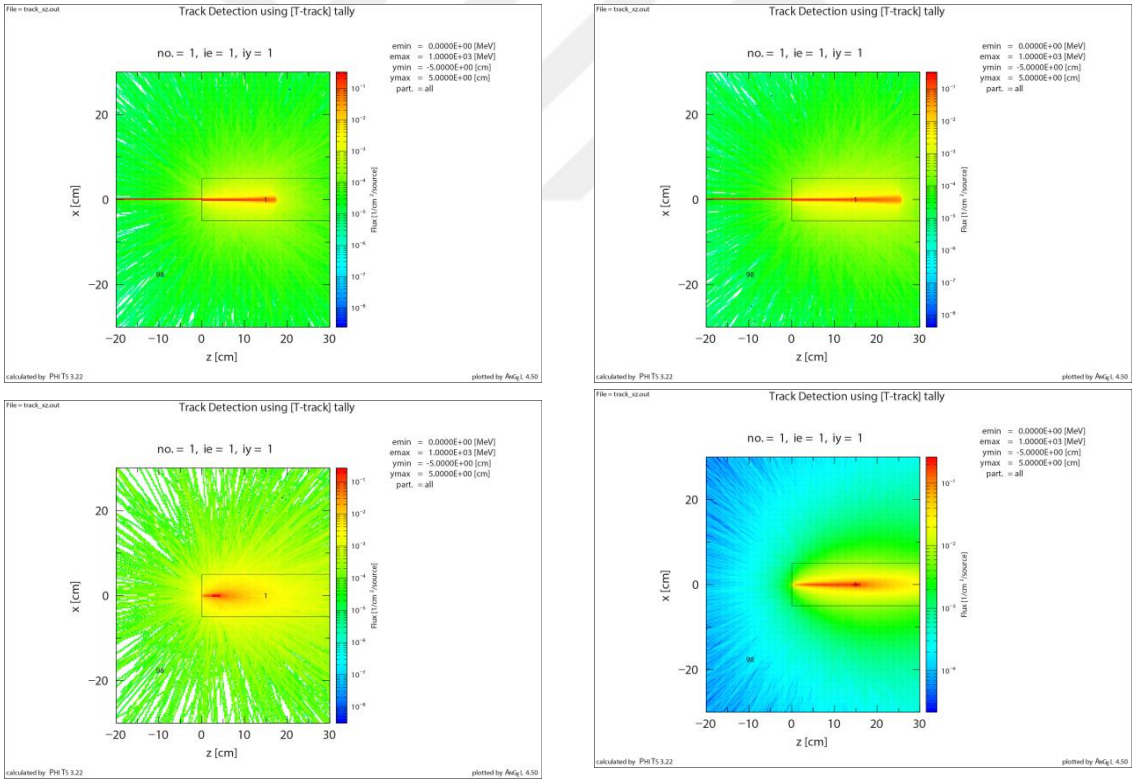
In figure 4.8, where the RBE calculations of 135 MeV / u and 290 MeV / u carbon ions in soft tissue are given, it was seen that nonpoisson calculations gave results that were in good agreement with experimental data. Again, as given, it was seen that other

calculations gave well-formed results in the low LET region and could be fitted to experimental results with a suitable shift coefficient.

5.2. A-150 Tissue-Equivalent Plastic

The maximum dose depths in the bullets and energies used for A-150 tissue-equivalent plastic were determined from the track files (Fig. 4.7). The maximum depths of dose distributions were verified with dose distribution values.

When the track graphs given in Fig. 4.8 are examined, it is seen that the maximum dose transfers are around 17 cm and 25 cm for protons with 160 MeV and 200 MeV energies, respectively. Similarly, it is seen that these values are 5 cm and 16 cm for 135 MeV and 290 MeV energy carbons, respectively.



c) d)

Figure 5.9. Track tallies of projectiles in A150 tissue equivelant plastic a) 160 MeV/u proton beam b) 200 MeV/u proton beam c) 135 MeV/u carbon beam d) 290 MeV/u carbon beam.

When the dose values given in Fig. 4.10 are examined, it is seen that the obtained dose distribution is at the expected values. Another detail seen in the dose distribution graph is that carbon peaks are sharper than proton peaks. And as expected high LET particles have smaller depths.

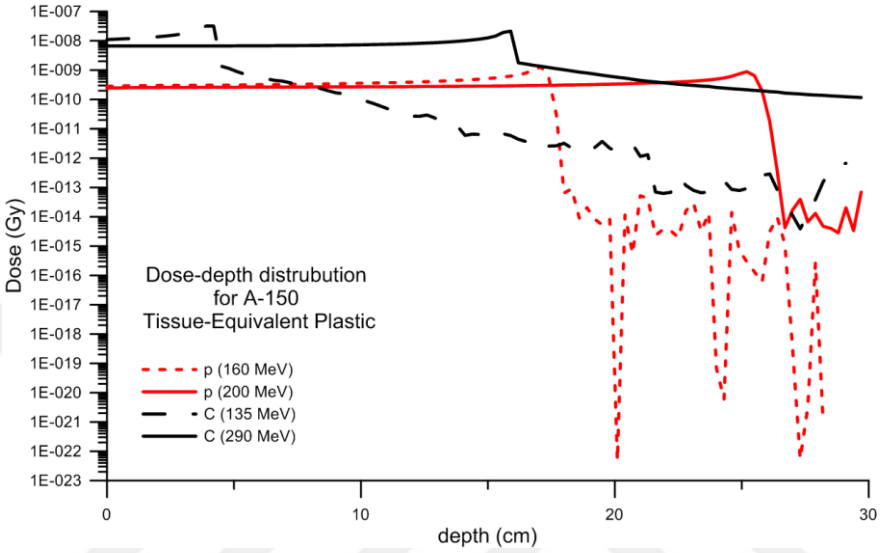


Figure 5.10. Dose distributions of 160 MeV/u proton beam, 200 MeV/u proton beam 135 MeV/u carbon beam, 290 MeV/u carbon beam in A150 tissue equivelant plastic.

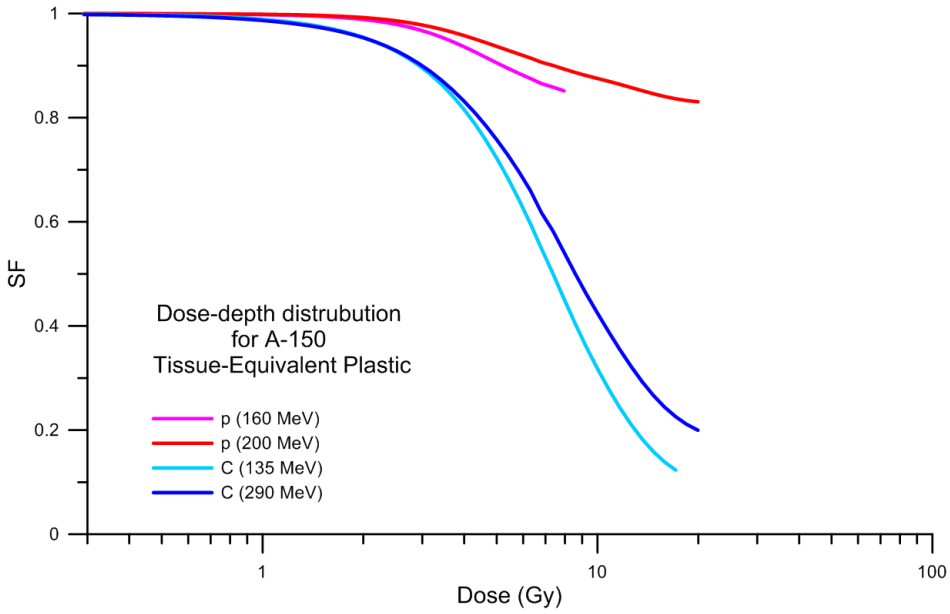


Figure 5.11. Survival fraction calculations of projectiles in A150 tissue equivelant plastic.

When survival fraction calculations were made using the dose values obtained from the linear energy distribution, the graph given in Figure 4.11 was obtained for A150 tissue. As can be seen from the graph, the highest cell death at the same dose value belongs to carbon beams with 135 MeV energy. This is because low energy carbon has a higher LET compared to high energy carbon. It is possible to establish a similar relationship between protons.

When the relative biological activity values for carbons with 160 MeV energy given in Figure 4.12 are examined, it is seen that analytical calculations and poisson calculations are similar, but translation is required for similar values. Although all three models give similar results in the low LET region, it is seen that especially analytical calculations give discordant results in the high LET region. Only calculations with non-poisson correction give the result compatible with the Bragg peak area. The Poisson calculation did not give the expected bending in the Bragg peak area.

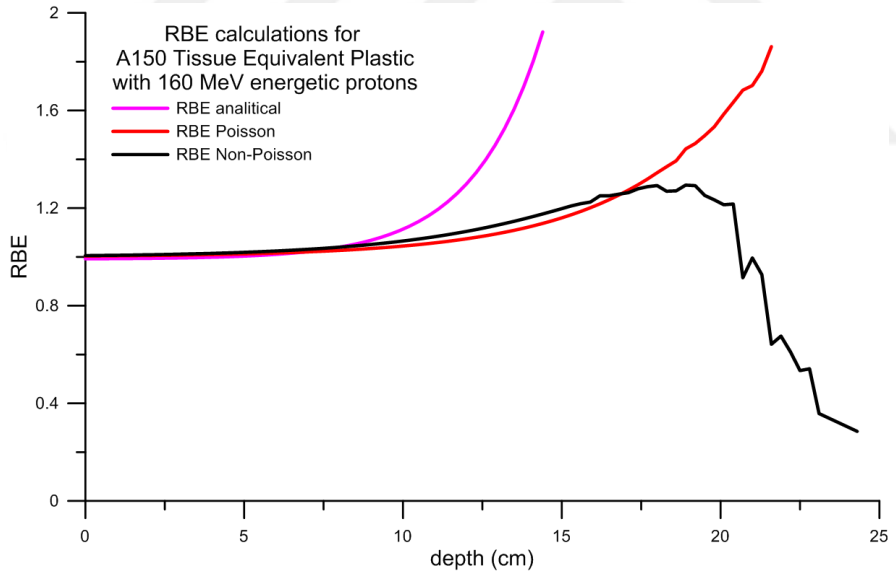


Figure 5.12. RBE results of 160 MeV/u protons in A150 tissue equivelant plastic.

Since we were able to reach experimental results regarding the change of RBE with LET in the literature, we made our evaluation on the graphs of these parameters. Therefore, only the depth RBE relation of the protons was given for A150 tissue equivalent plastic.

When the relative biological activity values for the 135 MeV energy carbon beam given in Figure 4.13 are examined, it is seen that analytical calculations and poisson calculations are similar, but translation will disrupt the correlation. Since the Brag peak is close to the point where the beam enters the surface, the peak in the non-poisson correction was observed close to the surface. However, the peak expected to be sharp has a wide distribution. The other two models, on the other hand, failed because the Bragg peak area was observed close to the surface and they were not capable of bending.

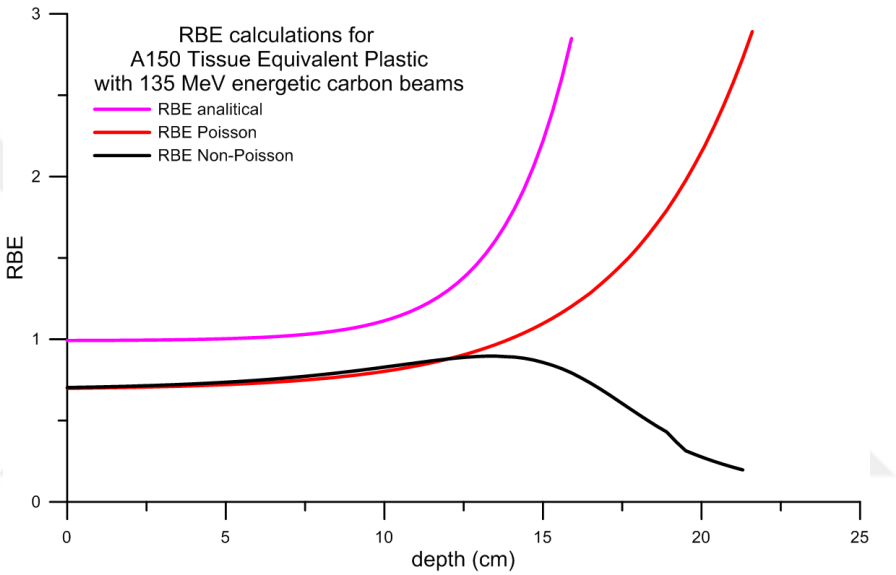


Figure 5.13. RBE results of 135 MeV/u carbons in A150 tissue equivelant plastic.

When the obtained results were evaluated, it was seen that the dose distribution and SF results obtained with the quasi-experimental parameters entered into the phits program were at the expected values.

In Fig. 4.14 for given results for analitycal, poisson and nonpoisson calculations of RBE gives expected shapes except fot 200 MeV/u protons. For low energetic protons it can be seen that the results are not agreement with the experimental results. But for higher LET protons nonpoisson calculations give aceeptable results compared with experimental measurement. And give a proper shape to make shifting with a convenient coefficient. As expected analitical and poisson calculations give the same shape on the graphic but poisson results are multiplied with 2.7 to gain good agreement.

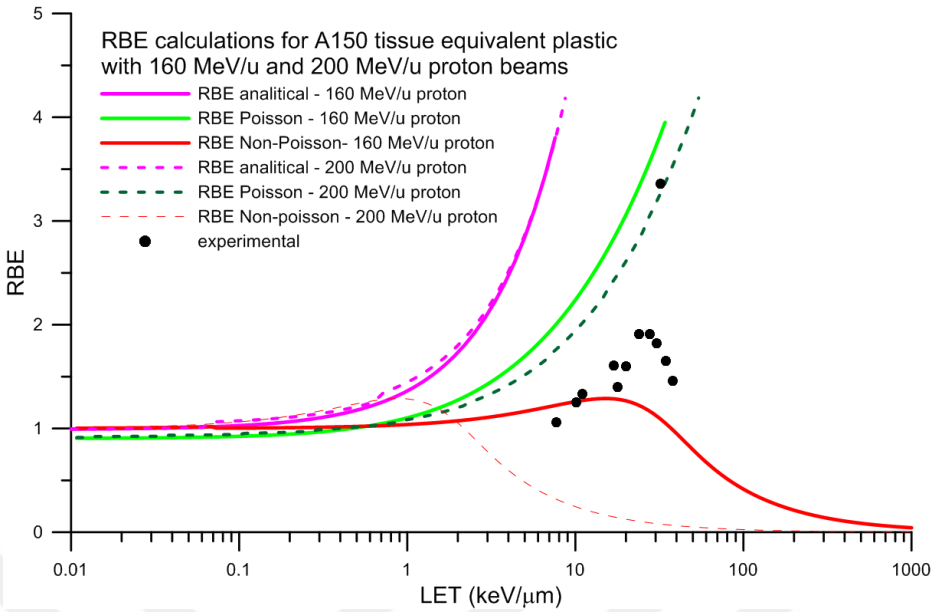


Figure 5.14. Analitycal, poisson and nonpoisson RBE results of 160 MeV/u and 200 MeV/u proton beams in soft tissue.

In figure 4.15, where the RBE calculations of 135 MeV / u and 290 MeV / u carbon ions in A150 tissue equivalent plastic are given, it was seen that nonpoisson calculations gave results that were in good agreement with experimental data for both energies. Again, as given, it was seen that other calculations gave well-formed results in the low LET region and could be fitted to experimental results with a suitable shift coefficient. Poisson calculations are fitted with 2.7 for these cvalculations and gave good results for low LET region.

It was seen that the analytical calculation results made with PHITS outputs gave appropriate results in the low LET region, but moved away from other model calculations in the high LET region and could not give the expected bending in the Bragg peak region.

It was seen that the RBE results obtained by Poisson distribution were similar to the analytical calculation results, but they were giving lower values. It was concluded that the similarity of the two calculation values can be evaluated with a displacement constant.

The information that the results of analytical and poisson calculations cannot give the bending in the high LET region in the literature has been reached in our calculations. We observed the bending in the Brag peak area in calculations with non-poisson correction.

However, instead of sharp peaks expected in this region, a distribution in the peak region was observed.

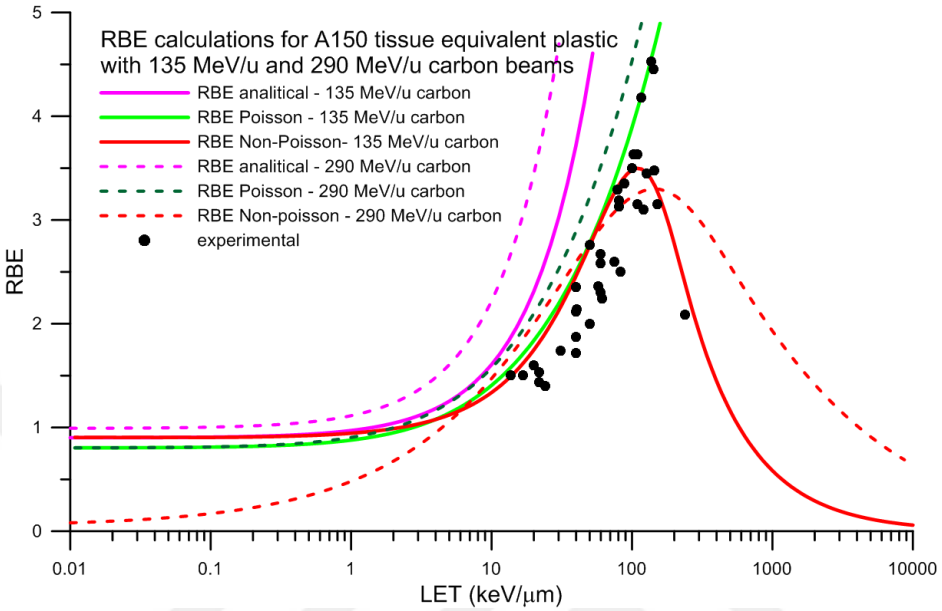


Figure 5.15. Analitycal, poisson and nonpoisson RBE results of 135 MeV/u and 290 MeV/u carbon beams in soft tissue.

6. CONCLUSION

Based on the findings we have obtained, it has been observed that the analytical calculation method from the MKM model calculations gives appropriate results in the low LET region as stated in the literature. The results of these calculations using the LET values obtained by the PHITS program can be matched with the experimental data with a translation constant, since the graph obtained with the experimental data is suitable for the form.

Poisson calculations using specific energy values obtained from the PHITS program were found to produce similar results as expected in analytical calculation, but a multiplier was applied to these lower-valued results. After the multiplier was applied, results in good agreement with experimental data were obtained, especially in carbon calculations.

In the calculations made with the nonpoisson correction recommended in MKM in order to obtain the bending in the high LET region, suitable results were obtained with experimental data in carbon calculations with high LET. Although the appropriate shape was obtained in the proton calculations, results were obtained that were far from compatible with the experimental data. Considering the standard acceptance of RBE as 1.1 in proton treatment, this calculation becomes difficult. Despite the negativity in nonpoison calculations for proton, it is possible to say that successful results were obtained in other calculations. As a result, it was seen that LET and specific energy distribution parameters obtained with PHITS program can be used in MKM calculations.

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EXTENDED TURKISH SUMMARY
(GENİŞLETİLMİŞ TÜRKÇE ÖZET)

AĞIR İYONLARIN BAZI BİYOLOJİK HEDEFLER ÜZERİNDEKİ BAĞIL BİYOLOJİK ETKİNLİĞİNİN TEORİK İNCELENMESİ

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Şubat 2021, 69 sayfa

ÖZ

RBE'nin LET ile değişimine ait kesin bir matematiksel teori henüz ortaya konulamadığından geliştirilen programlar farklı yaklaşımlar ve modellerle RBE için yarı deneysel sonuçlar üretmektedir. Uygulanan modellerin farklı fiziksel parametrelerle (enerji, doz vb.) farklı hedef derinliklerinde test edilmesi programların optimizasyonu ve geliştirilmesi için önemlidir. Bu çalışmada kullanılan PHITS programı RBE ve LET arasındaki ilişkinin çözümü için mikrodozimetrik kinetik modeli (MKM) kullanmaktadır.

Bu tez çalışmasında, hadron terapide kullanılan proton ve karbonun seçilen enerji değerleri için, yumuşak doku ve A150 doku eşdeğer plastik olarak belirlenen biyolojik hedeflerdeki etkilerinin bağlı olduğu fiziksel büyüklükler ile bağıl biyolojik etkinlikleri (RBE) incelendi. Çalışma kapsamında fiziksel büyüklüklerden LET ve spesifik enerji MC simülasyon yöntemi kullanılarak elde edildi ve RBE hesaplamaları MKM içerisinde verilen üç farklı yöntem ile yapıldı.

Anahtar kelimeler: LET, Monte Carlo**,** MKM, PHITS, RBE.

Radyasyonla tedavinin temel amacı, başta kötü huylu tümörler olmak üzere istenmeyen dokuların yok edilmesidir. Uygun dozlar verilebilirse x-ışınları, ağır yüklü parçacıklar (hadron terapi) ya da boron nötron yakalama terapisi (BNCT) gibi uygulamalarla kanserli hücrelerin kontrol altına alınabilmesi mümkündür. Hastaya uygun dozun verilebilmesi için, radyoterapi uygulamalarından önce doz dağılım planlaması yapılmaktadır. Doz dağılım planlamasında radyasyon enerjisinin maksimumunun tümör

üzerinde bıraktırılması, sağlam dokuya en az zararın verilebilmesi için, temel amaçtır. Yaygın olan x-ışınlı radyoterapide sağlıklı dokuların doz alması kaçınılmazken, ağır iyonlarla gerçekleştirilen uygulamalarda yüksek lineer enerji transferli (LET) radyasyonların kullanılması ile sağlıklı dokuların korunması mümkün olmaktadır.

Terapötik iyon ışınları genel olarak foton ışınlarına kıyasla belirgin bir Bragg maksimumumu ile derin bir doz dağılımı ve büyük penetrasyon derinliğinde keskin bir doz düşüş avantajı sunar. Bu yöntem hadron tedavi olarak isimlendirilir ve dış demet radyoterapisinin bir çeşididir. Linac ile elde edilen proton veya karbon gibi parçacık demetleri dokuya gönderilir. Hadron tedavide kullanılan ağır yüklü ($A \geq 1$) parçacıkların dokuda saçılmaları azdır. Parçacık demetinin saçılması az olduğundan enerjisinin büyük kısmını hedeflenen tümör üzerinde bırakabilir, böylece sağlam doku çok zarar görmez. Bu nedenle ağır yüklü parçacıklar, hedeflenen hacimde dozu biriktirmek ve çevredeki sağlıklı dokulardaki dozu en aza indirmek açısından radyoterapide avantaj sağlamaktadır.

Proton ve karbon tedavisinin klinik olarak kullanılmasının gerekçesi, foton kullanan radyoterapiye karşın tümöre daha yüksek doz verilebilmesi ve sağlam dokunun daha iyi korunabilmesidir. Ağır yüklü iyonlar ortama girdiğinde, yaklaşık olarak hızının karesiyle ters orantılı olarak enerjisini ortama aktarır ve doku boyunca ilerlerken duracağı ana kadar yavaşlar ve enerjisini aşamalı olarak kaybeder. Bu nedenle parçacık yavaşlarken ortamdaki atomların iyonizasyon olasılığı da artar ve iyonizasyon olaylarının maksimum olduğu derinliğe maksimum doz aktarılmış olur. Tüm bu enerji kaybı Bragg eğrisi ile gösterilir.

Hadron terapinin foton radyoterapiye göre temel avantajı, iyonların maddede belirlenebilen bir derinlikte durması ve Bragg pikinde maksimum bir enerji depolanmasıdır. Bu etki, elektronlar ve atom çekirdeği ile Coulomb etkileşimlerinden kaynaklanan, parçacığın ortamın birim uzunluğundaki ortalama enerji kaybı olarak tanımlanan durdurma gücü ile karakterize edilir. Foton radyoterapi de hastaya verilen dozlar, sağlıklı dokuları korumak amacıyla genellikle sınırlı enerjilerdedir. Oysa iyonlarla verilen daha yüksek dozlar daha iyi bir tümör kontrolünü mümkün kılar. Hadron terapi ile elde edilen avantajlar, kritik konumlardaki tümörleri tedavide daha iyi sonuçlar alınmasını sağlamıştır. Karbon gibi daha ağır iyonlar ise protonlara veya diğer daha hafif iyonlara göre daha fazla avantajlar sağlar: Bunlardan ilki, dokudaki yanal saçılmanın daha

az olması, ikincisi ise, Bragg zirvesindeki durdurma bölgesinde, yüksek bir bağıl biyolojik etkinliğe (RBE) sahip olmasıdır.

Hadron terapide deneysel verinin azlığı ve maliyetinin yüksek olması uygun doz planlaması için çok değişkenli ve sonucu öngörülemeyen bir problemin çözülmesini gerektirmektedir. Verilen doza bağlı LET ve RBE değerlerinin tayini için Monte Carlo (MC) simülasyon yönteminin kullanılması uygun bir yaklaşım olmaktadır ve medikal fizikçileri benzetim programlarına yönlendirmiştir. Ağır iyonların LET değerlerinin dokudaki dağılımını incelemek için MC simulasyon yöntemini kullanılarak geliştirilen programlardan bazıları Geant4, MCNPX, FLUKA ve PHITS'dir. Bu programlar sayesinde parçacık etkileşmelerinin zor ve karmaşık olan hesaplamaları yapılabilmektedir. Böylece uygulama yapılmadan önce muhtemel sonuçlar ve olasılıklar hesaplanabilir ve gerçeğe yakın sonuçlar daha az maliyetle ve daha az sürede gerçekleşebilir. Bu nedenle benzetim programları nükleer ve medikal fizik uygulamalarında önemli bir yer tutmaktadır.

RBE'nin LET değerine bağlı olduğu bilinmekle beraber kesin sonuçlar veren matematiksel modeller henüz tam olarak ortaya konulamamıştır. Bu nedenle geliştirilen programlar farklı yaklaşımlar ve modellerle RBE için yarı deneysel sonuçlar üretmektedir. Uygulanan modellerin farklı fiziksel parametrelerle (enerji, doz vb.) farklı hedef derinliklerinde test edilmesi programların optimizasyonu ve geliştirilmesi için önemlidir. Bu çalışmada kullanılan PHITS programı RBE ve LET arasındaki ilişki için mikrodozimetrik kinetik modeli (MKM) kullanmaktadır.

MKM'de, bir hücrenin çekirdeği birçok alana bölünür ve iyonlaştırıcı radyasyonun, alanda iki tip DNA lezyonuna neden olduğu varsayılır. Tip I lezyon her zaman hücre için öldürücüdür ve tip II lezyonun muhtemelen ölümcül olan ve doğru şekilde onarılabilen DSB (double strand break) olması muhtemeldir. Bir alandaki primer tip I ve tip II lezyonların sayısı, radyasyon kalitesinden bağımsız olarak λd ve kd orantılı sabitiyle alan tarafından emilen spesifik enerji z ile orantılıdır. Bir tip II lezyon dört ileri dönüşümden birine girebilir ve daha sonra L alanındaki etki alanındaki ölümcül lezyonların sayısı, denklem (3.1) 'de verilen doğrusal-kuadratik ilişkiye sahip denklemler çözülerek türetilir. İstatistik yaklaşımla, tüm çekirdeğin üzerindeki ölümcül lezyonların

sayısı hesaplanabilir ve yüksek LET parçacıkları için doygunluk düzeltmesiyle MKM'de hücre hayatta kalma fraksiyonu elde edilebilir:

RBE'nin tanımından, aynı etki için uygulanacak proton dozu; lineer Quadratic modelle elde edilen hayatta kalma fraksiyonu ve kinetik parametrelerle aşağıdaki gibi bulunur.

$$\alpha_x D_x + \beta_x D_x^2 = \alpha_p D_p + \beta_p D_p^2$$

RBE'nin foton dozu ve α_x / β_x hücre spesifik oranına açık bağımlılığını gösteren bir ifade elde etmek için, Dx ve β_x'e bölünürse;

$$\left(\frac{\alpha_x}{\beta_x} D_x\right) RBE^2 - \frac{\alpha_p}{\beta_x} RBE - \frac{\beta_p}{\beta_x} D_x = 0$$

RBE'nin aynı etki oluşturan X ışını ve protonlar için tanımı kullanılarak elde edilen denklem çözümü:

$$RBE = \frac{\frac{\alpha_x \alpha_p}{\beta_x \alpha_x} + \sqrt{\left(\frac{\alpha_x}{\beta_x}\right)^2 \left(\frac{\alpha_p}{\alpha_x}\right)^2 + 4\frac{\alpha_x \beta_p}{\beta_x \beta_x} D_x + 4\frac{\beta_p}{\beta_x} D_x^2}}{2\left(\frac{\alpha_x}{\beta_x} + D_x\right)}$$

şeklini alır. Son olarak, RBE'nin proton dozu ve ax / βx oranına bağımlılığını açıkça ortaya koymak için, elde edilen denklem D_p^2'ye bölünür ve böylece aşağıdaki ifade elde edilir.

$$RBE = \frac{-\frac{\alpha_x}{\beta_x} + \sqrt{\left(\frac{\alpha_x}{\beta_x}\right)^2 + 4\frac{\alpha_x \alpha_p}{\beta_x \alpha_x} D_p + 4\frac{\beta_p}{\beta_x} D_p^2}}{2D_p}$$

α'nın LET ile lineer ilişkisi

$$\alpha_p = \alpha_0 + \lambda . LET$$

şeklinde verilir. Burada α_0 normalizasyon parametresidir ve α_x'e bağlıdır

$$\alpha_0 = \alpha_x - 0.5\,\mathrm{keV}/0.5\mathrm{keV}\,.\,\lambda$$

ve ICRU raporu 49'a göre klinik proton ışınının giriş kanalındaki LET değerini temsil eder.$\beta_p = \beta_x$ kabulu ile RBE için analitik çözüm

$$\mathrm{RBE} = \frac{-\frac{\alpha_x}{\beta_x} + \sqrt{\left(\frac{\alpha_x}{\beta_x}\right)^2 + 4\frac{\alpha_x}{\beta_x}\left(1 + \frac{\lambda}{\alpha_x}(\mathrm{LET} - 0.5\mathrm{keV}/\mu\mathrm{m})\right)D_p + 4D_p^2}}{2D_p}$$

şeklini alır.

Bu tez çalışmasında,hadron terapide kullanılan proton (160 MeV/u ve 200 MeV/u) ve karbonun (135 MeV/u ve 290 MeV/u) yumuşak doku ve A150 doku eşdeğeri plastik şeklinde belirlenen biyolojik hedeflerdeki etkilerinin fiziksel büyüklükler ile değişimi göz önüne alınarak bağıl biyolojik etkinlikleri (RBE) incelendi.Hadron enerjileri klinik çalışmalarda kullanılan enerji aralığı göz önünde bulundurularak proton için 160 MeV/u ve 200 MeV/u, carbon için ise 135 MeV/u ve 290 MeV/u olarak belirlendi.Biyolojik hedef olarak seçilen yumuşak doku ve A-150 (tissue-equivalent plastic)için kimyasal ağırlıkları NIST veritabanından alındı.

Çalışma kapsamında fiziksel büyüklüklerden LET ve spesifik enerji MC simülasyon yöntemi kullanılarak elde edildi RBE sonuçları MKM'de verilen üç farklı hesaplama yöntemiyle incelendi.RBE hesaplamalarında PHITS programından elde edilen sonuçlar MKM'nin temel linear quadratik denklemlerinden (Eq. 3.2 ve 3.3) elde edilen analitik, poisson (Eq. 3.5) ve nonpoisson (Eq. 3.13) denklemlerinde kullanıldı. Hesaplamalarda referans radyasyonu için 200 kVp X-rays (α value: 0.19 Gy−1, β value: 0.05 Gy−2 in the linear quadratic model) değerleri ve domain yarıçapı rd: 0.282 μm giriş parametreleri olarak kabul edildi.

Programda kullanılan geometri literatürde verilen değerler göz önünde bulundurularak tüm dozu soğuracak kalınlıklarda seçildi (Şekil 4.1a, 4.1.b). Seçilen geometride doz dağılımının (enerji aktarımının) en çok gerçekleştiği derinlik (Bragg piki)

için hesaplamalar yapılarak elde edilen survival fraction ve RBE değerleri literatür bilgisi ile karşılaştırıldı.

Biyolojik hedefler için, kullanılan mermi ve enerjilerdeki maksimum doz derinlikleri track dosyalarından belirlenerek doz dağılımlarının maksimum derinlikleri doz dağılım değerleri ile doğrulandı. Verilen track grafikleri incelendiğinde yumuşak doku için maksimum doz aktarımlarının, 160 MeV ve 200 MeV enerjili protonlarda sırasıyla 17 cm ve 26 cm civarında olduğu benzer şekilde bu değerlerin 135 MeV ve 290 MeV enerjili karbonlarda ise sırasıyla 5 cm ve 16 cm olduğu görüldü. Benzer inceleme A150 doku eşdeğeri plastik için yapıldığında ise maksimum doz aktarımlarının, 160 MeV ve 200 MeV enerjili protonlarda sırasıyla 19 cm ve 25 cm civarında, 135 MeV ve 290 MeV enerjili karbonlarda ise sırasıyla 4 cm ve 16 cm civarında görüldü.

Doz değerleri incelendiğinde, elde edilen doz dağılımının keskin Bragg piklerine sahip olduğu görülmekte ve bu piklerin oluştukları derinlikler de beklenildiği gibi aynı parçacık için sahip olduğu enerjiye göre değişmektedir.

Phits programından elde edilen bir diğer parametre spesifik enerji dağılımı ile yapılan hesaplamalardan her bir mermi için seçilen biyolojik hedeflerdeki survival fraction (SF) değerleri hesaplandığında yüksek LET değerine sahip olan karbonun protona göre daha çok hücre ölümüne sebep olabileceği görüldü.

RBE hesaplamalarından elde edilen sonuçlar değerlendirildiğinde phits programına girilen yarı deneysel parametreler ile elde edilen doz dağılım ve SF sonuçlarının beklenen sonuçlar verdiği görüldü.

PHITS çıktıları ile yapılan analitik hesaplama sonuçlarının düşük LET bölgesinde uygun sonuçlar vermekle birlikte yüksek LET bölgesinde diğer model hesaplamalarından uzaklaştığı ayrıca Bragg piki bölgesinde beklenilen bükülmeyi veremediği görüldü.

Poisson dağılımı ile elde edilen RBE sonuçlarının analitik hesaplama sonuçlarıyla benzer şekilde olduğu ancak daha düşük değerler olduğu görüldü. İki hesaplama değerlerinin benzerliğinin bir öteleme sabiti ile değerlendirilebileceği sonucuna varıldı.

Analitik ve poisson hesaplamalarına ait sonuçların literatürde yer alan yüksek LET bölgesindeki bükülmeyi veremeyeceği bilgisine yaptığımız hesaplamalarda ulaşıldı. Brag piki bölgesindeki bükülmeyi non-poisson düzeltmesi yapılmış hesaplamalarda gözlemledik. Ancak bu bölgede beklenen keskin pikler yerine pik bölgesinde bir dağılım olduğu görüldü.

APPENDIX 1. Compilation of in vivo studies measuring the RBE of carbon ions in tumors. It was taken from (Karger et al., 2017)

Tumor	Host	Endpoint	*Fx*	LET (keV$\boldsymbol{\mu m^{-1}}$)	RBE	Reference
9L brain tumor	Fisher 344 rats	*In situ*/clonogenic survival	1	n.r.	1.33[f]	Wheeler *et al.*, (1979)
Rhabdomyo-sarcoma	WAG/Rij rats	$Growth\ delay$[c]	1	12	1.3	Tenforde *et al.*, (1981)
			1	80	2.3	
Human esophagus carcinoma	BalbC/Ajcl/nu mice	$Growth\ delay^{b}$	1	70	2.02	Takahashi *et al* (1998)
NFSa fibrosarcoma	C3H/He mice	$Growth\ delay^{a}$	1	14	1.4	Koike *et al* (2002)
			1	44	1.8	
			1	74	2.4	
			4	44	2.3	
			6	44	2.3	
			6	74	3.0	
Dunning prostate carcinoma	Copenhagen rats	Tumor control $assay$[e]	1	75	2.30	Peschke *et al* (2011), Karger *et al* (2013)
			2	75	2.39	
R3327-AT			6	75	2.67	
Dunning prostate carcinoma	Copenhagen rats	Tumor control $assay^{e}$				Glowa *et al* (2016)
R3327-HI			1	75	2.08	
R3327-H			1	75	1.62	
C3H mammary carcinoma	C3H/He mice	Tumor control $assay^{e}$	1	65	1.48	Sørensen *et al* (2015)

Appendix 2. Compilation of *in vivo* studies measuring the RBE of carbon ions in normal tissue. It was taken from (Karger et al., 2017)

Organ	Host	Endpoint	*Fx*	LET (keV μm−1)	RBE	Reference
Skin	Golden Syrian hamster	Average ventral thoracic skin reaction level	1 2 5	n.r. Modified Bragg peak	1.60 1.75 1.9	Leith *et al* (1981)
Skin	CDF1 mice	Residual skin damage 1 year after RT (ED50 equivalent)	4 4	10 80	1.04 1.53	Leith *et al* (1982a)
Skin	C3H/HeMsNrsf mice	Moist desquamation	1 2 8 	14 20 42 77 14 20 42 77 14 20 42 77	1.45 1.75 2.15 2.50 1.35 1.40 1.50 3.20 1.60 1.90 2.25 3.20	Ando *et al* (1998)
Developing brain	SLC Wistar rats	Microcephaly andhistology	1	50	1.3–1.6	Inouye *et al* (2000)
Liver (after partial hepatectomy)	Balb/c mice	Hepatic failure LD50/60 (50% lethal dose within 60 d)	1	50.7	1.86	Tomizawa *et al* (2000)
Brain	Copenhagen rats	MRI contrast enhancement 20 months post RT (50% Effect probability level)	1	155	1.95	Karger *et al* (2002)
Intestine	Balb/c mice	Intestinal crypt regenerationc	1	13.7 40.9 49.4 70.7	1.30 1.6 1.7 1.9	Gueulette et al (2004)

Appendix 2. Compilation of *in vivo* studies measuring the RBE of carbon ions in normal tissue. It was taken from (Karger et al., 2017) (continued)

Intestine	Balb/c mice	Intestinal crypt regenerationc	1	13.7 40.9 49.4 70.7	1.30 1.6 1.7 1.9	Gueulette *et al* (2004)
Intestine	Balb/c mice	Intestinal crypt regenerationf	1 3 	42 50 74 42 50 74	1.47 1.63 1.80 1.71 1.95 2.24	Uzawa *et al* (2009)
Skin	CDF1 mice	Radiation induced fibrosis(FD50)	1	65	1.50	Sørensen *et al* (2015)

Appendix 3. Physical and radiobiological parameters for various kind of ions in experiments on V79, CHO and T1 cell lines. It was taken from (Overgaard et al., 2011)

Particle type	Cell type	RBE10%	LET (keV/µm)	MeV/u	Reference
Protons	V79 753B	1.06	7.7	6	Belli et al 1998
Protons	V79 379B	1.25	10.1	3.66	Folkard et al, 1996
Protons	V79 753B	1.33	11	4.5	Belli et al 1998
Protons	V79 379B	1.61	17	4	Folkard et al, 1989
Protons	V79 379B	1.4	17.8	1.83	Folkard et al, 1996
Protons	V79 753B	1.6	20	3.3	Belli et al 1998
Protons	V79 379B	1.91	24	4	Folkard et al, 1989
Protons	V79 379B	1.91	27.6	1.07	Folkard et al, 1996
Protons	V79 753B	1.82	30.5	3	Belli et al 1998
Protons	V79 379B	3.36	32	4	Folkard et al, 1989
Protons	V79 753B	1.65	34.6	2.96	Belli et al 1998
Protons	V79 753B	1.46	37.8	2.93	Belli et al 1998

Appendix 3. Physical and radiobiological parameters for various kind of ions in experiments on V79, CHO and T1 cell lines. It was taken from (Overgaard et al., 2011) (continued)

Deuterons	V79 379A	1.97	26.3	2.14	Folkard et al, 1996
Deuterons	V79 379A	2.74	36.1	1.4	Folkard et al, 1996
Deuterons	V79 379A	3.04	49.8	0.93	Folkard et al, 1996
C	V79	1.74	31	135	Furasawa et al, 2000
C	V79	1.87	40	290	Belli et al 2008
C	V79	2.3	40	400	Chapman et al, 1979
C	V79	2.35	40.1	135	Furasawa et al, 2000
C	V79	2.14	40.6	135	Furasawa et al, 2000
C	V79	2	50	290	Belli et al 2008
C	V79	2.76	50.3	135	Furasawa et al, 2000
C	V79	2.36	57.6	135	Furasawa et al, 2000
C	V79	2.58	60	290	Aoki et al, 2000
C	V79	2.67	60	135	Furasawa et al, 2000
C	V79	2.6	75	290	Belli et al 2008
C	V79	3.29	78.5	135	Furasawa et al, 2000
C	V79	3.13	80.6	135	Furasawa et al, 2000
C	V79	3.35	88	135	Furasawa et al, 2000
C	V79	2.98	94	19	Belli et al 2008
C	V79	3.50	100	290	Zhou et al, 2006
C	V79	3.63	102	135	Furasawa et al, 2000
C	V79	3.15	110	290	Aoki et al, 2000

Appendix 3. Physical and radiobiological parameters for various kind of ions in experiments on V79, CHO and T1 cell lines. It was taken from (Overgaard et al., 2011) (continued)

C	V79	4.18	117	135	Furasawa et al, 2000
Deuterons	V79 379A	1.56	18.5	3.4	Folkard et al, 1996
C	V79	3.45	127	135	Furasawa et al, 2000
C	V79	4.53	137	135	Furasawa et al, 2000
C	V79	4.45	142	135	Furasawa et al, 2000
C	V79	3.15	152	135	Aoki et al, 2000
C	V79	3.5	153.5	11.4	Weyrather et al , 1999
C	V79	4.06	206	12	Furasawa et al, 2000
C	V79	3.17	222	6.7	Belli et al 2008
C	V79	3.27	232	12	Furasawa et al, 2000
C	V79	2.09	237	135	Aoki et al, 2000
C	V79	3.29	255	12	Furasawa et al, 2000
C	V79	3	275	6.12	Weyrather et al , 1999
C	V79	3.63	276	12	Furasawa et al, 2000
C	V79	2.9	295	--	Pathak et al, 2007
C	V79	2.25	303	4.5	Belli et al 2008
C	V79	2.6	339.1	5	Weyrather et al , 1999
C	V79	3.29	360	12	Furasawa et al, 2000
C	V79	2.59	432	12	Furasawa et al, 2000
C	V79	2	282	3.5	Weyrather et al , 1999
C	V79	2.57	493	12	Furasawa et al, 2000
N	V79	2.41	78	45	Tilly, 1998

Appendix 3. Physical and radiobiological parameters for various kind of ions in experiments on V79, CHO and T1 cell lines. It was taken from (Overgaard et al., 2011) (continued)

N	V79	3.22	125	21	Stenerlöv, 1995
N	V79	3.12	165	45	Tilly, 1998
N	V79 4	2.5	470	--	Cox et al, 1977
C	CHO K1	1.5	13.7	270	Weyrather et al, 1999
C	CHO K1	1.5	16.8	195	Weyrather et al, 1999
C	CHO K1	1.6	20	135/290	Saski et al, 1997
C	CHO K1	1.4	24	135/290	Saski et al, 1997
C	CHO K1	1.9	32.4	85	Weyrather et al, 1999
C	CHO K1	2.3	60	135/290	Saski et al, 1997
C	CHO K1	2.5	83	135/290	Saski et al, 1997
C	CHO K1	3.5	103	18.4	Weyrather et al, 1999
C	CHO K1	3.1	121	135/290	Saski et al, 1997
C	CHO K1	3.7	135.5	11.4	Weyrather et al, 1999
C	CHO K1	3.2	275	6.12	Weyrather et al, 1999
C	CHO K1	2.6	339.1	5	Weyrather et al, 1999
C	CHO K1	2.7	438	33.2	Czub et al, 2008
C	CHO K1	2.2	482	3.4	Weyrather et al, 1999
C	CHO K1	2.2	576	9.1	Czub et al, 2008
C	CHO K1	1.7	830	48.5	Czub et al, 2009
C	CHO K1	1.7	832	20.3	Czub et al, 2008
Li	T1 cells	2.6	55	6.58	Todd, 1967
B	T1 cells	3.4	165	6.58	Todd, 1967
C	T1 cells	1.1	10	400	Blakely et al, 1979

Appendix 3. Physical and radiobiological parameters for various kind of ions in experiments on V79, CHO and T1 cell lines. It was taken from (Overgaard et al., 2011) (continued)

C	T1 cells	1.2	13	400	Blakely et al, 1979
C	T1 cells	1.1	16	400	Blakely et al, 1979
C	T1 cells	1.53	21.8	135	Furasawa et al, 2000
C	T1 cells	1.44	21.8	135	Furasawa et al, 2000
C	T1 cells	1.4	23	400	Blakely et al, 1979
C	T1 cells	1.5	29	400	Blakely et al, 1979
C	T1 cells	2.12	39.7	135	Furasawa et al, 2000
C	T1 cells	1.72	39.8	135	Furasawa et al, 2000
C	T1 cells	2.24	61.5	135	Furasawa et al, 2000
C	T1 cells	3.19	80.4	135	Furasawa et al, 2000
C	T1 cells	2.6	83	400	Blakely et al, 1979
C	T1 cells	3.63	109	135	Furasawa et al, 2000
C	T1 cells	2.6	126	400	Blakely et al, 1979
C	T1 cells	3.48	144	135	Furasawa et al, 2000
C	T1 cells	4.1	220	6.57	Todd, 1967
C	T1 cells	3.93	252	12	Furasawa et al, 2000

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