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High Energy Radiation in the Treatment of Cancer

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ABSTRACT

The energy of ionizing radiation, directly charged particles or indirectly uncharged particles, when it is transferred or absorbed in the body, following a local interaction, can produce the most unfavorable biological effects on its health. These effects can be grouped into stochastic effects, at the level of a cell, such as cancer, and hereditary effects, without a threshold, in which the probability of occurrence increases linearly with the equivalent dose in tissues and organs, at the frequency of events in the cell nucleus below 1 event per 100 mGy of radiation with LET smaller than 10 keV/µm, and deterministic effects (meaning "causally determined by preceding events" i.e. harmful tissue reactions, early or late, at the level of a population of cells, due to the high values of absorbed energy in tissue or organ. The range of the radiation under the skin at all depths of the tumor volume is determined by the kinetic energy of the particle, and the intensity of the beam ensures the absorbed energy necessary for sterilization of the tumor. These energies are: (4 – 25) MeV for photons and electrons, (50 – 250) MeV for protons and (1200 – 5400) MeV for carbon ions. The biological effect of ionizing radiation increases with increasing the linear energy transfer (LET in units kV/µm), starting from storage of 0.1 -10 for X rays to storage of 100–200, for heavy charged particles (see the Bragg curve). Another important radiobiological factor, the relative biological effectiveness (RBE), is recommended 1.1 for clinical protons and increases depending on the LET to a maximum RBE of 2.5 to 3.5, for carbon ions. The last factor, the oxygen enhancement ratio (OER), is about 3 at high doses and falls to about 2 for doses of 1 to 2 Gy, for x-rays and electrons. The response of the environment (cell, tumor, organism) to the energy of ionizing radiation through the dose-effect relationship, which can be of linear, linear quadratic or sigmoid type, uses an incidence or a probability as an effect, in order to have a sigmoid-shaped increase (i.e. "S"). The sigmoid curve in radiotherapy can be described by the probit and logistic functions, with the inflection point at 50% and by the Poisson function with the inflection point at 37% (about 6 out of 10 tumors will recur). Also, for a good radiotherapy treatment, the tumor cure probability (TCP), i.e. the probability of zero surviving clonogens in a tumor, TCP ≥ 0.5, and the normal tissue complication probability (NTCP) as a function of the absorbed dose, NTCP ≥ 0.05. Maximizing the energy absorbed in the tumor and minimizing the energy absorbed outside the tumor is done using high homogeneity, characterizing the uniformity of dose distribution within the target volume and high conformity, characterizing the degree to which the high dose region conforms to the target volume, usually by the planning target volume (PTV). The distribution of tumor-specific doses is achieved by using new methods and associated devices, entitled: 3D conformal radiotherapy (or 3DCRT), the Intensity modulated radiation therapy (IMRT) and Helical tomotherapy (HT) in the case of electromagnetic radiation (photons), and Intensity modulated particle therapy (IMPT), based on the scattering and/or scanning method in the case of hadron therapy. These methods use particle beams with constant or variable radiation intensities, to cover the entire volume of the tumor, in 3D, and in 4D when the patient's breathing time and heartbeat are taken into account. The Standard Reference Conditions from external photon therapy of 2 Gy per fraction, 5 fractions per week, are recommended in hadron therapy. The aspects listed above are presented in the work.

Keywords
High Energy Photon Beam, Electron Beam, Proton Beam, and Carbon Ion Beam in Cancer Radiotherapy.

Introduction

Radiotherapy, one of the cancer treatment methods, uses electromagnetic radiation and the radiation of atomic and nuclear particles to destroy tumor cells, [1-3].

A cancer treatment center contains three systems: the first is the medical accelerator (Linac, SC isochronous cyclotron, SC synchrocyclotron and synchrotron), which provides radiation in the form of beams of photons, electrons, protons and ions; the second is the radiation transport system, for one or more treatment rooms; and the third is the radiation treatment system based on a treatment plan, IMRT and/or IMPT. This paper refers to some aspects related to the last system.

The work contains 7 chapters. After the introduction, the second chapter, entitled Some dosimetry aspects of ionizing radiation, presents energy transfer from electromagnetic radiation (photons) to secondary ionizing radiation (electrons), characterized by the kerma, the part of the kinetic energy of the charged particles released by the uncharged particles, absorbed in the mass element of the tumor, as the absorbed dose, the quantity of photon energy flux that describes the transport of energy via radiation to the tumor, and microdosimetry, stochastic quantities, specific energy and linear energy transfer.

Chapter Three Radiobiological Aspects of Radiation Quality presents several radiobiological factors as follows. Cell destruction and *in vitro* survival curves determined by "radiation-response" curves that share a sigmoidal (ie, "S") shape as a common element. The biologically effective dose (BED) is used in fractionated radiation therapy, when the total dose is given in very small dose fractions to produce a certain effect, as indicated by the linear quadratic equation. The relative biological effectiveness (RBE) is a simple ratio between the low linear energy transfer (LET) reference radiation dose and the high LET radiation dose to produce the same biological effect. The oxygen enhancement ratio (OER) is a simple ratio of the dose required under anoxic or hypoxic conditions to the dose required under aerobic conditions to produce the same biological effect.

Chapter four, Dose – response relationship in radiotherapy refers to the concepts of The tumor cure probability (TCP); Normal Tissue Complication Probability (NTCP) Model; Equivalent Uniform Dose (EUD); Dose homogeneity and dose conformity, and the dose-volume relationship, instead of the point dose.

Chapter five deals with High energy photons in radiotherapy. Here is presented the formula for calculating the absorbed dose as the product between a field quantity and the interaction coefficient that acts as a conversion unit from the energy fluence rate to the absorbed dose, for photon energies between 4 MeV and 25 MeV.

In order to reduce the normal damage of tissues adjacent to the target volume, three-dimensional conformal radiotherapy (3D-CRT) of constant intensity and the intensity-modulated radiation therapy (IMRT) based on optimized planning are used, the first stage in the management of cancer treatment.

Currently, the high-energy X-ray irradiation (treatment) system, Helical Tomotherapy, is based on two associated methods: Spiral CT scanning and Intensity Modulated Radiation Therapy (IMRT). There are some clinical examples mentioned, from which results the superiority of the IMRT method and the helical tomotherapy method in the case of cancer treatment with high-energy photons through Planning Target Volume (PTV) and Planning Organ at Risk Volume (PRV).

Chapter six: High energy electrons in radiotherapy. The finite path of the electron in the irradiated medium, similar to the SOBP peak of hadrons, led to The application of high energy electron-beam treatment methods in the treatment of breast cancer, in 1955, using a medical betatron of 24 MeV, and from 1961 a medical betatron of 36 MeV. Currently, electron beams are provided by linear electron accelerators. The linac, having small dimensions, and providing high doses of radiation, replaced the betatron in the treatment of cancer. For example, a 6 MeV linear electron accelerator is used for helical tomotherapy (HT).

Chapter 7 refers to High energy protons in radiotherapy, and Chapter 8 - to High energy carbon ions in radiotherapy. For the treatment of cancerous tumors with hadrons, the dose is delivered to the patient as a narrow beam through the pencil beam scanning active method or the passive scattering method, both components of the intensity-modulated particle therapy (IMPT). Several cases of treatment planning with therapeutic hadrons are presented, from which the application of the IMPT method for hadron radiation is equivalent to the IMRT method, the HT variant for electromagnetic radiation (photons). Clinical use of ion beams, such as protons and carbon ions, provides precise dose distribution due to their finite path. The physical phenomenon of the energy loss peak called the "Bragg peak" ensures a higher absorbed dose in the tumor than in the surrounding healthy tissues. Also, RBE values increase with depth and have a maximum near the depth where the Bragg peak appears.

Some Dosimetry Aspects of Ionizing Radiation

Energy conversion and Kerma

A beam of X or gamma γ radiation, monochromatic, collimated, of energy E per photon, is characterized by the quantities fluence rate, Ψ (photon/cm^2.s), and the energy fluence rate, $\dot{\Psi}$ (MeV/cm^2.s). When photons are incident on a target (or tumor), the photon energy is instantly converted into electron kinetic energy, through three major interaction processes, (f,e): the Compton effect, the photoelectric effect and the pair production (e+; e-).

The law of variation of the photon energy fluence rate when passing through a tumor of thickness ℓ is $\Psi = \Psi_0 \exp(-\mu_{tr}\ell)$ and the kinetic energy fluence rate received by the secondary electrons, $\dot{S}$,

through the conversion of photon energy, is defined as the energy transferred to the electrons, E_{tr}, through the area A, during t, i.e. $\dot{S}$, = E_{tr} /A.t. Here, μ_{tr}/ρ is the mass energy transfer coefficient, $\dot{\Psi}_0$ is the photon energy fluence rate upon entering the tumor and $\dot{\Psi}$ is thep photon energy fluence flow rate after traveling the distance ℓ. From the equality of the variations of the two rates. in the same elementary volume dV=Adℓ, that is, $d\dot{E}_{tr}$/Adℓ = $d\dot{\Psi}$/dℓ, the expression for the kerma rate quantity, $\dot{K}$ (≡ dK/dt), depending on the energy fluence rate, $\dot{\Psi}$ (≡ dΨ/dt), is

$$\dot{K} \equiv \frac{d\dot{E}_{tr}}{dm} = \frac{\mu_{tr}}{\rho}\dot{\Psi} \quad \text{or} \quad K \equiv \frac{dE_{tr}}{dm} = \frac{\mu_{tr}}{\rho}\Psi . \tag{1}$$

Here, eliminating the time interval dt, the integral quantities, Kerma (K) and Energy Fluence (Ψ), result, see equation (1). Kerma (K), for uncharged ionizing particles (photons, neutrons, etc.), is the ratio dE_{tr}/dm, where dE_{tr} is the average sum of the initial kinetic energies of all charged particles (electrons, positrons, etc.) released in a mass dm of a material by the incident uncharged particles per dm. The special name for the unit of kerma is gray (Gy);

$$1Gy = 1\,\frac{J}{kg} = 6.24 \times 10^9\,\frac{MeV}{g} \tag{2}$$

For the energy fluence of uncharged particles, $\Psi = \Phi.E$, where Φ is the fluence of particles of energy E, in a specified material, the collision kerma, $K_{col,}$ is given by:

$$K_{col} = \frac{\mu_{ab}}{\rho}\Psi = \Phi\, E\, \frac{\mu_{tr}}{\rho}(1 - g) = K(1 - g), \tag{3}$$

where μ_{ab}/ρ is the mass energy-absorption coefficient and μ_{tr}/ρ is the mass energy-transfer coefficient of the material for uncharged particles of energy E, and g is the fraction of the total kinetic energy of liberated charged particles that would be lost in radiative processes in that material.

Relation (1) can be generalized for dosimetry quantities: exposure, X, defined as electric charge (C) per mass of air (kg), kerma K, defined as the energy of electrons (J) transferred to the environment per mass of the environment (kG) and dose absorbed, D, defined as the energy of electrons (J) absorbed per medium mass (kg). They can be calculated as the product of a field quantity (energy fluence rate) and the interaction coefficient between the radiation in the field and the environment in which the interaction takes place.

Energy Imparted and Absorbed Dose

The basic quantity for radiotherapy that describes the energy imparted to matter is the absorbed dose. The absorbed dose D is defined as ICRU 1980,

$$D \equiv \lim_{m\to 0}\frac{\bar{\epsilon}}{m} = \lim_{V\to 0}\frac{1}{\rho}\frac{\bar{\epsilon}}{V} = \frac{\mu_{ab}}{\rho}\Psi = -\frac{1}{\rho}\,\mathbf{div}\,\boldsymbol{\Psi} \tag{4}$$

Where $\bar{\epsilon}$ is the mean energy imparted by ionizing radiation to matter of mass dm, and Ψ is the sum of the energy fluence of the uncharged ionized particles, u, of the primary charged ionizing particles, c, and secondary ionizing particles, c, s, that is $\Psi = \Psi_u + \Psi_c + \Psi_{c,s}$. The unit of absorbed dose is gray (Gy), 1 Gy = 1 J/kg = 10^2 rad = 10^4 erg/g = 1.83 x 10^{14} i.p./g of tissue, where i.p. is ion pair, and **div Ψ** is divergence of the energy fluence vector **Ψ.**

Example: In charge particle equilibrium (CPE), **div $\Psi_{c,s}$** = 0 and for Ψ_c = 0, $D = -\frac{1}{\rho}$ **div Ψ_u** = K – B = K_{col} for B = 0.

In relation (4), the average energy, $\bar{\epsilon}$ = R_{in} - R_{out} + ΣQ, is determined by the net transport (Rin - Rout) of the average radiant energy in the body, corrected with the term ΣQ, energy imparted , ϵ stochastic quantity, is the sum of all elemental energy deposits ϵ_i by those basic interaction processes which have occurred in the volume during a time interval considered: $\epsilon = \Sigma_i \epsilon_i$; and energy deposit ϵ_i is the energy deposited in a single interaction, i.

Example: The energy deposit ϵ_i by the pair production process is ϵ_i = hv – (T_+ + T-) – $2m_0c^2$, where hv is photon energy, T- and T_+ are kinetic energies for the electron and positron, and m_0c^2 is the rest mass of an electron.

Energy Fluence - Transport of Energy via Radiation

In macroscopic dosimetry, the second important quantity is the energy fluence rate. This is a radiometric quantity that provides a complete description of energy transport by radiation. It is defined as the energy density per unit area, transported by electromagnetic radiation (photons) to the tumor. According to ICRU Report 85, [4], the energy fluence rate, $\dot{\Psi}$, is the quotient of dΨ by dt, where dΨ is the increment of the energy fluence in the time interval dt, thus:

$$\dot{\Psi} \equiv \frac{d\Psi}{dt} = \frac{d^2R}{dt\,dA} \tag{5}$$

where dR is the radiant energy incident on a sphere of cross-sectional area dA, Ψ = dR/dA, in [J/m^2] and $\dot{\Psi}$ *in* units of (J /m^2•s).

The information regarding the amount of energy transferred, from the radiation field to the tumor, is given by the mass energy transfer coefficient, μtr /ρ. The relationship between this coefficient and the mass energy absorption coefficient is $\mu_{tr}/\rho = (\mu_{ab}/\rho)/(1 - g)$.

The energy of the incident photons on the tumor is obtained from the energy fluence rate, $\dot{\Psi}$(MeV/cm^2.s) of the photon beam, depending on the absorbed dose rate $\dot{D}$ (Gray per minute), at point P in the tumor environment (m) using equation (6)

$$\frac{\dot{\Psi}(P)}{\dot{D}_m(P)} = \frac{1.04 \times 10^8}{(\mu_{ab}/\rho)_m}\,[(MeV/cm^2/s)\cdot(Gy/m)^{-1}], \tag{6}$$

In the case of the dose absorbed in air, the conversion factor from the amount of exposure, X, to the amount of dose absorbed in air, Dair, is Wair/e- = 33.97 J/C, for X in C/kg and $W_{air/e-}$ = 87.64 x 10^{-4} Gy/R, for exposure X expressed in R. The calculation formula for the dose absorbed in air is presented in relation (7),

$$\Psi_{air} = \frac{W_{air}/e}{(\mu_{ab}/\rho)air}\boldsymbol{X} . \tag{7}$$

The unit of exposure in the SI is the coulomb per kilogram (C/kg), and in the CGS system it is the Roentgen (R), 1 R = 1 ues/cm^3 = 3.33 x 10^{-10} A.s / cm^3 of air.

1 R = 2.58 x 10^{-4} C/kg-air = 1.61 x 10^{12} i.p. /g of air. (8)

Relations (7) can also be written as follows:

$$P_n(k_1 \le \xi \le k_2) = \frac{1}{\sqrt{2\pi}} \int_{k_1}^{k_2} e^{-\frac{1}{2}x^2}\, dx. \quad (9)$$

Measuring the exposure, X. can lead to the deduction of both the dose absorbed in the air and the energy flux.

Defining the quantities $\dot{X}$ and $\dot{D}$ by calculation is not preferable because these quantities are measured directly. The numerical values for interaction coefficients, μtr/ρ, and μab/ρ, depending on the energy of the photons, are tabulated.

Note. All dosimetry quantities, and the corresponding units of measure, integral or differential, can be estimated as follows: integral quantity (or rate) in UM (or UM per unit time).

Specific Energy and Lineal Energy, Random Variables

In microdosimetry, [5], the average macroscopic quantities become random variables, as follows: specific energy, z [Gy] ≡ ϵ /m, is the random analog of absorbed dose (D) and linear energy, y [keV/μm] ≡ $\epsilon_s/\bar{\ell}$, is the random analog of Linear Energy Transfer (LET = L_Δ). While TLE results from the limitation to a given value of the energy transferred to produce local effects, the linear energy is limited geometrically for a value of a length in the region of interest.

Here, stochastic quantity, ξ, is the energy imparted by indirectly or directly ionizing radiation to a reference region of mass m, and stochastic quantity ϵ_s, is the energy imparted to the matter in a given volume by a single energy-deposition event, and $\bar{\ell}$ is the mean chord length of that volume. Linear energy is a quantity similar to stopping power and linear energy transfer (LET).

Any random variable, discrete or continuous, in probability theory, is represented by three functions: 1. the probability distribution associated with the random variable, $P_n(k)$; 2. the cumulative distribution function, F(x), and 3. the probability density, f(x). These functions, for example, can be obtained using Laplace's formula (or integral theorem). This states: the probability P_n that the random variable ξ, which can take discrete values k, is contained between two given values, $k_1 \le \xi \le k_2$, for a very large number n of events, is

$$P_n(k_1 \le \xi \le k_2) = \frac{1}{\sqrt{2\pi}} \int_{k_1}^{k_2} e^{-\frac{1}{2}x^2}\, dx. \quad (10)$$

In relation (10) by substituting $k_1 \to -\infty$ and $k_2 = k$, the distribution function (or the cumulative distribution function) is obtained, i.e. the probability that the random variable will take a value less than or equal to a certain value k,

$$F(k) = \int_{-\infty}^{k} f(x)dx. \quad (11)$$

The function f(x) is the probability density function, defined as the derivative of the distribution function, which, in the case of the standard normal distribution, is given by the relation,

$$f(x) \equiv \frac{dF(x)}{dx} = \frac{1}{\sqrt{2\pi}} \cdot e^{-\frac{1}{2}x^2}. \quad (12)$$

The probability of the certain event, equal to unity, is given by the relation

$$\int_{-\infty}^{+\infty} f(x)dx = \sum_{k=1}^{n} P(x_k) = 1. \quad (13)$$

The probability that an event point is found in the interval x, x + dx, is f(x)dx, that is, the probability is proportional to the interval dx.

In this way, the contribution to the absorbed dose of interactions with linear energies between y_1 and y_2 is given by the Laplace integral, as follows:

$$D = \int_{y1}^{y2} d(y)\, dy = \ln(10) \int_{y1}^{y2} y\, d(y) d(\log y). \quad (14)$$

The spectra for C0-60, protons and neutrons, at the microdosimetric level are presented in Figure 1. For cobalt-60 gamma rays, the maximum yd(y) values occur to about 0.3 keV/μm. For protons and neutrons, the maxima are observed at about 3 keV/μm and 10 keV/μm, respectively.

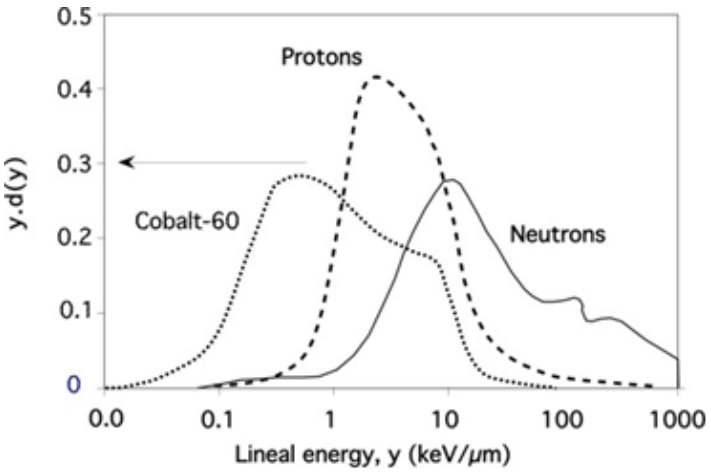


Figure 1: Comparison of microdosimetric spectra of y.d(y) vs. y obtained for cobalt-60 gamma rays, 65 MeV protons, and p (65) + Be neutrons, [6].

Radiobiological Aspects of Radiation Quality

The probability of the appearance of biological effects to people exposed to ionizing radiation leads to their classification into deterministic effects and stochastic (random) effects. Deterministic effects appear after exceeding a threshold of exposure to ionizing radiation, they are certain, and their severity increases with the dose, while stochastic effects have no threshold and show a proportionality between the dose and the probability of the effect occurring.

Dose limits to ensure that the occurrence of stochastic effects is kept below unacceptable levels and tissue reactions are avoided, are specified in the sizes, equivalent dose and effective dose defined in radiological protection, not for radiotherapy [7],

Survival curves *in vitro*

Studies on mammalian cell cultures have shown that cell survival varies depending on the absorbed dose, a fact that can be described by the "survival curve". Many mathematical models have been developed to describe the shape of the cell survival curve [8].

From these, we choose the typical survival curves for cells irradiated with dense ionizing radiation (high LET) and with weak ionizing radiation (low LET), Figure 2 and Figure 3, [9].

The linear dose-response curve, $\log_e$ SF = -D/D_0, for high TLE radiation (Figure 2) is given by the equation,

$$SF \equiv N/N_0 = e^{-D/D_0} \quad (15)$$

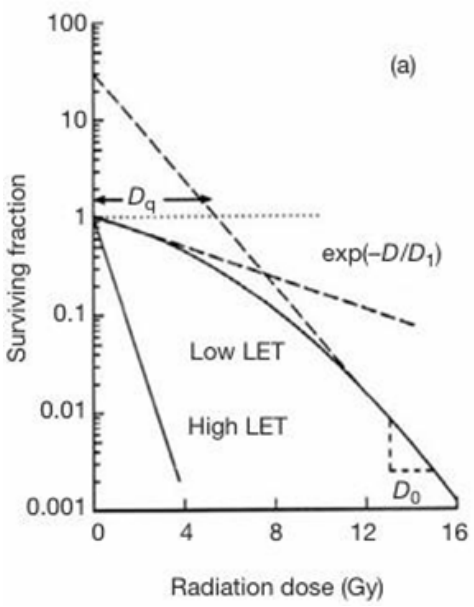


Figure 2: Survival curves for mammalian cells exposed to high LET and low LET ionizing radiation at high dose rate (> 0.1 Gy/min), [9].

where SF is the probability of survival, D/D0 is the average number of hits per target (and in this case per cell), N0 = the initial number of cells, N = the number of surviving cells. At dose D = D_0, SF = 0.37, that is, survival is e^{-1} = 1/e = 37%.

The curve for the radiation that produces weak ionization (radiation with low LET), illustrated in Figure 2, is given by the survival fraction,

$$SF = e^{-D/D_1}\,[1 - (1 - e^{-D/D_0})^n], \quad (16)$$

where "n" is the number of survivals obtained by extrapolation to zero dose and D_1 is the inverse of the initial slope of the curve.

Radiobiological experiments have demonstrated that the killing of cells by radiation can be described by the linear-quadratic equation based on the average frequency of lethal events, after the administration of a uniform dose, D,

$$SF = e^{-(\alpha D + \beta D^2)} \quad (17)$$

where the parameters α and β characterize the initial slope and the degree of curvature of the survival curve, respectively, Figure 3.

The constant α describes the linear component of the cell's sensitivity to killing on a semi-logarithmic graphic representation of the cell (on the logarithmic axis) (on the linear axis), and depending on the absorbed dose, and β describes the cell's sensitivity to higher radiation doses. The α/β ratio represents the dose at which the linear and quadratic components of cell killing are equal.

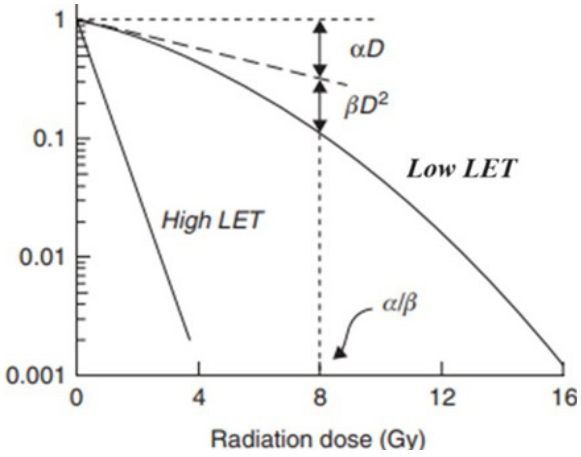


Figure 3: The dose response for cell survival in the linear quadratic model.

Biologically effective dose (BED)

The linear quadratic (LQ) cell survival model described by relation (17) can be used to describe the relationship between the total isoeffective dose and the dose per fraction in fractionated radiotherapy [10]. The survival fraction (SFd) of target cells after a dose of fraction d is given by the equation, $SF_d = \exp(-\alpha d - \beta d^2)$. The effect of n fractions, with the total absorbed dose, D = nd, is given by the equation,

$$E = -\ln (SF_d)^n = \alpha D + \beta d D). \quad (18)$$

The biologically effective dose (BED) is defined as:

$$BED \equiv E/\alpha = D[1 + d/(\alpha/\beta)] \quad (19)$$

where D is the total dose in fractions of size d. For a reference treatment, $BED_{ref} = D_{ref}\,[1 + d/(\alpha/\beta)]$, is obtained the equivalent dose in 2 Gy fractions (EQD_2),

$$EQD_2 = D\,\frac{d+(\alpha/\beta)}{2+(\alpha/\beta)}, \quad (20)$$

where EQD_2 is the dose in 2 Gy fractions that is biologicaly equivalent to a total dose D give with a fraction size of d [Gy]. The diagram, from Figure 4, shows how the total dose must be modified to maintain a constant level of effect when the fractional dose is changed.

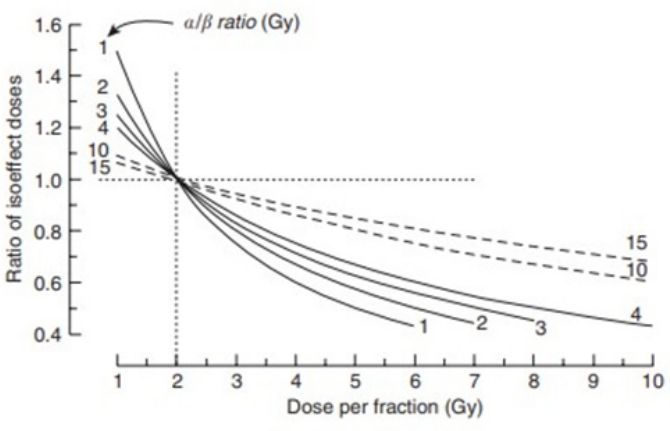


Figure 4: Compared with a reference treatment using 2 Gy per fraction [11].

Relative Biological Effectiveness

The Relative biological effectiveness (RBE) of a radiation under test is defined as [12]:

$$\text{RBE} = \frac{\text{dose of reference rdiation quality } (D_\gamma)}{\text{dose of test radiation } (D_{ion})} \quad [21]$$

to give the same survival fraction, based on LQ model, Figure 5.

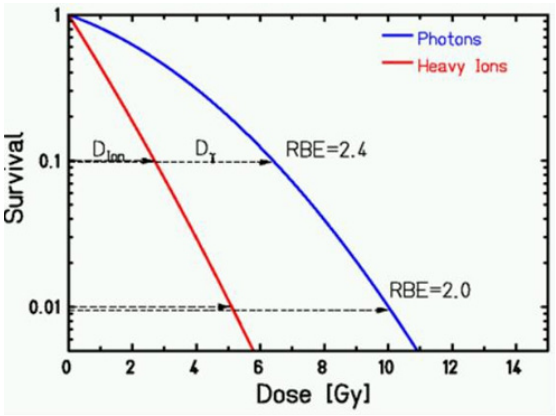


Figure 5: Theoretical cell survival curves for x-rays and particle, illustrating the increase in relative biological effectiveness (RBE) with decreasing dose.

The RBE of a particular type of radiation will vary with particle type and energy, dose, fractional dose, degree of oxygenation, cell or tissue type, biological endpoint, etc.

Example: RBE of photon beam = 1, - of proton beam = 1.1, - of neutron beam = 3 - 3.5, and for carbon ion beam RBE (10%) = 2.73, and RBE (1%) =2.29.

Oxygen Enhancement Ratio

The oxygen enhancement ratio (OER) compares radiation dose in hypoxia, $D_{H,}$ with radiation dose in air, $D_{A,}$ for the same level of biological effect, Figure 6, [13].

$$\text{OER} = \frac{\text{Radiation dose in hipoxia } (D_H)}{\textit{Radiation dose in air } (D_A)} \quad [22]$$

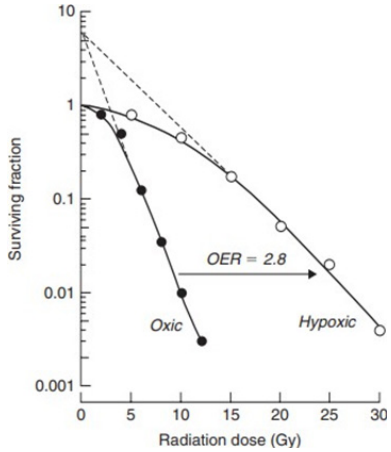


Figure 6: Survival curves for cultured mammalian cells exposed to X-rays under oxic or hypoxic conditions, illustrating the radiation dose-modifying effect of oxygen.

Example: OER of photon beam = 2.5 – 3; -of proton beam = 1.5 – 2; and - neutron beam = 1.

Dose - Response Relationships in Radiotherapy

Clinical radiobiology contains a wide range of doses in which the risk of a particular radiation reaction increases from 0% to 100% with increasing dose (ie, a sigmoidal (or logistic) dose-response relationship). With increasing dose of radiation, the effects of radiation may increase in severity (i.e., degree), frequency (i.e., incidence), or both.

The dose-effect curve in radiotherapy uses as effect an incidence or a probability of response depending on the absorbed dose, P(D).

The graph of the mathematical functions that correspond to these properties are presented in Figure 7. The solid curve is the Logit, the dashed curve is the Probit and the dotted curve is the Poisson expression. In this case D50 = 50 Gy and $\gamma = 2.5$, [14].

In specialized literature, four standard formulations are studied that are used to describe the sigmoid shape of the dose-response curve for tumors and normal tissues.

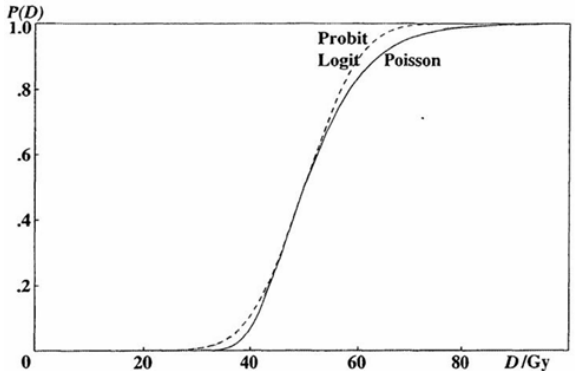


Figure 7: The three different dose-response curves based on equations (24), (27) and (30) from [14].

The probit dose - response model is based on the error function, Erf (U), which can be deduced from "Laplace's integral theorem", just like the distribution function F(z), see relation (4), making the change of variables, U = u/σ $\int_0^{\sigma} e^{-x^2} dx$ and X = x/σ $\int_0^{\sigma} e^{-x^2} dx$

$$\text{Erf}(U) = \frac{2}{\sqrt{\pi}} \int_0^U e^{-X^2}\, dX \tag{23}$$

The dose response relationship for tumors and normal tissues in the Probit model is

$$P(D) = \frac{1}{2} \{ 1 - \text{Erf}[\, \gamma_{50} \sqrt{\pi} - (1 - D/D_{50}) \,] \}, \tag{24}$$

where D50 =50 Gy is the dose at the 50% response level and the factor γ = 2.5, is the normalized dose gradient. The γ_{50} concept has the advantage of being a simple descriptor, that is, the choice of the mathematical model for tumor cell inactivation is independent.

The logistic dose-response model is based on the logistic function (P) of the type

$$P = \frac{exp\,(u)}{1+exp\,(u)}, \tag{25}$$

and

$$u = \text{logit}(P) = \ln\left(\frac{P}{1-P}\right). \tag{26}$$

The ratio P/(1-P) is called odds of a response and the natural logarithm is called logit of P, to indicate that P is a logistic function.

The dose-response relationship for tumors and normal tissues for the logistic model is

$$P(D) = [\, 1 + (D_{50}/D\,)^{4\gamma}\,]^{-1}, \tag{27}$$

where the factor γ ≡ ΔP/(ΔD/D) is proportional to the "probability density" (ΔP/ΔD and dose D, which indicates the point on the logistic curve of the considered probability density and D_{50} is the dose that corresponds to the 50% probability level.

The Poisson dose-response model is based on the Poisson probability distribution law, i.e. the probability P (n, λ) that a tumor has n surviving cells when the mean number of surviving cells is λ,

$$P_n(n, \lambda) = \frac{\lambda^n}{n!} e^{-\lambda} \tag{28}$$

For tumor control, the important parameter is P (0; λ) which is the probability that a tumor will contain no surviving stem cells (i.e., n = 0). From the above equation $P_0 = e^{-\lambda}$ so for λ = 1, the survival fraction (SF) is

$$SF = e^{-D/D0} = P(0; 1) = \frac{1^0}{0!} e^{-1} = e^{-1} \approx 0.37 \tag{29}$$

In target theory, the dose D = D0 is often called the mean lethal dose or the dose that releases, on average, one lethal event per target. Cell survival is reduced from 1 to 0.37. For a tumor of 1 gram (10^9 cells), a dose that reduces the level of survival to 10^{-10} (i.e., 10 cells surviving in 100 tumors) with an expected probability of control of $e^{-0.1}$ = 0.90. This corresponds to a dose of 66 Gy administered in 33 fractions of 2 Gy.

The dose response relationship for tumors and normal tissues for the Poisson model is described by the function

$$P(D) = 2^{-e^{[e\gamma(1-D/D_{50})]}} \tag{30}$$

where γ factor is the normalized dose gradient, defined for relation (31) and D_{50} is the dose that corresponds to the probability level of 50 % [15].

Dose – Response Relationships in Radiotherapy

Tumor cure probability (TCP)

The tumor cure probability (TCP) is the probability of zero surviving clonogens in a tumor that is of interest. Based on the Poisson distribution, according to the principle that no clonogenic cells survive after treatment, TCP, is in this case [16],

$$TCP = \exp(-N) = \exp(-N_0 SF), \tag{31}$$

where N is the average number of surviving clonogens per tumor, N_0 is the number of clonogens per tumor before irradiation and SF is the surviving fraction of target cells, after a dose per fraction d, according to the linear quadratic model, is given by

$$SF_d = \exp[-(\alpha d + \beta d^2)], \tag{32}$$

Here, n (≡ D/d) is the number of fractions of equal absorbed dose d. The parameters α and β are obtained by fitting the linear-quadratic relationship to clinical data.

Normal Tissue Complication Probability (NTCP) Model

Normal tissue complication probability (NTCP) describes the probability of organ/structure complications related to radiation treatment specified by physical and clinical factors in radiation oncology.

Normal tissues irradiated together with the tumor limit the total dose that can be delivered to the tumor. As such, a balance must be found between what is considered acceptable between the dose-response curve for the probability of a radiation-induced complication in a normal tissue and the dose-response curve for the probability of tumor control (Figure 8).

The curves in Figure 8 show that normal tissue rescue is achieved by shifting the NTCP curve to the right (B to C), allowing a lower incidence of normal tissue damage for the same dose (dose 1) or the same level of NTCP for a higher dose high (dose 2). Standard treatment in conventional therapy is based on tumor control probability (TCP) ≥ 0.5 and probability of normal tissue complications (NTCP) ≥ 0.05, [9].

For the calculation of the sigmoid NTCP dose curve, there are several radiobiological dose-response models based on cell

survival biology and others based on statistical distributions. [18]. In Figure 9 shows an NTCP vs absorbed dose, calculated with the Gaussian model), Lyman, Kucher and Burman (LKB).

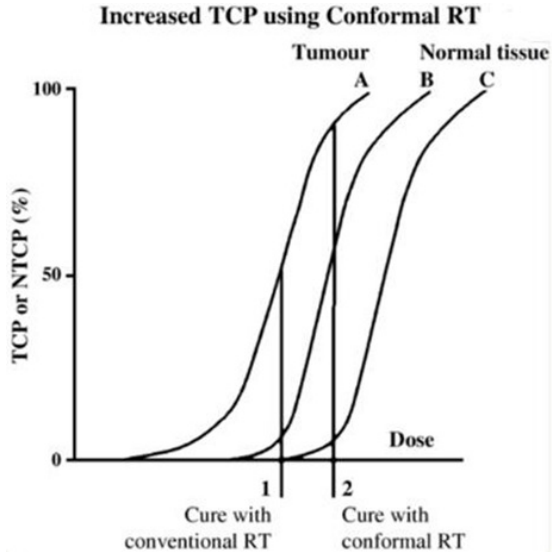


Figure 8: Diagrammatic plot of tumor control probability (TCP) or normal tissue complication probability (NTCP) vs. radiotherapy dose [17].

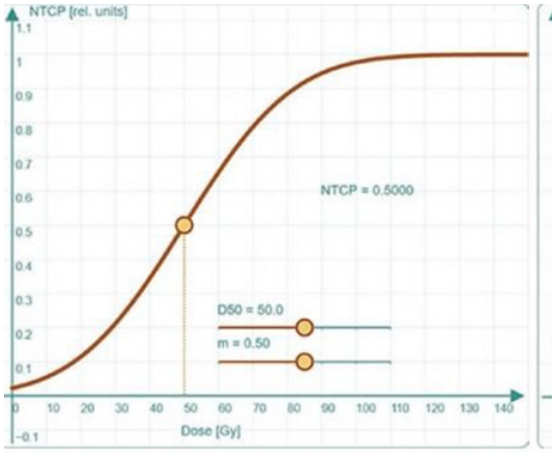


Figure 9: NTCP curves calculated from Lyman-Kutcher - Burman model for two parameter combinations. Parameter m is inversely proportional to the steepness of the curve, [19].

This model gives the normal tissue complication probability (NTCP) as a function of the absorbed dose, D, in an organ of volume, V, as:

$$\text{NTCP (D,V)} = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{u(D,V)} e^{-\frac{1}{2}x^2} dx \quad (33)$$

The LKB radiobiological model in Fig. 9, was calculated for D_{50} = 50 Gy and m = 0.50. For a dose of 50 Gy, the value of NTCP is 0.50.

Equivalent uniform dose (EUD)

The concept of equivalent uniform dose (EUD) was proposed by Niemierko in 1997. This concept was redefined (1999) according to the relation

$$\text{EUD} = (\sum_i v_i D_i^a)^{1/a} \quad (34)$$

where vi is the volume of the dose-volume container with the absorbed dose Di, and the exponent "a" is a complication-specific parameter. There are no recommended publications documenting values for a. EUD for all biological parameters, it should be used with caution if the parameters are not well known, [20].

Example 1: The dose-volume histograms together with unconstrained EUD and constrained EUD corresponding to absorbed dose distributions for PTV are shown in Figure 10.

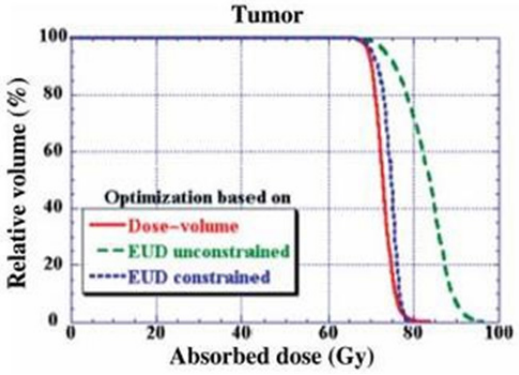


Figure 10: Dose–volume histograms corresponding to the absorbed-dose distributions of interest, [20].

Example 2: Dose homogeneity characterizes the uniformity of the dose distribution in the target volume and dose conformity characterizes the degree to which the high-dose region conforms to the target volume, usually the PTV.

There is a definition for the homogeneity index (HI):

$$\text{HI} = \frac{\text{D 2\% } - \text{D 98\%}}{D_{50\%}} \quad (35)$$

A HI = 0 indicates that the dose distribution is nearly homogeneous. D50% is suggested as a normalization value because its reporting is recommended in planning. For example, for D50% = 60 Gy, D2% = 63 Gy and D98% = 57 Gy, it results that HI = 0.10,

The dose distribution for High Homogeneity Dose (left) and High Conformity dose (right) are illustrated in Figure 11.

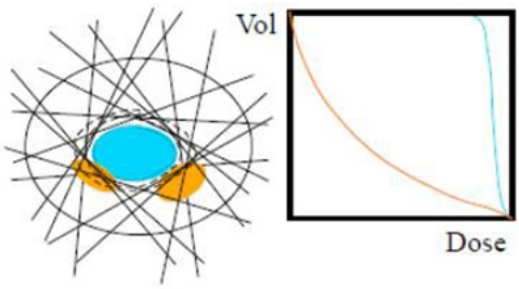


Figure 11: High homogeneity and high conformity [20].

For the conformity index, there are several proposals [21], among which we mention the healthy tissues conformity index (HTCI), defined as:

$$HTCI = \frac{TV_{RI}}{V_{RI}} \quad (36)$$

where TV_{RI} target volume covered by the reference isodose (RI), and V_{RI} volume of the reference isodose.

High Energy Photons in Radiotherapy

Clinical energy of photons

The clinical energies (4 - 25 MeV) of photon beams have generally replaced X and γ radiation therapy with lower energy, ^{60}Co (1.25 MeV) or ^{137}Cs (0.62 MeV), [22]. As sources for photon therapy, there were betatron medical accelerators and linear accelerators. 1953-1954). Currently, linear accelerators are used that provide higher absorbed doses, both for photons and electrons, and reduced weight compared to the betatron, because they do not use the magnetic field to induce the electric field to accelerate the electrons.

Radiotherapy with a beam of photons, with the energy hv = 10 MeV per photon, monochromatic, collimated, for the irradiation of a clinically detected tumor, for example a tumor with a diameter of 3 cm^3, 10^9 clonogenic tumor cells, applies the standard reference conditions for the treatment of cancer. The beam must deliver small daily dose fractions, of approximately 2 Gy per liter of tissue, 5 days per week, a period of over 5 to 7 weeks to total doses of 50 to 75 Gy. Assuming that each fraction of 2 Gy inactivates 50 percent of the clonogenic cells, after 25 and 30 treatment sessions (or half-life periods), the fractional number of surviving cells per tumor is 2.98 x 10^{-8} and 2.91 x 10^{-11}. with the tumor control factor (percentage) of 37%.

According to the local effect model (LEM), the tumor absorbs the energy corresponding to the dose per fraction of 2 Gy, i.e. 2 x 6.24 x 10^9 MeV/g of tissue at any point in the tumor volume. For the absorbed dose of 1 Gy per minute, in air, the energy flux rate is about 1mW/cm^2 and the photon flux is 6.80 x 10^8 photons/cm^2. s. In the case of an irradiation field of 500 cm2, the photon flux is 3.4 x 10^{11} photons of 10 MeV each per second. The energy absorbed in Joules per kilogram in soft tissue is about 1.105 times that in air for the same incident energy fluence rate.

A comparison between the dose absorbed in depth, in the case of treatment with a 15 MeV photon beam and a 150 MeV proton beam with a 7 cm SOBP and a 10 MeV electron beam, is shown in Figure 12.

The maximum absorbed energy at the end of the finite path of the protons, practically zero, and the maximum absorbed energy at the beginning of the photon path. They are highlighted in Figure 12.

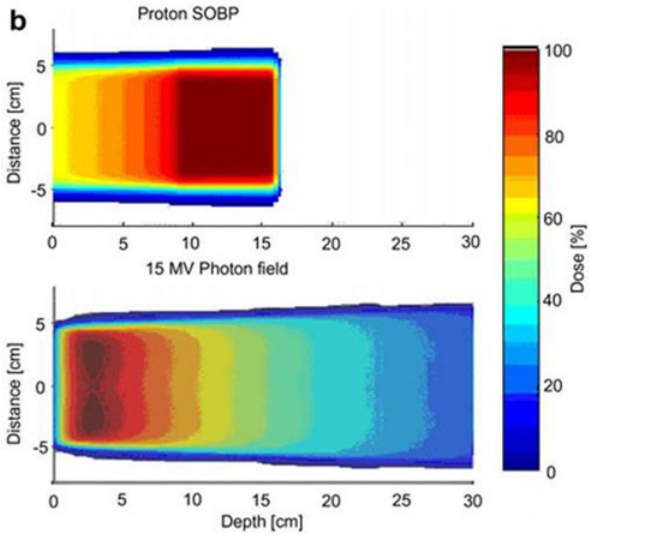


Figure 12: Comparison between the depth dose curve of a 15 MeV X-ray beam and the absorbed dose vs depth for a 150 MeV proton beam with a 7 cm SOBP [23].

Absorbed Dose in Water

Figure 12, clearly shows the maximum absorbed energy at the end of the finite path of the protons, practically zero, and the maximum absorbed energy at the beginning of the photon path. In radiation therapy water is used as tissue reference medium. The mean energy deposited by ionizing radiation in a mass element dm of tissue (or tumor) is the most important physical quantity in radiotherapy [24].

The energy absorbed per unit of mass in the tumor, that is, the point absorbed dose, $D \equiv dE_{ab}/dm = \frac{MeV}{s.cm^2}.t((s)$, and $\frac{MeV}{s.cm^2}$ the dose rate at electronic balance is given by the equation (38),

$$D = 1.602 \times 10^{-10} \left(\frac{g.Gy}{MeV}\right) \frac{\mu_{ab}}{\rho} \left(\frac{cm^2}{g}\right). \dot{\Psi} \left(\frac{MeV}{s.cm^2}\right). T(s), \quad (37)$$

where 1.602 x 10^{-10} Gy = 1 MeV/g, μ_{ab}/ρ is the mass energy absorption coefficient (in units cm^2/g), $\dot{\Psi}$ is energy fluence rate of photons and electrons (in units MeV/cm^2.s) and T (s) is irradiation time (in units seconds).

If the dose absorbed in an environment (m) is measured, at electronic equilibrium, the ionization chamber performs a measurement in the radiation field in the place where the irradiated substance is subsequently placed.

In the assumption that the photon energy fluene is the same in both situations, the air in the measurement cavity and the environment surrounding cavity, $\Psi_a = \Psi_m = \Psi$, it can be written, for the dose absorbed in air, Da, and for the dose absorbed in the environment, Dm, relations

$$D_m = \Psi \left(\frac{\mu_{ab}}{\rho}\right)_m ; \quad D_a = \Psi \left(\frac{\mu_{ab}}{\rho}\right)_a . \tag{38}$$

Here, the dose absorbed in the cavity from the specific ionization J_{air}, in units of Joules per kilogram, is given by the relation

$$D_c = D_a = \frac{W_a}{e} J_{air} . \tag{39}$$

The formula for the dose absorbed in the environment is

$$D_m = \frac{(\mu_{ab}/\rho)m}{(\mu_{ab}/\rho)a} \frac{W_a}{e} X . \tag{40}$$

Tumor (target)

The tumor is represented by three concentric volumes in Figure 13. The first of these two volumes is the position and extent of the primary tumor, known as the gross tumor volume (GTV). The second, the clinical target volume (CTV) that surrounds the GTV and describes the microscopic spread of the tumor. The third volume is the planning target volume (PTV); this was developed in ICRU Report 62, 1999.

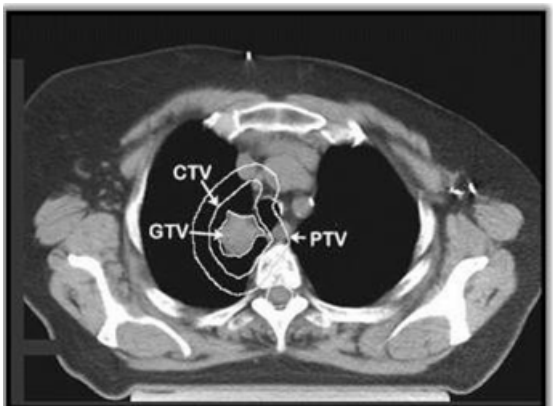


Figure 13: Volume definitions in radiotherapy according to the International Commission on Radiation Units and Measurements (ICRU, 1999) & Report 62 (ICRU, 1999), [25].

To respond to appropriate radiotherapy. there is also the treatment volume (TV) for the prescribed dose and the irradiated volume (IV) which is exposed to significant doses in terms of normal tissue tolerance, and Planning Organ at Risk (PRV).

The original concepts and functions of these volumes are detailed in Report 50 (ICRU) of 1993. Classification revised treatment volumes is made in ICRU 2010 and Report 83. In the following, we will present some clinical cases regarding the energies and methods of forming dose distributions used in the treatment of cancer.

Clinical examples

Example 1: Comparison between two photon beam energies, provided by a linear accelerator; the isodoses for the energy of 6 MeV and the isodoses for 15 MeV are illustrated in Figure 14.

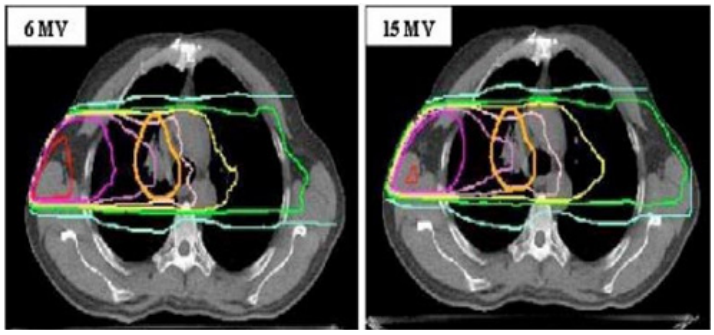


Figure 14: Dosimetry advantage of using 6 MV over 15 MV photons in conformal therapy of lung cancer [26].

From the analysis of isodose images, the advantage of using X-radiation of 6 MeV compared to the energy of 15 MeV results. X-rays provide images of tumors in two dimensions, 3DCRT and IMRT give the image in three dimensions, 3D, when taken into account of the patient's breathing and heartbeat, we have 4D (x, y, z, t) [27].

Example 2: The standard tumor conformal radiotherapy system, 3D CRT, uses photon beams of constant intensity) to conform high energy regions with the target volume Figure 15.

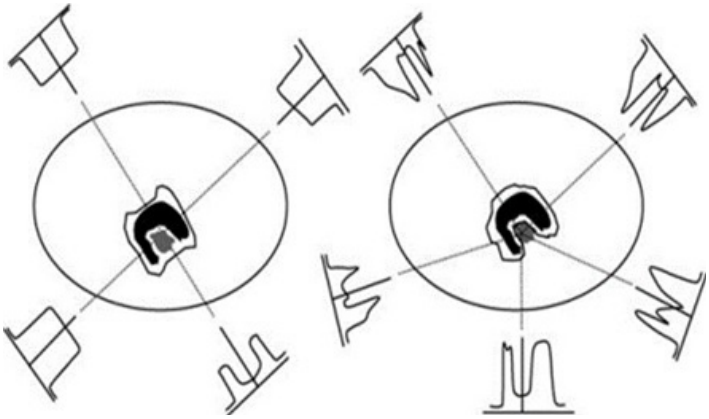


Figure 15: Comparison of CRT (left) and IMRT (right), [20].

By using a variable radiation intensity applied in several directions, Figure 15, we switch to a new method and device, called Intensity Modulated Radiation Therapy (IMRT).

Intensity Modulated Radiation Therapy (IMRT) is an advanced high-precision radiation therapy technology that uses computer-controlled linear accelerators to deliver precise absorbed doses within the malignant tumor volume or specific areas within the tumor volume.

Example 3: Planning through calculations of isodose distribution in 3D, CRT and IMRT methods, is given in Figure 16.

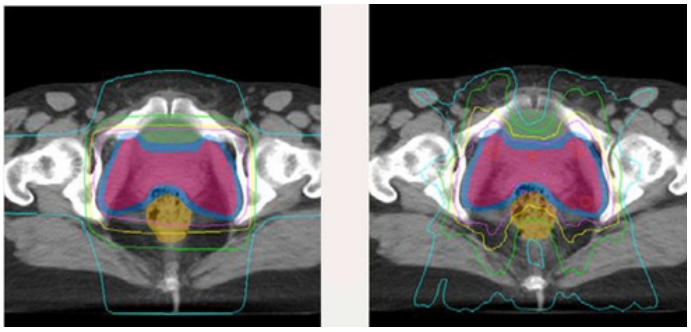


Figure 16: Comparison of CRT (left) and IMRT (right), conform ICRU 83 [9,20].

The distribution of an absorbed dose in the target volume can be characterized by the homogeneity of the dose, and the conformity of the dose which characterizes the degree in which the high dose region is in conformity with the target volume, described by PTV, see Figure 16.

Example 3: Currently, there is the possibility of by passing a prohibited area, i.e. U - type targets, Alfa, etc., with the help of a new technology called "tomotherapy", Figure 17.

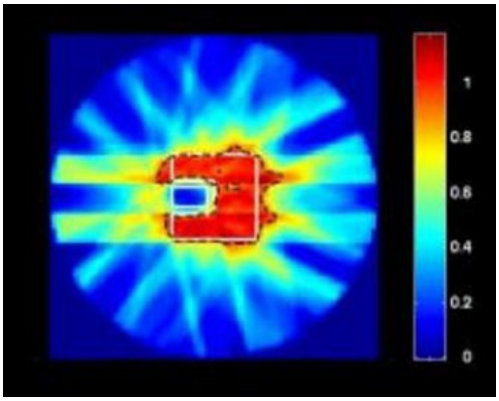


Figure 17: A schematic example of a "U"- shaped high dose region (red) [28].

It is based on two types of technologies: Intensity Modulated Radiation Therapy (IMRT) and Spiral CT Scanning. The radiation source uses a 6 MeV linear accelerator and a multileaf collimator (MLC). For more detailed explanation, see Ref [28].

Example 4: Comparative radiobiologic studies regarding the application of 3DCRT, HT and IMRT in treating lung cancer accounting for secondary malignancy risks [29].

High energy electrons in radiotherapy

Radiotherapy with electrons whose energies are between 4 MeV and 25 MeV, is based on their finite course in the tumor environment. The first application of high energy electron beams was initiated in 1955, in the treatment of breast cancer, using a medical betatron of 24 MeV [30]. Then followed breast cancer treatments with electron beams in the 10 - 35 MeV range, provided by the 36 – MeV Brown-Bovery betatron [31,32].

The electron is an elementary particle with rest mass, m_0 = 0.511 MeV/ c^2, diameter of 10^{-18} m, electric charge, q = e^- = - 1.602 x 10^{-19} C,

Radiotherapy with electron beams applies the standard reference conditions recommended by the dose of 2 Gy per fraction 5 days per week, over a period of 5 to 7 weeks to total doses of 50 to 75 Gy.

Clinical Energy of Electrons

Knowing the dose per fraction at the level of the tumor and the energy lost by electrons when crossing the tumor, through the interaction factor, the mass stopping power in water $(S/\rho)_{el}$ in units of MeV.cm2/g, the value of the electron flux is obtained from the dose equation from the incident beam, Φ_{el} in units of electrons/ cm2.second.

When the beam meets the tumor, the information on the energy absorbed by the tumor is given by the interaction coefficient for electrons, which acts as a conversion factor from the electron fluence rate, Φ, to the energy absorbed per unit mass of the tumor, i.e. the dose.

Considering the kinetic energy of an electron, E = 10 MeV, the mass stopping power corresponding to the energy, (S/ρ) = 1.978 MeV.cm^2/g, and 1 A = 6.24 x 10^{18} e/s, at a dose of 2 Gy/fr = 2 x 6.24 x10^9 MeV /g, resulting in the electron flow rate Φ = 3.18 x 10^9 electrons/cm^2.s and the energy flow Ψ = 3.18 x 10^{10} MeV/cm^2. For a standard field of 10 x 10 cm^2, and for an irradiation time of 100 seconds, the energy flux is Ψ = 3.18 x 10^{14} MeV/cm^2. This flux corresponds to a current of intensity I = 0.1 μA.

Doza Absorbed in Water

According to the cavity theory developed by Bragg – Gray for the measurement of energy absorbed in a cavity, its dimensions must be smaller than the path of the secondary electrons of energy E, released into the medium, represented by the flux Φ_{el}.

The Bragg-Gray relation refers to the dose absorbed in the sample material in the cavity, Dc, and to the dose in the medium, m, that surrounds the cavity, Dm, both related to the uniform flux Φ_{el} of the secondary electrons released into the medium through the restricted mass stopping power (LΔ /ρ),

$$D_c = \Phi_{el} \cdot \left(\frac{L_\Delta}{\rho}\right)c \quad ; \quad D_m = \Phi_{el} \cdot \left(\frac{L_\Delta}{\rho}\right)_m , \tag{41}$$

From relations (41) and (39) we obtain the expression for the dose D_m

$$D_m = \frac{(L_\Delta/\rho)m}{(L_\Delta/\rho)a} \cdot \frac{W_a}{e^-} \cdot J_a \tag{42}$$

where Ja is the electric charge produced in the volume of the reference cavity, filled with air of density ρ, W_a is the average energy expanded in the air per ion pair formed, e^- is the charge of the electron, and (L_Δ/ρ) S_{col}/ρ - mass stopping power of the medium, according to ICRU Report 37. The values for $(S/\rho)_{col}$ for various materials exists in Tables of Berger and Seltzer [33].

Clinical example 1: Dose – response relationship

Dose-response curves for ionizing radiation are sigmoid (ie "S") shaped, with radiation incidence, effects tending to zero as dose tends to zero and tending to 100 percent at very high doses, see Figure 18.

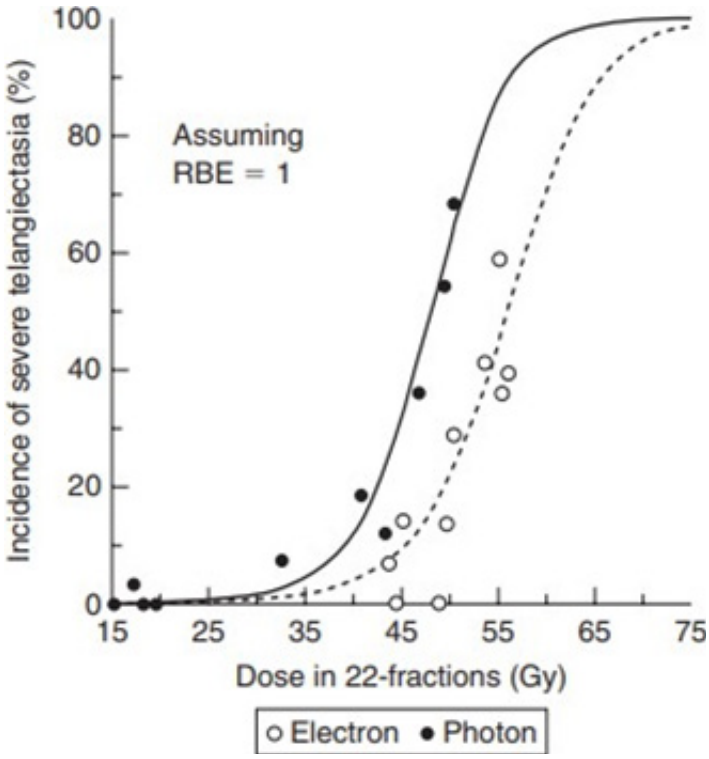


Figure 18: Examples of dose-response relationships in clinical radiotherapy from Bentzen and Overgaard [34].

Holthusen demonstrated the sigmoidal shape of the dose-response curves for both reactions in normal tissue and local control of skin cancer. He noted the similarity between these curves and cumulative distribution functions known from statistics.

Munro and Gilbert starting from "the object of treating a tumor by radiotherapy is to damage every single potentially malignant cell to such an extent that it cannot continue to proliferate", the random nature of cell killing by radiation, they showed that the tumor cure probability (TCP) depends only on the average number of surviving clonogens per tumor after irradiation.

In The Poisson dose–response model derived by Munro and Gilbert, rezulta, TCP = exp (-λ), unde λ este numărul mediu de clonogene per tumoră după iradiere,

Clinical example 2: Linac for breast cancer treatment

A treatment room equipped with a medical linear electron accelerator for the treatment of breast cancer is shown in Figure 19.

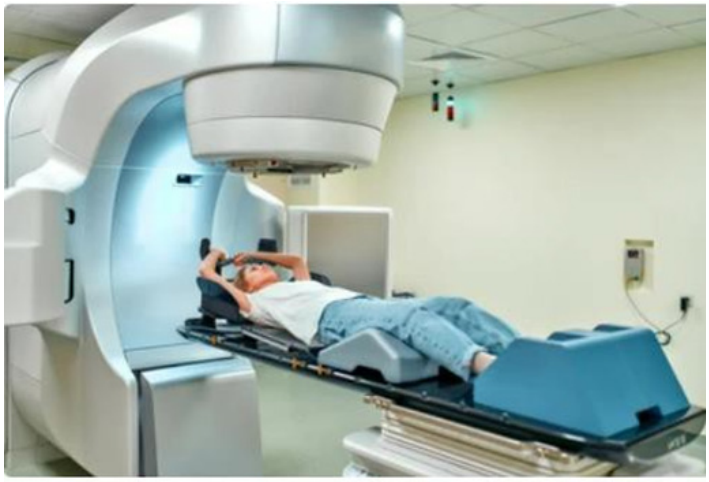


Figure 19: The gantry therapy room during electron treatment of brest cancer [35].

Example 3: Comparison between 3DCRT si IMRT.
An example of 3DCRT treatment (left) and by the IMRT method (right) is illustrated in Figure 20.

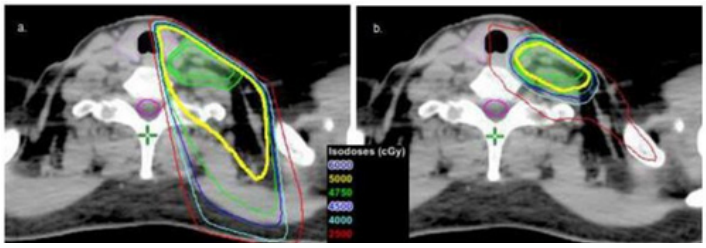


Figure 20: The dose distribution with 3D-CRT versus IMRT for the treatment of the supraclavicular nodes [36].

High Energy Protons in Radiotherapy

Proton beam radiotherapy may offer clinical advantages over conventional photon radiotherapy for many types of cancer, mainly as a result of a more favorable distribution of absorbed dose in depth.

The first irradiations on patients were performed in 1954 by Tobias and his colleagues [37]. The first hospital-based proton treatment facility was in 1993 (Loma Linda, US).

The proton is the nucleus of the hydrogen atom. It has a rest mass 1836 times greater than the mass of the electron, $m_0 = 932.27$ MeV/c^2, and magnetic rigidity $B\rho = 3.11$ Tesla.m. Charge $q = Q.e^+ = +1.602 \times 10^{-19}$ Coulombs; 1 C = 1 A.s. The diameter of the proton is 10^{-15} m and the diameter of the atomic nucleus formed by protons and neutrons is 10^{-14}. The diameter of the atom is 10^{-10} m and that of the Corona virus, 1.5×10^{-7} m, [38].

The comparison between photon treatment technology and proton treatment technology is given in Figure 21.

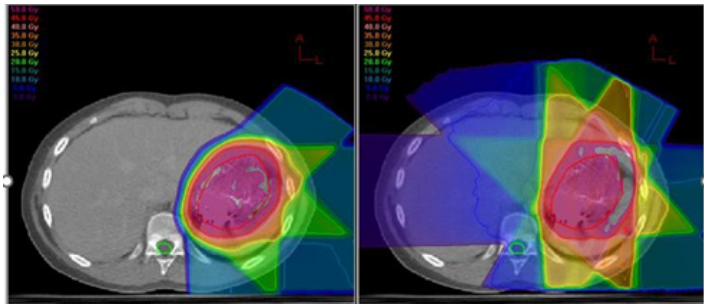


Figure 21: Comparison. Proton vs. IMRT Chest Tumor, [39].

The advantages of proton therapy are evident from the analysis of the images from Figure 21.

Clinical energy of protons

IAEA TRS 398 recommends, in radiotherapy, protons with energies between 50 MeV and 250 MeV, which have paths in water from 2.19 cm to 37.4 cm. The intensities of the proton beam vary between 10^{10} protonis/s and 10^{13} protons/s to ensure a dose rate of 1 Gy/m. When the proton meets the tumor, the energy given by them per unit mass of the tumor, according to the standard conditions in radiotherapy and radiobiology, must have the value of 2 J/kg per fraction, and 5 fraction per week.

A proton beam with a kinetic energy of 50 MeV, and a beam current of 0.34 nA, ensures, at the level of the tumor, a dose of 1 Gy = 1 J/kg = 6.24 x 10^9 MeV/g, the energy absorbed in one minute, E (MeV) = 50 MeV x 0.34 nA x 60 seconds = 1 J (for one minute). This means that the flow of protons is about 5 x 10^{11} p/s. Under the same conditions, for the proton energy of 250 MeV, the proton flow is about 10^{11} p/s.

The loss of energy during the periods of acceleration, extraction, transport and in the methods of passive or active modeling of the particle beam, are not taken into account [40].

The expression for the energy (E) and momentum (p) of a proton in motion is given by equation (43)

$$E^2 = c^2p^2 + A^2m_0^2c^4, \quad (43)$$

where E = (T + E_0), T = kinetic energy, $E_0 = m_0c^2$ = 932.27 MeV is the rest energy and A is the atomic mass.

Absorbed Dose in Water

For proton beams with kinetic energy between 50 MeV and 250 MeV, the determination of the energy absorbed per unit mass of the tissue is done using the basic formalism in TRS-398, which expresses the absorbed dose in water, $D_{w,Q}$, for a beam of quality Q, thus:

$$D_{w,Q} = M_Q N_{D,w,Q0} k_{Q,Q0}, \quad (44)$$

$$k_{Q,Q0} = \frac{(S_{w,air})_Q}{(S_{w,air})_{Q_0}} \frac{(W_{air}/e)_Q}{(W_{air}/e)_{Q_0}} \frac{p_Q}{p_{Q_0}} \quad (45)$$

where MQ is the reading of the dosimeter at the reference point of the chamber positioned at zref according to the reference conditions, $ND_{w,Qo}$ is the calibration factor in terms of absorbed dose in water for the dosimeter at the reference quality Q_o, and $k_{Q,Qo}$ is a chamber-specific factor that corrects for differences between the quality of the reference beam Q_o and the actual quality of the used beam Q, $S_{w,air}$ is the mean water to air mass stopping power ratio, Wair/e is the mean energy to form ion pair in ionization chamber air filling, and p is the product of chamber perturbation factors [p_{wall}, p_{cav}, p_{cel}, p_{disp}], [22].

Depth Dose Profile of Proton Beam in Water

The distributions of the absorbed dose depending on the kinetic energy of the therapeutic proton, at the values of (40, 80, 120, and 160 MeV, are presented in Figure 22.

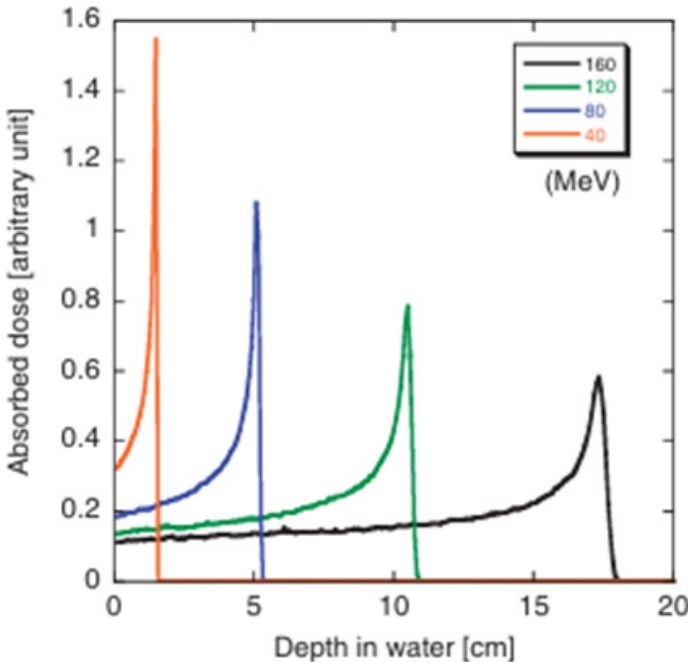


Figure 22: Absorbed dose distributions for protons, in water [41].

The range in water for these energies is: 1.49 cm at 40 MeV; 5.2 cm at 80 MeV; 10.5 cm at 120 MeV and 17.4 cm at 160 MeV. In the Figure, their finite path can be distinguished, compared to electrons, and even carbon ions.

The Static Scattering Method

The proton beam used for hadrontherapy must be formed to the size of the tumor both in terms of surface, homogenization, and depth, using the energy variation and the intensity variation. In this sense, there are two methods of obtaining the distribution of the absorbed dose specific to the tumor, one static and the other dynamic wobbling type both methods have a common part that consists in broadening the beam by scattering, simple or double in the static method and by wobbling or scanning in the dynamic method. Figure 23 shows the variable part of the static method, specific to each patient, which refers to the tumor volume and the treatment volume.

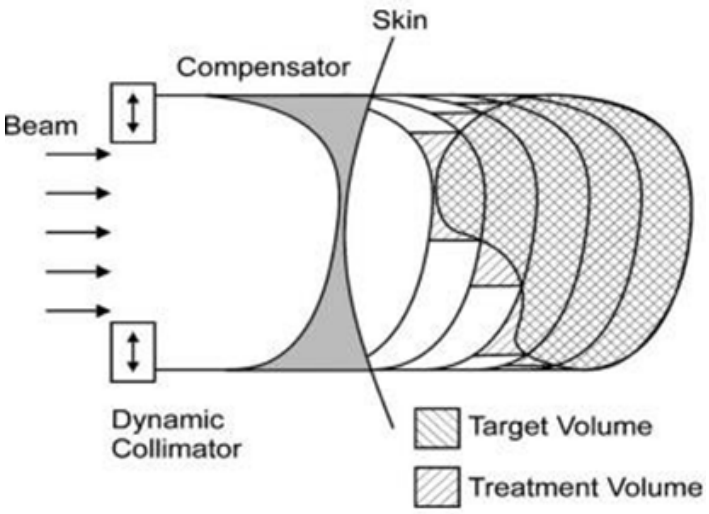


Figure 23: Conforming to target by field – specific range compensator [42].

It contains two important components: a dynamic collimator that forms the beam to cover the transverse surface of the tumor, and a compensation bolus to form a distribution of the particle path that focuses the dose on the tumor and at the same time minimizes the dose in the tissues adjacent to the tumor. In the static method, the energy control is given by the ridge filter, and in the dynamic Wobbling/scanning method, this is given by the range modulator.

The disadvantage of this passive method is that it is applied to each patient, and it increases the treatment time. Another disadvantage refers to the additional radiological protection of the patient in the therapy room due to the elements located in front of the patient's tissue, the collimator (high Z material) and the compensator (low Z material).

RBE for protons

Effectiveness (RBE), i.e. the ratio of photon and ion doses to produce the same biological effect has the advantage of reducing the physical absorbed dose practically by the value of this ratio.

The distribution of the absorbed dose in depth of a clinical proton beam of 152 MeV in the variants: monoenergetic (dashed line); clinical beam (continuous line, ordered left); and the weighted absorbed dose with the value of RBE = 1.1, at all depths (red dotted line, ordered right), is illustrated in Figure 24.

Proton absorbed dose (D) delivered under the same conditions as the photon standard Reference conditions (2 Gy, 5 fr week), proton iso-effect dose (D_{IsoE}) or RBE dose weighted (D_{RBE}) is simply,

$$D_{ISoE} = D_{RBE} = D \times 1.1. \quad (46)$$

Since both the absorbed dose, D, and the iso-effect dose, (DIsoE), are expressed using the same gray unit (Gy), and to avoid confusion, the weighting is indicated by adding "RBE" clearly separated from the Gy unit, i.e."Gy_(RBE)", [44]. A constant RBE value of 1.1 is used for clinical proton therapy.

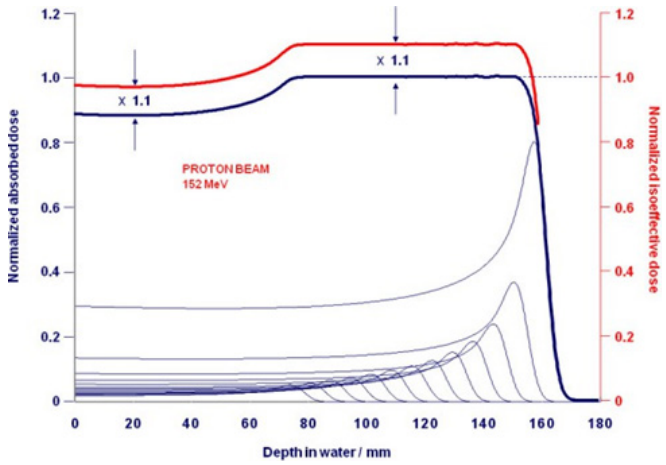


Figure 24: Depth variation of the absorbed dose of a monoenergetic 152 MeV proton beam [43].

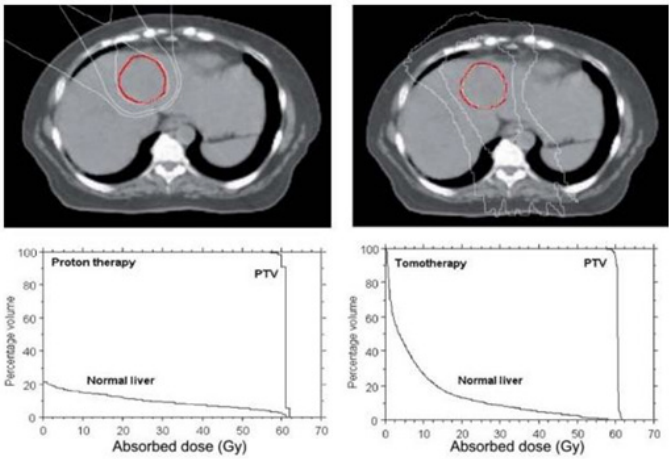
Example of calculation for a given clinical situation, the prescribed absorbed dose is: D = 63 Gy and $D_{ISoE} = D_{RBE}$ = 70 Gy_(RBE) or more explicitly (RBE=1.1).

In particular cases, for the provision of protons in non-standard conditions, the ICRU procedure is applied.

Clinical Examples

Example 1: In ICRP 83, two modalities for the treatment of the liver are presented: IMPT and Helical tomotherapy, regarding the Equivalent Uniform Dose (EUD), a concept proposed by Niermierco in 1997, Figure 25.

Figure 25 illustrates that the EUD formula can favor either tomotherapy or proton therapy depending on the value of parameter 'a. At lower values of parameter "a", the two-field proton IMPT case has a lower integral absorbed dose than in the case of helical tomotherapy, and at higher values, the situation is reversed, tomotherapy being more appropriate with a smaller volume at higher levels of the absorbed dose.



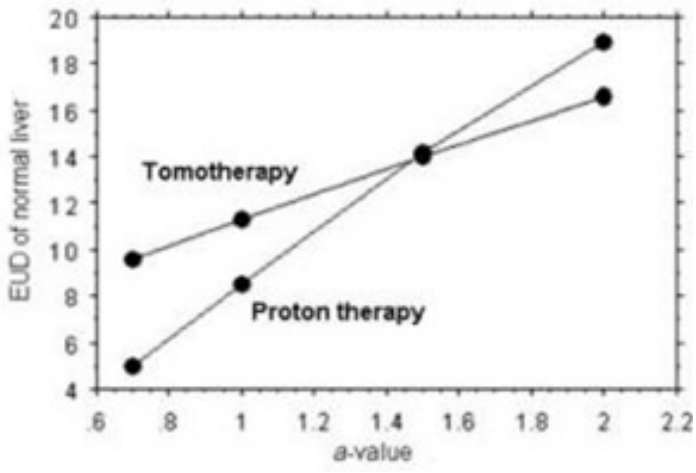


Figure 25: The EUD for normal liver as a function of parameter "a" [20].

Example 2: The clinical example from Figure 26 shows a comparison between 3D CRT, IMRT and IMPT technologies.

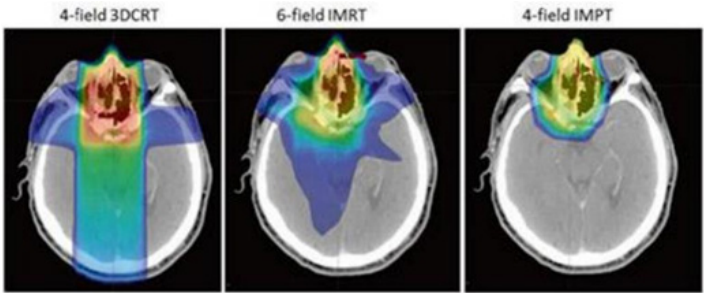


Figure 26: Comparison of absorbed dose distributions in the case of application "4 – field 3DCRT, 6-field IMRT si 4-field IMPT [45].

Under the conditions given by the number of irradiation fields, the advantage of applying the IMPT technology results.
Example 3: The clinical example from Fig. 27 refers to Single field uniform dose technology (passive) and

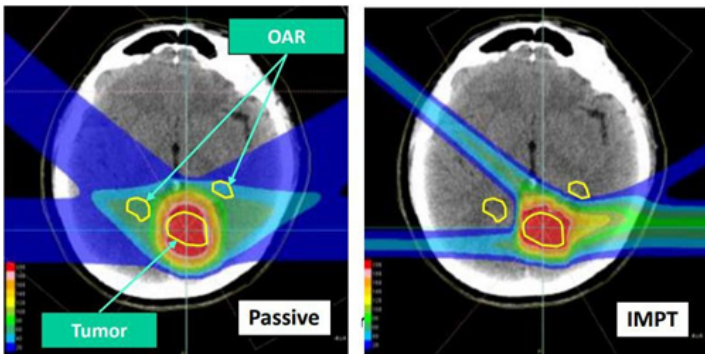


Figure 27: Passive technology and IMPT technology [46].

IMPT technology. Image analysis shows that organs at risk (OR) can be protected in IMPT therapy.

High Energy Carbon Ions in Radiotherapy

In 1977, the first patients were treated with Carbon/Neon, and the first carbon ion treatment facility was put into operation in 1994, in Japan.

Compared to proton therapy, carbon ion therapy has two important advantages. The first, physically, the dose distribution in depth has the BG peak closer to the "delta function (δ)" and the second, radiobiological advantage, the relative biological effectiveness at the peak level can reach up to RBE = 3 compared to the recommended RBE = 1.1 value for the proton particle.

Clinical Energy of Carbon Ions

The kinetic energy of the carbon ion (A = 12, Z = 6) for treatment, recommended by the IAEA TRS 2000 is in the range between the energy of 100 MeV/n (or 1200 MeV, range 2.58 cm) and the energy of 450 MeV/n (or 5400 MeV, range 33.7 cm). The intensity of the carbon ion beam is about 10^8 -10^{12} C-ions/s.

Considering that the minimum kinetic energy of the therapeutic ion is 1200 MeV, the number of 5.2 x 10^9 ions with the energy of 1200 MeV immediately results. To obtain 1 Gy in one minute, an ion beam current of 14 pA is required. x 60 s = 1 joule. At the energy of 5400 MeV, 1 Joule = 1.2 x 10^9 ions, the ion current decreases by 4.4 times, i.e. I = 3 pA for 1 Gy. By definition, we have: 1 Gy = 6.24 x 10^{12} MeV/ (kg ≡ L = 1000 cm^3 of H_2O). The rest energy is $E_0 = Am_0 c^2$ =11198 MeV, T = kinetic energy, A = atomic number and p = Q e B ρ is the impulse or momentum of the particle.

Absorbed dose in water

Energy lost by the charged particle for a parallel beam with particle fluence Φ_e, the kinetic energy lost over the distance dℓ, which automatically becomes the absorbed dose, D [Gy], is given by the equation,

$$D=1.6 \times 10^{-9} \cdot \frac{1}{\rho}\left[\frac{cm^3}{g}\right] \cdot \left(-\frac{dE}{d\ell}\right)\left[\frac{keV}{\mu m}\right] \cdot \Phi_i \ (cm^{-2}), \quad (47)$$

where the dE/ρdℓ coefficient is the mass stopping power, for which there are calculated, tabulated values [33].

Here, the isoeffect dose concept applies similarly for C+ as for protons:

$$D_{ISoE} = D_{RBE} = W_{IsoE} \cdot D \quad (48)$$

Where the W_{IsoE} weighting factor includes all parameters that could affect the clinical outcome, [47].

Depth Dose Profile of Carbon Beam in Water

The distribution of deeply absorbed doses is shown in Figure 27 for the kinetic energies of carbon ions between 1200 MeV and 5400 MeV, the rest energy of the carbon ion being 11,188 GeV

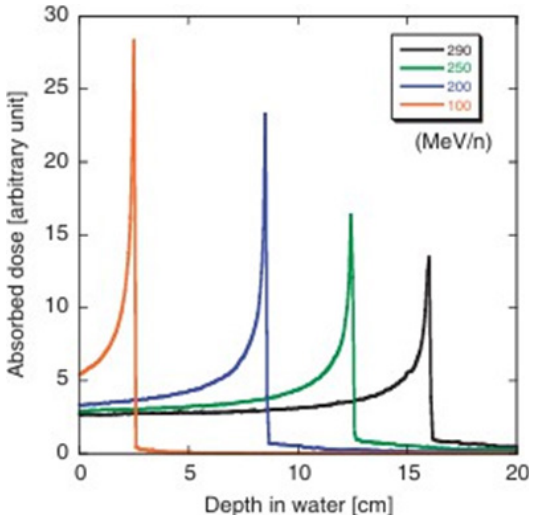


Figure 28: Absorbed dose distributions for carbon ions, in water [41].

The paths of the carbon ion in water are 2.59 cm at 1200 MeV, 8.76 cm at 2400 MeV, 12.81cm at 3000 MeV, and 16.4 cm at 3480 MeV.

Active Scanning Method

The active method consists in using the magnetic field for scanning with a pencil beam to obtain a radiation field extremely consistent with the tumor. These types are are described in detail in the works: [48], spot scanning at PSI, Switzerland [49], pixel scanning at HIMAC, Japan and [50] raster scanning at GSI, Germany.

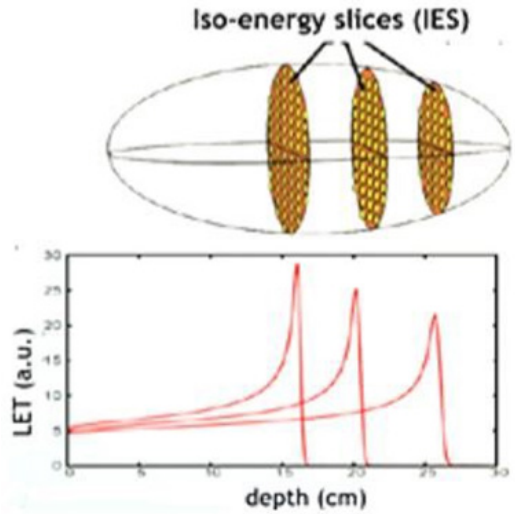


Figure 29: Active method from GSI [51].

Figure 29 shows the ballistics of the hadron beam, the last part of the pencil beam scanning method, namely the choice of energy depending on the depth at which the slice designed for irradiation is located [51].

Clinical Example 1: RBE (Reference Co-60)

An example of Carbon 12, 290 MeV/u, 6 cm SOBP, with change of RBE along SOBP is shown in Figure 30.

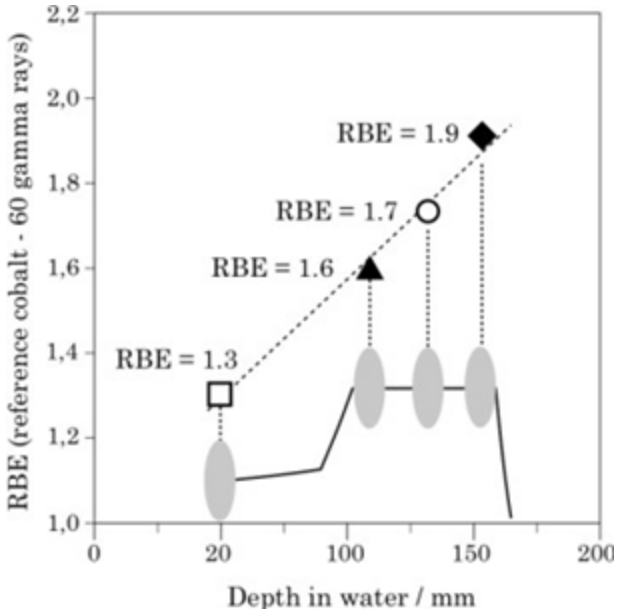


Figure 30: RBE variation as a function of depth in the C+ beam at Chiba, 60Co is the reference radiation [52].

Clinical Example 2: The method for determining the RBE at the center of the SOBP for clinical situations is shown schematically in Figure 31.

The distributions for physical dose, biological dose and clinical dose are presented for a prescribed clinical dose of 2.7 GyE and biological dose of 1.84 GyE. Concept of the doze – isoeffect can be applied as well to C+ as to protons.

$$D_{ISoE} = W_{IsoE}. D \quad (49)$$

Where the W_{IsoE} weighting factor includes all parameters that could affect the clinical outcome.

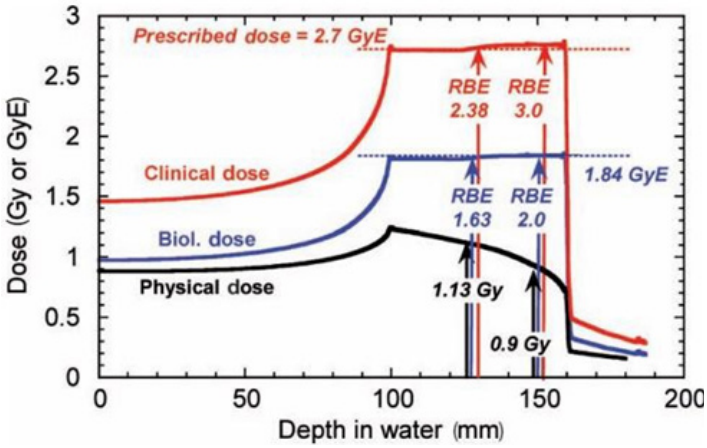


Figure 31: Schematic method used to determine the RBE at the centre of the SOBP for the clinical situation, [53].

The quantities D and D_{ISoE} are both expressed using the same unit: gray. To avoid confusion, whenever "Gy" refers to an isoeffect

dose, the symbol Gy is followed, after a space, by (IsoE) in parentheses. For example: D_{ISoE} = 70 Gy_(IsoE).

Clinical Example 3: The treatment plan for carbon ions (with two fields), a, and the treatment plan for IMRT (with 9 fields), b, are presented in Figure 32.

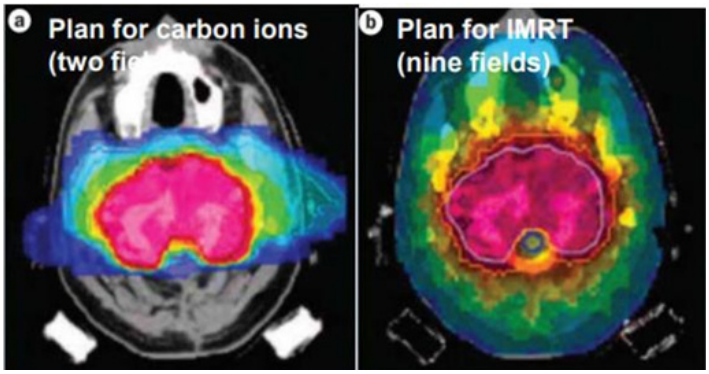


Figure 32: Treatment plan for carbon beam in IMPT technology and IMRT technology [39].

The analysis of the images in Figure 31 [39], indicates the advantage of the integral dose for the tissues outside the tumor for the IMPT method. A plan for proteins is given in [54].

Conclusion

The energy absorbed in the tumor mass, i.e. the absorbed dose D, is a fundamental quantity in radiation biology, clinical radiology, and clinical radiotherapy.

The body's response to ionizing radiation is characterized by a sigmoid-shaped dose-effect curve (that is, S), which can be described mathematically by various functions, among which we mention the logistic function, probit and Poisson.

The location of the tumor being anywhere inside the body, radiotherapy applies the principle of maximizing the energy absorbed in the tumor and minimizing the energy absorbed outside the tumor environment, especially outside the organs and tissues at risk.

The application of this principle is ensured by the 3D irradiation system (length x height x depth) based on CT, MRI and computer, together with the treatment planning software. The ballistics problems that occur when the tumor moves due to breathing and heartbeats represent 4D(x,y,z,t) radiotherapy.

Photon beam radiotherapy uses the Intensity-Modulated Radiation Therapy (IMRT) method in the treatment of cancer, in which it replaced the spot dose with a volume dose, uniform fluency with non-uniform fluency, uniform dose with high gradient dose and analog dose with digital dose. Currently, the most advanced method of photon therapy is Helical Tomotherapy (HT). Photon beams (X-rays, γ-rays) are low-LET radiation with the characteristic of weakly ionizing radiation.

The quality specifications of the dose distribution are dose homogeneity for characterizing the dose distribution within the tumor volume by the homogeneity index, and dose distribution conformity characterizing the degree to which the high dose region conforms to the target volume.

The total dose that can be administered in the tumor is limited by the normal tissues, because they are irradiated together with the tumor. As such, a balance must be found between what is considered acceptable between the dose-response curve for the probability of a radiation-induced complication in a normal tissue (NTCP) and the dose-response curve for the probability of tumor control (TCP).

The standard treatment in radiotherapy is the one with probability of tumor control (TCP) ≥ 0.5 and probability of normal tissue complications (NTCP) ≥ 0.05.

Electron radiotherapy is used for superficial tumors due to the finite path of electrons (as in the case of breast cancer). We can compare the distribution of energy absorbed from electrons with the distribution in depth of hadrons with a wide SOBP.

Radiotherapy with protons and ions offers clinical advantages through the finite course, the Bragg peak of the absorbed dose distribution, in depth, and the biological advantage RBE = 1.1 recommended by the ICRU for protons. At the level of the Bragg peak for carbon ions, the RBE varies between 1.5 and 3. For the treatment of cancer with hadrons, the standard reference conditions from photons are recommended, 2 Gy per radiotherapy session and 5 sessions per week.

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