CHAPTER 1. PHYSICAL AND BIOLOGICAL BASIS OF RADIOTHERAPY

Radiotherapy is a medical speciality which teaches to use ionizing radiation as a medical factor.The radiotherapy is used in oncology. Its biological effect lies in the basis of ionizing radiation.

Ionizing radiation is electromagnetic radiation (x-ray and gamma ray photons) or particulate radiation (alpha particles, beta particles, electrons, positrons, protons, neutrons, and heavy particles) capable of producing ions by direct or secondary processes.

Biological effect of ionizing radiation is defined by two factors:

1. Radiosensitivity of tissues and organs essential to the survival of an organism.
2. The absorbed dose of radiation and its distribution in space and time.

Today, as well as in the times when radiotherapy was discovered, its general problem consists in achievement of maximum selectivity of tumours destruction with the minimum consequences to normal tissues.

The basic features of biological effect of ionising radiation in comparison to other physical factors are:

1. Big discrepancy between insignificant amount of the absorbed energy of ionising radiation and the extreme degree of expressiveness of reactions of a biological object up to lethal effect (the basic radiobiological paradox).
2. Absence of specific receptors in a human body, perceiving ionising radiation.
3. The latent character of beam effects, especially of irradiation in small doses, presence of the latent period (in a wide range of doses).
4. Possibility of nonthreshold effect.

1.1. Physical properties of various kinds of ionising radiation

X-rays are electromagnetic ionizing waves with length 10-0,001 nm (produced by roentgen machine or linear accelerator). Energy is 40 keV – 45 MeV.

Gamma-rays are electromagnetic ionising waves which are produced by decay (the process of disintegration of a radionuclide) or annihilation of electrons and positrons. Gamma rays are electromagnetic radiation similar to X-rays, light, and radio waves. In general, gamma rays, depending on their energy, can pass right through the human body, but can be stopped by thick walls of concrete or lead. Ionisation density of X-rays and gamma-rays in tissues is 1-2 pair of ions on μm. Gamma rays energy of ^{60}Co is 1,25MeV.

Alpha radiation (α-particles) is a stream of particles with the weight equal to four, and double positive charge, i.e. a stream of nucleuses of helium atoms. The

alpha particle consists of two neutrons and two protons. Alpha radiation of natural radioactive isotopes (energy to 9 МэВ) possesses a very small penetrating ability making in tissues of the man 50-70 μm. It is applied only in the form of the general or local radonic baths (^{222}Rn) in physiotherapeutic practice. Alpha particles with high energy (800 MeV), received on cyclic accelerators, possess high penetrating ability. Alpha radiation consists of heavy positively-charged particles emitted by atoms of elements such as uranium and radium. Alpha radiation can be stopped completely by a sheet of paper or by a thin surface layer of skin (epidermis). Ionisation density of alpha radiation in tissues is 3000-4000 pair of ions on μm. However, if alpha-emitting materials get into the body by breathing, eating, or drinking, they can expose internal tissues directly and may therefore, cause more biological damage. Alpha radiation of high energy are produced in cyclotrons for radiation therapy. Energy is 9 - 800 MeV. Symbol is α.

Beta radiation (β-particles) are the particles with negative or positive charge and weight, equal to 1/1840 weights of hydrogen atom. Beta radiation consists of electrons. They are more penetrating than alpha particles and can pass through 1-2 centimeters of water. Their energy varies in considerable limits: from minimum, practically zero, to maximum – in some millions elektron-volt. In general, a sheet of aluminum a few millimeters thick will stop beta radiation. Beta radiation of high energy are produced in linear accelerator for radiation therapy. Ionisation density of beta radiation in tissues is 50-70 pair of ions on μm. Beta radiation sources are natural and artificial radioactive substances (^{32}P, ^{90}Y, ^{131}I), and also linear and cyclic accelerators. Energy is 3 - 45 MeV. Symbol is β.

Neutron radiation is a stream of the neutrons representing elementary particles, without an electronic charge, with the weight equal to 1,00897 nuclear mass units. Neutrons are uncharged particles. Therefore, they do not produce ionization directly. But, their interactions with the atoms of matter can give rise to alpha, beta, gamma, or X-rays which then produce ionization. Neutrons are penetrating and can be stopped only by thick masses of concrete, water, or paraffin. In clinical practice fast neutrons with energy from 20 keV to 20 MeV are applied. The basic sources of neutrons used with medical purposes are accelerators and nuclear reactors (for a remote irradiation), and also radioactive californium (^{252}Cf) (for a contact irradiation). Energy is up to 20 MeV. Symbol is η.

Proton radiation is a stream of elementary particles with the weight equal to 1,00758 nuclear mass units, and a positive charge. Protons are nucleuses of hydrogen atoms, formed by ionisation of atoms of hydrogen. Accelerators are used as a source of protons for the medical purposes. Advantage of protons and alpha particles received from accelerators in comparison with above mentioned kinds of radiation, is

their ability to form a maximum ionisation in tissues in the end of the run that is called peak of Bragg. Thus the dose in peak surpasses that in surrounding tissues in 2,5-3,5 times. Energy is up to 200 MeV. Symbol is p.

1.2. Clinical dosimetry

The outcome of beam influence is defined by radio sensitivity and the radiation dose in the irradiated volume and irradiation time.

A person doesn't have specific receptors perceiving ionising radiation. Though it should be measured and the results of its interaction with a substance should be registered.

The effect of interaction of ionising radiation with a substance can be observed in physical, chemical and biological environments that allows to distinguish physical, chemical and biological methods of clinical dosimetry. Each of these dosimetry methods includes the big number of ways of ionising radiation registration, not equivalent in accuracy of measurement.

Among physical methods the most widespread is registration of ionisation in gaseous and hard substances (the dosimeters equipped with ionization cameras, Gejger-Mjuller counters, scintillating dosimeters and semi-conductor dosimeters). Among chemical methods of dosimetry the photographic way is widely applied.

Biological methods of dosimetry have completely lost the value now and are not used in clinics anymore.

Ionisation cameras. At interaction of radiation with substance the energy of particles and photones is passed to atoms of this substance and causes their ionisation and excitation. Ionisation process arises in cameras with gas.

Under the influence of ionising radiation positive and negative ions appear in the gas filling the camera. Thanks to electric field the chaotic movement of ions becomes directed, when positive ions move to negatively charged electrode, and negative – to positively charged one.

In that case the electric current arising from ionisation is proportional to number of the ions formed in the chamber, and, hence, is proportional to intensity of ionising radiation.

Scintillation dosimeters. In penetration of radiation into a substance not only ionisation occurs, but also excitation of atoms and molecules. In some substances the share of primary radiation energy, converting in visible radiation, is great enough (about 20 % from energy of primary radiation). The substances possessing such ability are called scintillators. Some inorganic substances concern them, for example, iodide sodium, iodide caesium, and also a certain organic substances.

Semiconductor dosimeters. The method of semiconductor dosimetry is based on ability of some substances to change resistance under the influence of ionising radiation. A number of the semiconductors possessing sufficient sensitivity can be used for clinical dosimetry. For example crystals of cadmium sulphide (CdS) which are the semiconductors. Semiconductors have conduction electrons, capable of moving under the influence of a magnetic field, and electrons that do not suffice enough energy to become conduction electrons. This energy can be received by radiation ionising. In that case resistance of the semiconductor considerably decreases and arising electric current increases in proportion to intensity of radiation. Detectors made of cadmium sulphide have the small sizes (some cubic millimetres); a range of sensitivity varies from 1 to 120 roentgen/hour (R/h). These properties allow the usage of dosimeters with CdS for measurement of deep doses, especially at intracavity dosimetry.

Photographic method of dosimetry. Under the influence of an ionising radiation a latent image appears in emulsion. Chemism of the process consists in the fact that under the influence of radiation the bromic silver, being a basis of a photoplate sensitive layer, resolves and produces free atoms of silver. After that the irradiated sites become black. The degree of film blackening indicates the dose of radiation. This method is widely used in individual dosimetry.

Thermoluminescent method of dosimetry. Thermoluminescent method of dosimetry allows to measure the light energy precipitated when irradiated detectors are heated to certain temperature. Advantages of these detectors are following: they have small sizes, they are not connected to a measuring device, have a wide range of doses, with the help of these detectors the measurements can be carried out after irradiation. To produce these detectors fluoric lithium and calcium compounds are used. This method is widely used in individual dosimetry.

1.3. Kinds of doses and unit of their measurement

The dose is amount of energy absorbed by a mass unit or volume of irradiated substance. There are some kinds of doses: a dose in the air, on a surface, in the centre of the irradiated object.

The dose attributed to a time unit is called capacity of a dose.

Capacity of a dose is the energy absorbed in a mass unit or volume of irradiated substance for a time unit.

Dose: a general term denoting the quantity of absorbed radiation energy. Used for special purposes, dose should be qualified; if unqualified, it refers to the absorbed dose.

The exposition dose (exposure) represents a dose in free air, in absence of disseminating bodies. It is defined by degree of air ionisation and characterises, mainly, a source of x-rays and γ-rays. If a distance from a source to irradiated object increases the exposition dose decreases in inverse proportion to a square of distance from the source to an irradiated object. Coulomb/kilogram (C/kg) is the unit of an exposition dose of x-rays and γ -rays. Coloumb/kg is an exposition dose of x-rays andγ-rays in which the interfaced to it corpuscular emission bears a charge in 1C of electricity of each sign in air. Conventional unit of an exposition dose of x-rays and γ-rays is the roentgen (R). The R is a dose that in 1 sm^3 of dry air contains ions bearing a charge in one electrostatic unit of an electricity of each sign. 1 C/kg = 3880 R.

Capacity of an exposition dose is an exposition dose calculated per time unit. In SI it is measured in amperes per kg (A/kg). Conventional power units of an exposition dose are: a roentgen per second (R/s), a roentgen per minute (R/m) and a roentgen per hour (R/hour). There are following ratios between them:

1 R/s = $2{,}58\times10^{-4}$ A/kg; 1 R/m = $4{,}30\times10^{-6}$ A/kg, 1 R/h = $7{,}17\times10^{-8}$ A/kg.

Absorbed dose is quantity of energy imparted by ionizing radiation to unit mass of a matter such as tissue. The absorbed dose is the basic quantitative indicator of ionising radiation influence on irradiated tissues. The units of absorbed dose are rad (rad, conventional unit) and gray (Gy, SI unit). It is characterised by quantity of energy absorbed in a mass unit of an irradiated substance. In SI unit of the absorbed dose is joule per kg (J/kg). This magnitude received the name "Gray" (Gy). Gy is unit of the absorbed dose, in which energy of ionising radiation in 1 J is transferred to the 1 kg mass of the irradiated substance.1 Gy = 100 rads.

Linear energy transfer (LET) is the average energy lost by ionizing radiation per unit distance of its travel through a medium. High LET is generally associated with protons, alpha particles, and neutrons, while low LET is associated with x-rays, electrons, and gamma rays.

Quality factor (QF): different types of radiation produce the same types of effects. However, the magnitudes of the effects can be quite different even though the doses (Gy) are identical. The extent of the biological damage inflicted by a given type of radiation increases with the linear energy transfer (LET) of the radiation. The more energy per unit distance is lost, the higher is LET and the greater is density of ions and free radicals in the charged particle. The latter phenomenon is the most probable reason for the greater biological effects of high LET radiation.

In radiation biology these differences are indicated by the relative biological effectiveness (RBE), the ratio of the doses from two different types of radiation required to produce the same effect. Conventionally the dose required from 250 kV x-rays is used as the standard for comparison.

Although the RBE is a more precise estimate of a radiation's biological effect than the quality factor (QF), its use is restricted to radiation biology. The linear energy-transfer-dependent factor by which absorbed doses are multiplied to obtain (for radiation protection purposes) a quantity that expresses the effectiveness of the absorbed dose derived from various radiation sources on common scales. For low linear energy transfer radiations (x-rays, gamma and beta radiation) the QF is approximately 1; for high linear energy transfer radiations such as alpha a QF of 20 is recommended. The QF for neutrons varies with energy from 2 to 11. The QF for high energy proton or neutron of unknown energy is 10.

Equivalent dose is a dose absorbed in a body or tissues multiplied by corresponding weighing radiating coefficient (quality factor) for the given kind of radiation. The radiating coefficient is used for the record of efficiency of various kinds of radiations. Notion of an equivalent dose is used to estimate the biological effect irrespective of a radiation kind. Unit of an equivalent dose in SI is the sievert (Sv). Sievertis the equivalent dose of any radiation absorbed in 1 kg of a biological tissue, creating the same biological effect, as well as the absorbed dose in 1Gy photon radiation. Conventional unit of an equivalent dose is radiation equivalent in man (rem). 1 Sv = 100 rem.

Effective dose is a value of influence of the ionising radiation, used as a measure of occurrence risk of the remote consequences of human body irradiation taking into account its radiosensitivity. It represents the sum of products of an equivalent dose in organs and tissues and corresponding weighing factors. Weighing factors for tissues and bodies in calculation of an effective dose are multipliers of an equivalent dose in organs and the tissues, used in radiation protection for record of various sensitivity of different organs and tissues in occurrence of stochastic effects of radiation. Unit of an effective dose is sievert (Sv). Conventional unit of an effective dose is radiation equivalent in man (rem). 1 Sv = 100 rem.

The deep dose is the dose measured at certain depth from a surface of irradiated object. The relation of a dose in depth to a dose in the free air, expressed in percents, is called relative, or a percentage, deep dose. The relative deep dose increases with the increase in distance from a source, energy of radiation and an irradiation field.

Decay (radioactive is the process of spontaneous disintegration (transformation) of a radionuclide. The decrease in the activity of radioactive substance.

Radioactivity it is a measure of radioactive substance quantity, expressed by a number of radioactive transformations per unit of time. In SI activity unit is an

inverse second (c^{-1}), named Becquerel (Bq) equals to one decay per second. Earlier used conventional unit of activity curie (Ci) equals to $3,7\times10^{10}$ Bq.

1.4. The basic stages of biological action of an ionising radiation

The first is purely physical stage of interaction proceeding for a milliard shares of second. It consists in transfer of a part of photon (particle) energy to one of atom electrons with the subsequent ionisation and excitation of atoms (molecules).

The increased chemical reactivity is characteristic of ions and the excited atoms possessing extra energy, borrowed from a photon (particle).

The second is a physical and chemical stage of radiation interaction with substance. It occurs depending on structure of irradiated substance. Presence of water and oxygen plays the major role in the irradiated system. If water and oxygen are absent, the possibilities of chemical influence of the atoms activated by radiation are limited and localized. In presence of water under the influence of radiation there are positively charged ions of water H_20^+ and dissolved electrons in water. Joining one of the neutral molecules, electrons form H_20^-. Water ions, as well as its excited molecules, are chemically active and are less stable, than non-excited molecules. In presence of the dissolved oxygen these active products of irradiation easily react with them, forming longer lived and chemically active forms, as free radicals: hydroxyl free radical $OH^{\bullet}$, superoxide free radical $0_2^{\bullet}$, hydroperoxid free radical $HO_2^{\bullet}$, and also peroxide of hydrogen H_2O_2. Free radicals are neutral (uncharged) atoms or molecules with unpaired electrons. They are extremely reactive. Within a microsecond of their formation they may react with some molecule (the target) and damage it. Hydrogen peroxide has the potential to be highly damaging to cellular constituents. It is much longer lived than free radicals and can travel substantial distances in a cell, even across membranes, to attack its target.

The third is a chemical stage of beam influence. It lasts, as a rule, several seconds. At this stage there are biochemical damages of biologically important macromolecules (nucleinic acids, lipides, proteins, carbohydrates).

They distinguish direct action of radiation when there is a direct interaction of an ionising radiation to critical molecules, and indirect action through products radiolysis of water.

It is supposed, that indirect action prevails in low LET (x- and γ-rays, β-radiation), and direct – in high LET (alpha rays, protons and neutrons).

Direct effects. These are effects produced when the initial interaction of radiation (e.g. alpha particle, beta particle or electron) takes place with the target molecule.

Indirect effects. These are effects mediated by free radicals. The primary interaction of radiation takes place with water. As a result in free radicals that damage the target molecule(s). Free radical hydroxyl ($OH^{\bullet}$) is believed to mediate the most damage.

The basic arena of ionising radiation action on live systems is «atoms live» – cells and endocellular structures.

Chromosomes are critical endocellular structures in ionising radiation. They consist of nucleinic acids – keepers of the hereditary information and special proteins. As the majority of cells have only one or two copies of each molecule of DNA, a chromosome's defeat will be more significant, than in a case with a molecule with thousands of copies (for example, enzymes).

Under the influence of ionising radiation electron separates from a protein molecule, forming a defective area without an electron. It migrates along polypeptide chains. Here, in lateral chains of amino acids free radicals appear. Such events occur as a result of direct action of an ionising radiation.

Under indirect action free radicals are formed in a result of interaction of albuminous molecules with water radiolysis products. Free radicals formation causes changes in the structure of protein what leads to infringement of its functions (enzymes, hormonal, etc.).

Membranes under ionising radiation influence become critical endocellular structures as well; changes in proteins and lipides which participate in formation of biomembranes can increase their permeability for various molecules. In lysosomes it causes unregulated emission of its catabolic enzymes into the cell what could be disastrous. Damage of the nuclear membrane can affect cell division and thus their viability.

In waterproof lipides, mainly, in the presence of oxygen, ionisation and excitation also causes formation of free radicals and peroxides with chain reactions of oxidation of organic conjunctions.

There are three major types of damage to the DNA: base damage, single strand breaks and double strand breaks.

DNA base damage. The most common influence of radiation on DNA. It occurs primarily due to interactions of free radicals with the nitrogenous bases. The "classical" (rather slow) repair mechanism operates in the following way: first the damaged section is excised by an endonuclease. Next the excised segment is resynthesized by a polymerase using the undamaged strand as a template. Finally ligases attach the newly synthesized segment in place. If the damage remains unrepaired, the cell may survive and reproduce although its function may be

impaired. Or, the effect on the cellular metabolism may be severe enough to lead to a cell death.

Single strand breaks (SSBs). Only one strand of the DNA breaks but not the other. It is required approximately 10-20 eV per break. Break of carbon bonds in sugar molecules develop under the influence of $OH^{\bullet}$ radicals. These breaks are quickly repaired. SSBs are not considered to be as important as either of the other two types of damage (fig. 1.1).

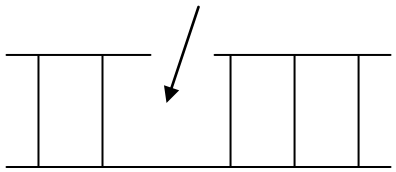

Fig. 1.1. Rupture of one DNA spiral.

Double strand breaks (DSBs). Both strands of the DNA may be broken by a single event or by two separate events (fig. 1.2). The relationship between the dose and the number of double strand breaks appears to be linear-quadratic.

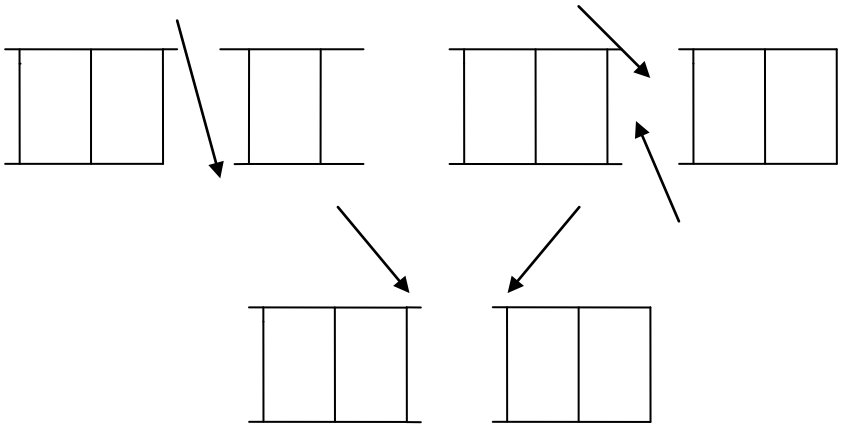

Fig. 1.2. Rupture of a double spiral of DNA.

Repair mechanisms for DSBs have not been identified. Double strand breaks, if unrepaired, result in broken chromosomes. The ends of the chromosomes at the place of the break are said to be "sticky" and tend to attach to other broken or unbroken chromosomes. The results depend on the stage of the cell cycle at which the exposure occurred, i.e., in G2 each chromosome consists of two DNA molecules (chromatids) whereas in G1 each chromosome consists of only one DNA molecule. The results of breaks in G1 are called chromosomal aberrations. The results of breaks in G2 are called chromatid aberrations. Besides, under the influence of ionising radiation there are sutures between DNA threads, DNA-protein sutures, infringements of nitrogenous bases of DNA. There are two types of DNA lesion consequences: the cell

survives, but changes the functional status; the cell dies. Infringement of a functional status of cells can be expressed in delay or the change of cellular division leading to their uncontrollable growth (malignant tumors). It is well-known, that cells with the damaged mechanisms of DNA tend to turn to malignant cells and as well as malignant tumours contain the big quantity of chromosomal aberrations. Hereditary effects of an ionising radiation can be found throughout many generations.

Biological stage of a radiation injury. Among many examples of radiation influence on cell ability to live the most important property is to suppress the ability of its division. The destruction of cells can become apparent in a wide time range: from hours to years. According to the mechanism of cells radiation injuries it is necessary to distinguish two basic forms of destruction: interphase (not connected with a mitosis) and reproductive – destruction at the moment of division.

The nucleus plays a role of the keeper of the hereditary information of a cell, organism and even a biological kind, it passes this information from a cell to a cell, from an organism to an organism, providing successive communication of generations. This information is ciphered in chromosomes.

Chromosomal and chromatid aberrations are rings, fragments, dicentrics, etc.

Dicentric chromosomes, the chromosomal aberration most uniquely identified as being caused by radiation, can be quantitatively related to a radiation dose. In fact, a dose from an acute exposure can be estimated by counting the number of dicentrics produced and comparing this with the number known to be produced by the particular type of radiation involved.

Consequences of radiation damage to chromosomes:

1. Cell survives but with impaired metabolism.

The nature of the "malfunction" may be inconsequential or more severe. It may delay or alter cell differentiation and division, even resulting in cancer (needless to say, that dead cells don't become cancerous).

2. Cell dies.

High doses of radiation can result in the immediate death of a cell (interphase death) while lower doses may slow down a cell cycle.

A cell can divide and its death occurs after mitosis (reproductive death).

High doses of radiation can result in the immediate death of a cell (interphase death) while lower doses may slow down a cell cycle. The latter is due to a lengthening of G_2 brought about by some unknown mechanism. If the exposed cell passes through G_2 and attempts to divide, the survival of the daughter cells requires that each one receives a complete complement of chromosomes.

The above-mentioned chromosomal aberrations can prevent a proper distribution of chromosomes and result in the death of a cell during division

(reproductive death). A chromosome should have a single centromere to divide properly; acentric fragments have none while fragments have two. The assumed involvement of double stranded breaks in the formation of chromosome aberrations and the absence of any known repair mechanisms for double stranded breaks leads to conclusion that they are most important contributor to cell death. However, other possibilities exist and considerable uncertainty still remains about the role of DSBs in cell death. Unrepaired single strand breaks or base damage can cause an incomplete duplication of the DNA in S. This in turn could lead to an unequal distribution of the DNA at mitosis and hence, cell death. Alternatively, radiation damage to the nuclear membrane is known to play a role in the behavior of chromosomes at mitosis.

For low LET radiation the most sensitive stages of the cell cycle, with respect to cell death, are mitosis and late G_l (at the G_1,-S border) although individual cell types show some variation in this regard. During mitosis the chromosomes are condensed and the repair mechanisms have poor access to the DNA molecule. During transcription of RNA the cell appears to be least sensitive to radiation damage because the uncoiled "open" nature of the DNA makes the repair mechanisms especially effective. All phases of the cell cycle appear equally sensitive to high LET radiation.

1.5. The major factors modifying radiosensitivity

Radiosensitivity is the ability of biological objects to react to action of ionising radiation by destruction processes and infringement of functions.

Bergonie and Tribondea law can be used to interpret cells and tissues radiosensitivity, taking into account certain restrictions. The law was formulated in 1906 and it characterizes tissues which are most radiosensitive. According to the law, the most radiosensitive tissues possess cells which:

a. are dividing at the time of exposure;

b. undergo numerous divisions in the normal course of their lifetime;

c. don’t have a distinct differentiated type, i.e., unspecialized in structure and function.

Lymphocytes and oocytes which are highly radiosensitiv being in interphase are exceptions.

Radiosensitivity of malignant tumor tissues doesn’t have very big difference with normal tissues.

Oxygen tension. Cells containing normal levels of oxygen (40 mm Hg) tend to be 2-3 times more sensitive to low LET radiation than cells low in oxygen (hypoxic). For a given effect this difference is referred to as the oxygen enhancement ratio (OER). The relationship between oxygen and radiosensitivity is most evident below 20 mm Hg. More over, an increase in oxygen concentration does little to increase the

radiosensitivity of a tissue. Poorly vascularized tissues, i.e., tumors, tend to be hypoxic; tissues well supplied with blood tend to have normal oxygen tensions. This effect of oxygen might be due to a resulting increase in the production of hydrogenperoxide. Another explanation involves the affinity of oxygen for electrons.

Temperature as a modifying factor. In many experiments a dramatic increase in radioresistance has been produced by lowering of an animal's body temperature. The increase in radioresistance apparently occurs due to a reduction in oxygen tension that accompanies a lower body temperature. If the effect is simply delayed it may be due to a reduced mitotic rate; once the animal warms up and mitosis resumes, reproductive cell death can occur.

The success of radiotherapy depends on the greatest concentration dose of a radiation in a tumour and the directed change of a tumour radiosensitivity and normal tissues surrounding it by means of various methods.

Hence, the central problem of radiotherapy is artificial management of beam reactions of normal and tumoral cells for the purpose of the maximum damage of a tumour and preservation of normal tissues elements. The means in forcing beam reactions of healthy cells are called radio modifying agents.

1.6. Optimisation of radiotherapy of malignant tumours

There are three independent ways of optimisation of methods of beam therapy of malignant tumours on a radio biological basis:

1. Use of new technologies and new kinds of ionising radiation intended for peculiarities of their biological action and primary localisation of energy in the tumoral centre (in particular, it concerns the loaded nuclear particles).
2. Working out of irradiation modes considering distinctions of cytokinetic parametres of malignant and normal tissues, and distinctions in mechanisms of development of the direct and remote effects of an irradiation as well.
3. Development of artificial methods of healthy and tumoral tissues radiosensitivity management by means of various modifying agents of selective action.

Use of new kinds of radiations. So, along with traditionally used electromagnetic ionising radiation (x-ray and gamma radiation), beta radiation the use of "new" kinds of ionising radiation for treatment of tumours is possible, namely heavy nuclear particles. Protons concern them, α-particles, negative π-mezons and neutrons. Except for the last, the listed heavy particles are charged and their application is calculated on increase of efficiency of radiotherapy at the expense of improvement of spatial distribution of radiation and its concentration in a tumour. The charged nuclear particles accelerated to great speeds in modern accelerators and after a certain (depending on their energy) run in tissues are slowed down and lose a

maximum of the energy at the end of run, forming so-called peak of Bragg. If this peak occurs in a tumour zone, it is possible to lower radiation exposure to surrounding tissues along a beam and almost completely to exclude irradiation of the tissues which are behind the irradiated target.

Besides, deceleration of heavy charged particles causes:

1. Increase of their LET.
2. Additional increase of efficiency in a zone of Bragg peak occurs as a result of RBE increase.
3. The decrease of oxygen effect.
4. Difficultly repaired cell damages occur.
5. Levelling in radiosensitivity of a cellular cycle separate stages.

The set of these properties allows counting on additional increase of therapeutic efficiency of the heavy charged particles. Neutrons possess the same properties, however they have no Bragg peak, and their dose distribution is near to photon radiation what does not allow concentrating a dose in a tumour.

However taking into consideration all obvious advantages of using the bunches of heavy nuclear particles it is necessary to consider, that their application in wide medical practice is restrained by the big technical difficulties and demands considerable economic expenses. Besides, efficiency of their use is considerably complicated by difficulty of definition the exact borders of the tumoral centre because of tumour germination in surrounding tissues. It predetermines the necessity of irradiation volume increase.

Schedules of an irradiation and cytokinetic parametres. The first problem of radiotherapy consists in bringing of an optimal dose to a tumour. Optimum is a level at which the highest possible percent of treatment is reached at comprehensible percent of radiation damages of normal tissues.

In practice the optimum is a size of a total dose at which more than 90 % of patients with tumours of the given localisation both histologic structure and damages of normal tissues are cured, occur not more than in 5 % of patients. The importance of localization is highly important, as, for example, in treatment of central nervous system diseases even 5 % of brain necrosis is inadmissible.

The tumour 1 sm in diameter contains one billion cells (10^9). In that case theoretical calculations show the necessity of a unitary dose more than 30 Gy if cells are well oxygenated. For anoxic cells this dose should be increased more, than twice. Thus destruction of tumoral cells is inevitably accompanied by destruction of the healthy cells which are localized directly in a zone of irradiation.

For treatment of the primary tumour in case of its sizes increase a dose of ionising radiation should be increased as well. Thus the increase of tumour diameter per each more centimetre increases the additional irradiation dose in 3-5 Gy.

The data of theoretical calculations show, that a tumour with diameter more than 1 cm creates a difficult situation for radiotherapy.

Real calculation on radical treatment of patients without risk of reception of heavy beam damages can be only within cases of early clinical detection of a cancer.

Besides quantity of tumoral cells, other factors have also great value for the outcome of radiotherapy. These factors include radiosensitivity of cells, a saturation of cells oxygen, immune factors, etc. Thus, the tumour size is a determinative factor for the outcome of radiotherapy.

The biological effect is defined not only by quality of radiation, size of the single and total absorbed dose, but also by its distribution in time. At the beginning of the 20th century scientists have noticed that continuing irradiation of smaller doses gives more intensive biological effect, than a greater irradiation dose during the short period of time. Experimental and clinical data testify that the same total absorbed dose, but brought simultaneously or fractionally with certain intervals of time between irradiation fractions, gives various biological reaction.

On the final result of fractional irradiation influences:

1. Extent of the single absorbed doses.
2. Duration of breaks between irradiation sessions.
3. The general extent of irradiation course.
4. A total dose.

The influence of fractional irradiation on reaction degree can be judged by a following example. A unitary deadly dose of radiation for a dog is 6 Gy, and in 0,1Gy daily irradiation dose the total deadly dose increases in 10 times.

Nowadays following methods are used in clinical practice:

1. One-stage irradiation.
2. A continuous irradiation (interstitial, intracavitary and applicational methods).
3. Fractional irradiation – one of the basic methods of an external irradiation.

Following types are applied:

- small fractionation 2 - 2,5 Gy (week 10-12 Gy),
- average fractionation 3 - 4 Gy and
- large fractionation 5 Gy and more – a single day dose.

In 1940th of the 20th century there was standard to have courses of tumours irradiation 5 times a week with 2 Gy per day. Such course consisting of 30 fractions by 2 Gy is widely used in modern radiotherapy and is designated as "conventional".

What processes occur in cells and tissues at fractional irradiation?

Most important of them are:

Restoration of cells from sublethal and potential lethal damages. This process begins during irradiation and, basically, comes to an end during the first 6 hours after irradiation.

The process second in duration is desynchronization of cellular population which in the result of irradiation becomes enriched in cells which were in radioresistant phases of a cycle during a session.

The third process – oxygenation – is specific only for tumours as they initially have a fraction of hypoxemic cells. The death of part of the tumorous cells population increases oxygen diffusion in earlier hypoxic zones. Due to oxygenation under conditions of fractionation it is possible to deal with more radiosensitive population of tumorous cells, what is impossible in unitary influence. Oxygenation duration comprises 1-3 days.

The fourth process is repopulation of tumours and normal tissues. The greatest attention is paid to this process when modes of fractionation maximally increasing the therapeutic interval are developed. Therapeutic interval is a difference between biological action of radiation on a tumour and on normal tissues. Repopulation is usually defined as restoration of number of cells in the irradiated volume which has decreased as a result of beam influence. The term «accelerated repopulation» is used as well; it defines more rapid cells reproduction in comparison with reproduction before irradiation. Reserve for accelerated proliferation is the reduction of cellular cycle duration, i.e. time of growth of a cell from one division to another, a smaller exit of cells from a cycle in a resting phase $G_{0.}$ After radiation influence the part of cells dies, and the remained cells have more oxygen, nutrients, outflow of exchange products is accelerated, pressure from the surrounded cells decreases. Earlier it was considered, that acceleration of a tissue weight increase is characteristic only for normal tissues. Now it is known, that accelerated repopulation occurs in tumours as well.

New modes of irradiation fractionation. Split-course is the course which differs from "conventional" one by presence of a 2-3 week interval in the middle of irradiation course. It has been offered to decrease the intensity of sharp beam reactions, which do not allow bringing a needed dose in treatment of tumours of some localisations (for example, in head and neck). Split-course saves the value in treatment of weak elderly patients or those tumour localisations (for example, in oral cavity) where sharp beam reactions block a continuous irradiation course.

Hypofractionation, i.e. use of a small amount of large fractions. A usual kind of hypofractionation is a large fractionation mode which includes some fractions in 5-6, or rarer10 Gy, which are performed with an interval in 5-7 days to a total dose of 30-45 Gy. Course of treatment lasts 3-9 weeks. The irradiation in this mode promotes a rapid stop of tumour growth, is well tolerated by patients and is very convenient for out-patient radiotherapy. In a hypofractionation mode the irradiation of metastasises

in a bone is traditionally used. Use of 2-3 fractions in 6-8 Gy gives a fast anaesthetising effect.

If schemes of hypofractionationare mostly directed to creation of more convenient conditions for patients irradiation, what gives the same result as a "conventional" mode, multifractionation modes are used to improve treatment effectiveness and decrease of beam complications.

Multifractionation is a mode of beam therapy with 2 or 3 sessions of irradiation per day. To determine various variants of multifractionation such terms, as hyperfractionation, accelerated fractionation are used.

Hyperfractionation is defined as the use of smaller doses per fraction, i.e. less than 1,8-2,0 Gy, in the same overall treatment time as used in conventional fractionation. In clinical practice hyperfractionation is usually applied as two daily fractions of 1,1-1,3 Gy.The biological basis of hyperfractionation is to exploit the postulated different capacity of target cells in tumor tissue and late responding normal tissue to recover from sublethal radiation damage,taking into account that the time interval between the two fractions is sufficiently long. So, hyperfractionation might be useful to improve the therapeutic effect and to decrease chronic radiation damage. Thus, from a radiobiological perspective, hyperfractionation with increased total dose compared to conventional fractionation appears to be a promising option to improve local control and survival in some malignant tumors without increasing the risk of late normal tissue damage.

Accelerated hyperfractionated radiotherapy.

Accelerated fractionation is defined as the shortening of overall treatment time compared to conventional fractionation, or more precisely, as the application of an average dose per week of more than the 10 Gy used in conventional fractionation. In clinical practice accelerated fractionation is often combined with a decreased dose per fraction, i.e. a hyperfractionation component (accelerated hyperfractionation). For example, if the overall treatment time of a radiation schedule is shortened from 6 to 2 weeks and the dose per fraction is reduced from 2,0 to 1,5 Gy, itis necessary to accelerate the treatment.

The biological basis of accelerated fractionation is to counteract the so-called time factor of fractionated radiotherapy, i.e. the loss of local tumor control with increasing overall treatment time. This time factor is generally explained by rapid repopulation of clonogenic tumor cells during treatment, which is supported by studies on tumor models under well defined experimental conditions. However, in clinical studies and in experiments, simulating the clinical situation, alternative mechanisms such as increasing cellular radioresistance, or selection of highly malignant tumor cells might also contribute to the time factor. In contrast to tumors,

overall treatment time has no or little impact on classical late radiation damage. Short overall treatment times increase acute normal tissue reactions.

Definition of tolerant doses at various modes of fractionation. The major condition of successful beam therapy is preservation of viability of normal tissues and the organs which are in a zone of influence of radiation. It concerns not only to anatomic structures surrounding a tumour, but also to the "target" which is exposed to the most intensive irradiation.

Besides tumour elements, it contains vessels and other connective tissue structures, regeneration ability of which influences the further course of disease. Even in annihilation of all tumour cells the disease outcome will be unfavourable if tolerance of normal tissues is exceeded. The resulting radiation injuries take a severe course as well as the basic disease. Tolerance is the maximum radiation dose not leading to irreversible changes of tissues. It depends not only on quantity of the absorbed dose, but also on its distribution in time. In conditions of fractionation irradiation the tolerance degree is expressed in the form of a nominal standard dose (NSD).

Concept of NSD is offered by F.Ellis (1969, 1971, 1973):

$$NSD = Д / (N^{0,24} \times T^{0,11}), \text{ where}$$

Д - the total absorbed dose (sGy); N - number of fractions of a dose; T - duration of treatment course, including first and last day.

Tolerant level of a connective tissue under concept NSD is equal to 1800 rad equivalent therapy (ret).

The amount of biological effect accumulates gradually with each subsequent fraction of a dose and consequently has received the name of "cumulative radiating effect" (CRE). It was offered by I. Kirk, Grey W., Etc. (1971).

It is expressed in the form of the formula:

$$CRE = V \times q \times d \times (T / N)^{-0,11} \times N^{0,65}, \text{ where}$$

d is a single dose, sGy; V is the deduction to the irradiated volume; q is the factor of relative biological efficiency of radiation.

Unit CRE is “ure”. It is the unit of radiation effect. Tolerance of a connective tissue and a skin makes nearby 1800 ure, that corresponds to 60 Gy by the area of irradiation of 100 sm^2 and by a single dose in 2 Gy daily, 5 times a week. The given formulas are empirically proved in the numerous experimental and clinical researches which have received a general recognition. NSD and CRE can be applied in courses of therapy characterised by a regular rhythm of irradiation with number of fractions more 4, by a constant of a single dose and the general duration from 10 to 100 days in capacity of a dose not less than 20 sGy/minutes. Simple addition of CRE amount, for

example, in splitted or recurring courses of radiotherapy, and also in change of irradiation rhythm is inadmissible.

To overcome these difficulties factor TDF – «time - a dose - fractionation» has been offered. Factor TDF was offered by C.Orton and F. Ellis (1973). It is based on the same preconditions and is expressed as:

$$TDF = N \times d^{1,538} (T / N)^{-0,169} \times 10^{-3}, \text{ where}$$

d a single dose, sGy, N - number of fractions of a dose, T - duration of course of treatment, including first and last day.

TDF corresponds to full tolerance of a connective tissue; it is accepted for 100, what corresponds to 1800 ure. Great advantage of TDF is possibility of simple addition of the values received at various treatment courses, differentiated in the rhythm. By mathematical transformations the possibility of TDF factor calculation for each separate fraction of a dose that allows to apply it at arrhythmic courses of radiotherapy with various single doses and intervals between separate sessions has been received. CRE and TDF are connected among themselves by a parity:

$$CRE = (TDF \times 10^{3})^{0,65}$$

In practical job corresponding schedules and tables for definition of tolerance and transition from one system to another, that is simple enough. Both systems CRE and TDF inseparably linked also have the advantages and lacks. In some cases it is possible to apply only factor TDF (for example, arrhythmic course of treatment), in others – only CRE (the split course, the amendment on the irradiated volume). However transition from one system to another on final or the calculation intermediate stage is always possible. It is recommended to express an end result in «ure» since only such by it is possible to consider all important factors, including size of the irradiated volume.

Nowaday most isoeffect relationship used clinically are based on the linear-quadratic (LQ) model. In the LQ formalism, the yield of lethal DNA lesions by is the sum of lethal lesions produced from a single radiation track (which are linearly related to dose, αD) and lethal lesions produced from two radiation tracks (which are quadratically related to dose, βD^2). The α/β ratio: dose (Gy) where the α linear component is equal the quadratic component β. The α/β ratio, number of fractions (n), dose per fraction (d) are using for receive a biologically effective dose (BED) in units of Gy:

$$BED = n \times d \times [1 + d / (\alpha/\beta)]$$

The limited data available for normal human tissues suggest that α/β ratio for late -responding tissues have values in the range 2 to 4 Gy, while early responding tissues have values in the range 8 to 12 Gy. Most tumours appear to have α/β values similar to or greater than those for early -respoding tissues, although recent data

suggest that certain slow growing tumours (e.g. prostate cancer) may have low α/β values between 1 and 3 Gy. There is no consideration of the effect of treatment time in LQ model. In the LQ model it is also assumed that there is complete repair between the fractions and each dose in fractionated regimen produces the same biologic effect.

Thus, the dose of radiation tolerable by an organ cannot be characterized as an absolute number. Rather, a dose of radiation to the entire substance of an organ may be associated with a certain probability of a radiation-induced complication. This concept is referred to as the minimal tissue tolerance dose (TTD). The TTD 5/5 is usually used in clinical practice and is defined as that dose of radiation associated with a 5% rate of complications occurring within 5 years of treatment. The TTD 5/5 is usually higher if less than 100% of an organ is irradiated. For example the TTD 5/5 when the entire heart is irradiated is 45 Gy. When, however, only 20% of the heart is irradiated, the TTD 5/5 is 60 Gy. As the dose/fraction increases, the TTD 5/5 decreases.

Radisensitisation of tumours. Depending on sensitivity of tumours to radiation they are classified as radiosensitive which disappear completely after irradiation without necrosis of a surrounding connective tissue, and radioresistant which do not disappear in doses destroying a connective tissue.

Radiosensitivity of tumors:

- high radiosensitivity: seminoma, lymphosarcoma, Ewings tumor, bazalioma of skin;
- average radiosensitivity: squamous cell carcinoma;
- low radiosensitivity: adenocarcinoma;
- radioresistant tumors – fibrosarcoma, melanoma, chondrosarcoma, osteogenic sarcoma.

Radiomodification includes various ways of increasing tumours radiosensitivity increase not only literally, but also by its relative increase by radioresistance reduction of healthy surrounding tissues.

Radio updating on the basis of oxygen effect. Hyperbaric oxygenation (HBO). Oxygenation of tumors cells according to oxygen effect should lead to increase of their radiosensitivity. Thus normal tissues with oxygen pressure of 40 mm Hg and more possess the maximum radiosensitivity when breathing the air and do not increase in additional oxygenation. However carried out clinical tests have shown, that potential HBO possibilities are insignificant. Today a principal cause of it is considered to be an actual impossibility of delivery of enough oxygen in hypoxic zones, because great oxygen activity prevents from it. Besides, oxygen surplus leads to narrowing of blood vessels.

Radiomodification on a basis hyperthermia (thermoradiotheraphy). High efficiency of hyperthermia as radio modifier is caused by several circumstances among which it is necessary to specify the following:

1. Hyperthermia possesses own damaging action at cellular level, and the effect depends on temperature and duration of heating.
2. Hyperthermia results in increasing radiosensitivity of cells because of temporary disorders in reparation processes.
3. Hyperthermia allows to overcome radioresistance hypoxic tumoral cells.
4. In hyperthermia another dependence of sensitivity on a stage of a cellular cycle, than that which is characteristic for ionising radiation. So, the greatest radio resistance characterises the late S-period; when heating the period of synthesis of DNA is most sensitive. Last years it is believed, that damage of one of enzymes of DNA synthesis β-polimerazy is key in a chain of all processes conducting both to thermal destruction, and to a thermal radio sensitisation.
5. Usually tumour cells possess the same thermosensitivity, as cells of surrounding normal tissues, but because of a number of features of a tumour: a low blood-groove, presence of sharply lowered values of pH in hypoxic zones, nutritious insufficiency, its cells are damaged more seriously than normal cells.

Chemical radioprotectors (cystamine, мexamine) haven’t found wide application because of narrow spectrum of their therapeutic action: their application in nontoxic doses is ineffective.