Radiation Physics and Chemistry in Heavy-ion Cancer Therapy

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Heavy ions, such as carbon and oxygen ions, are classified as high-LET radiations, and produce a characteristic dose-depth distribution different from that of low-LET radiations such as γ-rays, x-rays and electrons. Heavy ions lose less energy at the entrance to an irradiated biological system up to some depth than the low-LET radiations, while they deposit a large amount of dose within a very narrow range at a certain depth, producing the characteristic sharp peak called the Bragg peak. Therefore, by controlling the Bragg peak, it becomes possible to irradiate only the tumor region in a pin-point manner, while avoiding irradiation of the normal tissue, thus making heavy-ion therapy ideal for deep-seated tumor treatment. Clinical results on more than 2400 patients are very encouraging. However, very little is known about what is going on in terms of physics and chemistry inside the Bragg peak. In this paper the current status of our understanding of heavy-ion interactions and remaining problems of physics and chemistry for the heavy-ion treatment are explored, particularly in the Bragg peak region. Specially, the survey of the basic physical quantity, the mean energy required to form an ion pair (*W* value) for heavy ions of interest for radiotherapy is presented. Finally, the current clinical status of heavy-ion therapy is presented.

Key words: *Heavy ions, radiation therapy, W value, Bragg peak, oxygen enhancement ratio (OER), relative biological effectiveness (RBE), radicals, ion-bio-molecule interaction, deep-seated tumor*

Introduction

Clinical applications and testing of new medical irradiation facilities using heavy ions such as carbon-ions were started in Japan and Germany in 1994. A successful control rate of various tumors in over 2400 patients with otherwise mostly untreatable cases was achieved. The basic principle underlying radiation cancer therapy is to induce damage in cancerous cells (mostly by ionizations) so that they cannot grow and multiply, while minimizing damage to the surrounding healthy tissue. Following this principle, heavy ions (high-linear energy transfer (LET) radiations) have several advantages over conventional radiation therapies based on γ-rays, x-rays and electrons (low-LET radiations) in clinical applications particularly for tumors in deep-seated hypoxic conditions. Photons lose their energy and deliver the dose before they reach the (deep-seated) tumor, and travel beyond the location of tumor, thus damaging healthy cells and causing undesirable side-effects. Low-LET particle beams (protons, helium ions) improve the physical selectivity of the irradiation; however, little benefit is obtained with respect to radiobiological effects (relative biological effectiveness ranges between 1.1 and 1.3).[1–3] High-LET radiations (fast neutrons, heavy ions) produce different biological effects. What makes the heavy-ion therapy so unique is based on a few physical aspects of their interaction with irradiated matter in comparison to those of low-LET radiations: (i) heavy ions deposit their energy at a certain well-defined depth of tissue (the Bragg peak) which depends on the energy of the ion, and beyond that depth the ions are completely stopped, while between the entrance into a human body and the Bragg peak the delivered dose is almost constant but lower than at the Bragg peak position, (ii) heavy ions are more efficient in producing biological damage for the same delivered dose, and thus they have been assigned higher relative biological effectiveness (RBE), in comparison to other radiations such as γ-rays, and (iii) the reduction in OER (Oxygen Enhancement Ratio) is obtained. The lower the OER, the more effective (i. e. less damaging to normal tissue) the treatment with a given radiation. Hence, by controlling the Bragg-peak position, it should be possible to establish an efficient and a close-to-ideal treatment plan involving only tumor region in a much pin-point fashion, while not affecting normal tissues in front of or beyond the tumor. By targeting tumors more accurately and delivering larger radiation doses, the treatment can eventually be accelerated. There is also evidence for the reduction of differences in radio-sensitivity to high-LET radiations related to cell cycle phase, to cell line, or a reduced importance of repair phenomena.[4] Under these conditions, all cell populations, in all situations when exposed to high-LET, as com-

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pared to low-LET radiations, tend to respond in a similar way.

For the more effective use of radiations, it is essential to understand radiation physics and chemistry in the Bragg peak region, although systematic understanding of what is going on along the entire path of radiation (track) would be important, as well as beyond the Bragg peak.[5] In this article, we will review radiation physics and some chemistry when radiations (electrons and heavy-ions) with the initial energy of up to a few MeV are acting on biological systems, particularly in the Bragg peak region. Finally, we discuss actual applications and clinical test cases.

Radiation physics and chemistry

Heavy charged particles slow down, i. e. lose their initial energy, as they travel through a material as a result of electromagnetic interactions between the positive charge of the ion and the negative charge of the orbital electrons of the material. The products of these interactions are either excited atoms or ion pairs, i. e. pairs consisting of a free electron and the corresponding positive ion. For photon and electron impacts, ionization and excitation processes also take place and many secondary electrons are released. In both cases these secondary free electrons are used as a basis for the detection of ionizing radiation by a detector. The initial energy of photons, electrons and protons is usually expressed in keV or MeV, while that of heavy ions is expressed as MeV/amu, where amu is the "atomic mass unit".

Dose, LET, and OER

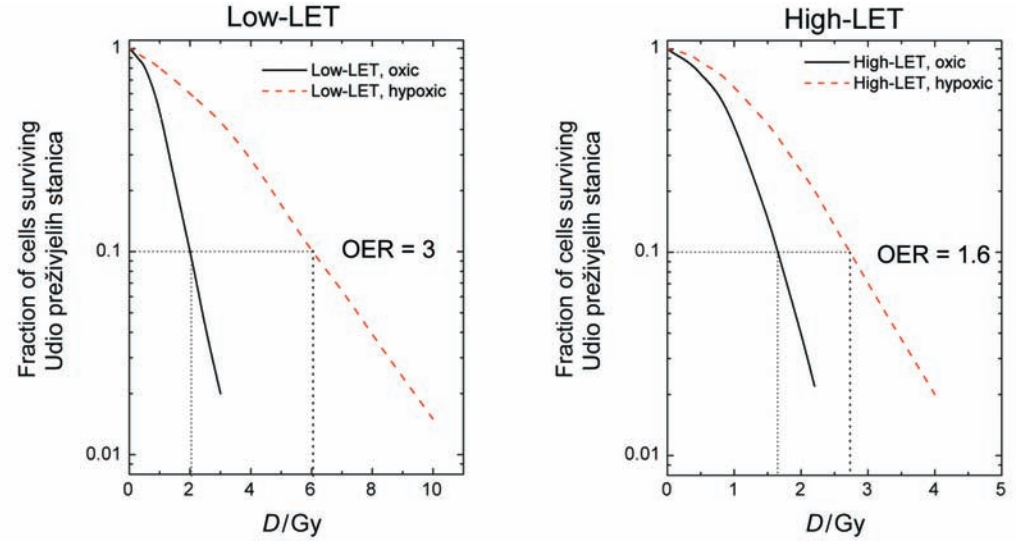
Two different materials, exposed to the same radiation field, will in general absorb different amounts of energy. The energy absorbed per unit mass is called the absorbed dose, and the unit is 1 Gy = 1 J kg^{-1}. The absorbed dose is a meaningful measure of chemical and/or physical effects created in an absorbing material by a given amount of radiation energy. Therefore, measurement (or the knowledge) of the energy absorbed per unit mass is of fundamental interest in the studies of physical and chemical effects of radiation in matter.

However, when the effects of radiation on living organisms are studied, the absorption of equal amounts of energy per unit mass (the same absorbed dose) under different irradiation conditions may cause different biological effects. The magnitude and the severity of the biological effect can differ by as much as an order of magnitude depending on the local rate of energy deposition (through excitation and ionization processes) along the particle track. This quantity is known as *LET* – linear energy transfer, i. e. the amount of energy (dE) dissipated by the incident charged particle per unit distance (dl) as it traverses through the matter, $LET = \mathrm{d}E/\mathrm{d}l$. *LET* is expressed usually in keV/μm. Regarding their *LET*, ionizing radiations can be generally divided into low-LET and high-LET radiations, with the demarcation value of 10 – 20 keV/μm.[6,7] High-LET radiations, such as heavy ions (*LET* = 100 – 200 keV/μm[6]), tend to result in greater biological damage than low-LET radiations (x-rays, electrons) even though the total energy deposited per unit mass (dose) may be the same.

Biological effect of ionizing radiation can be influenced by the presence of molecular oxygen within the cell – the larger the cell oxygenation, the larger the biological effect of radiation.[6] The oxygen enhancement ratio (OER) is thus defined as the ratio of the dose without oxygen to that in the presence of oxygen that produces the same biological effect (Fig. 1).[6,8] The OER for low-LET radiation is about 3, and it decreases as the *LET* increases, approaching OER = 1 at about *LET* = 150 keV/μm (Fig. 2). It has been a widely accepted notion in radiation-physics and radiation-chemistry communities that two modes of radiation action are possible: a direct one and an indirect one.[6] The direct effect is apparently the consequence of a direct hit of DNA molecule by radiation causing single- and double-strand breaks, and it is the dominant process in the interaction of high-LET particles with the biological material.[6] The indirect effect is the consequence of radiation hitting water and other molecules surrounding DNA producing radicals and ions, which, in turn, attack DNA, thus causing its damage. Hence, the presence of water and other molecules is essential for the indirect effect. Generally, the direct effect amounts to about 30 % of the total radiation effect induced by low-LET radiation (x-rays), while the indirect effect is about 70 %, and hence, the indirect effect is considered to dominate the total radiation effect,[4,6] and it will be discussed in detail later. Blood circulation in the central area of a large deep-seated malignant formation is poor, and hence sufficient oxygen is not brought into the center of the malignant formation resulting in hypoxia, while the normal tissues are – in general – well oxygenated. As Fig. 1 shows, the radiation effect is higher under oxic conditions, and because of this, radiation treatment is considered relatively less effective. However, the oxygen enhancement ratio is lower for high-LET radiations than for low-LET radiations (Fig. 2),[7] and the lower the OER , the more effective (i.e. less damaging to normal tissue) the treatment with a given radiation. This certainly means that high-LET radiation is more effective regardless of the presence of oxygen.

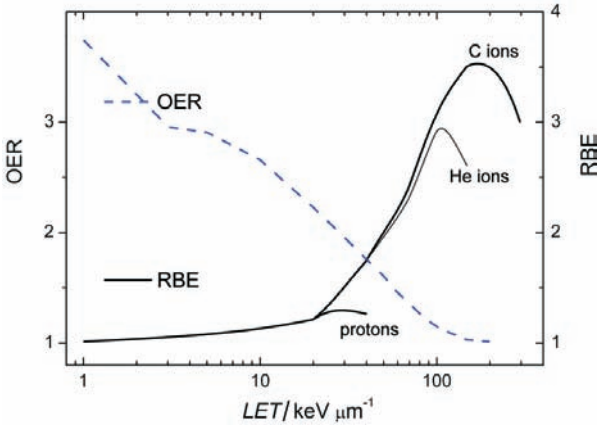
The Bragg peak and RBE

The characteristic of heavy ions when interacting with the material is that they are more efficient at ionizing atoms along their path as they move slower. This means that the highest radiation dose is delivered at the point in the body at which they stop while the dose elsewhere is much lower. The plot of absorbed dose as a function of depth of the absorbing medium/tissue (the Bragg curve or dose-depth distribution) has then a characteristic, very pronounced peak at a certain depth – the so-called Bragg peak (Fig. 3). The Bragg peak can be moved to shallower or deeper depths by changing the energy of the ion beam or by interposing material upstream to alter the beam energy,[9] thus allowing one to control the Bragg peak position. Moreover, by combining several ion beams of slightly different energies, an almost uniform dose distribution over a certain depth of tissue (over the entire tumor) can be obtained, and such a distribution is called the spread-out Bragg peak (SOBP).[10,11] This makes the clinical application more effective. In contrast, the dose-depth distribution for photons/x-rays shows a maximum close to the surface (skin), which is a consequence of the build-up of secondary electrons, followed by the nearly exponential decrease (Fig. 3), and the ratio of the dose delivered to the tumor relative to the dose delivered to



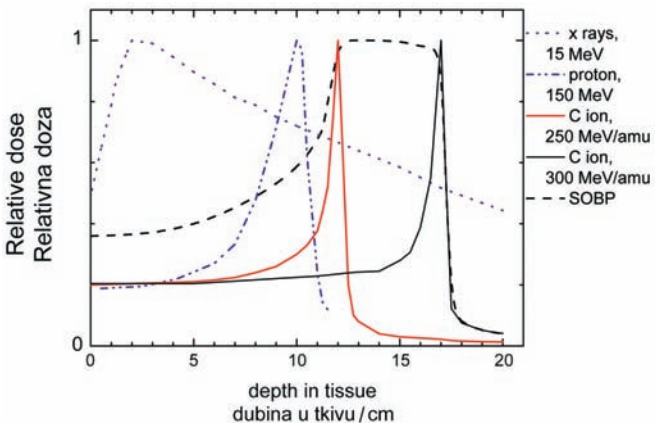
F i g. 1 – *Dependence of the biological effect of radiation (i.e. fraction of cells surviving irradiation by a given dose, cell surviving curves) on the absorbed dose in oxic and hypoxic conditions for low-LET (left) and high-LET radiations (right). Oxygen Enhancement Ratio (OER) is defined as the ratio of doses resulting in the same biological effect under hypoxic and oxic conditions, as illustrated by dotted lines. Schematic presentation prepared after ref.*[6,8]

S l i k a 1 – *Ovisnost biološkog učinka zračenja (t. j. udio stanica preživjelih ozračenost danom dozom) o apsorbiranoj dozi u uvjetima s prisustvom kisika (oxic) i bez prisustva kisika (hypoxic) za zračenje niskog LET (lijevo) i visokog LET (desno). Omjer pojačanja zbog prisustva kisika (OER) definiran je kao omjer doza koje daju isti biološki učinak u uvjetima bez kisika i s kisikom, što je ilustrirano istočkanim linijama. Shematski prikaz prema ref.*[6,8]



F i g. 2 – *Dependence of OER and RBE on LET of radiation. Schematic presentation prepared after ref.*[6,8]

S l i k a 2 – *Ovisnost omjera pojačanja u prisustvu kisika (OER) i relativne biološke učinkovitosti (RBE) o linearnom prijenosu energije (LET) zračenja. Shematski prikaz prema ref.*[6,8]



F i g. 3 – *Dose-depth distributions, i.e. dose delivered throughout the depth of the tissue, for x-rays, protons, carbon ions of two energies, and the spread-out Bragg peak (SOBP). The distinctive Bragg peaks in the curves for protons and C ions are observed. Dose-depth distribution peak is observed at deeper depths for higher ion energy. The SOBP is obtained by combining ions of different energies. Prepared after ref.*[10,11]

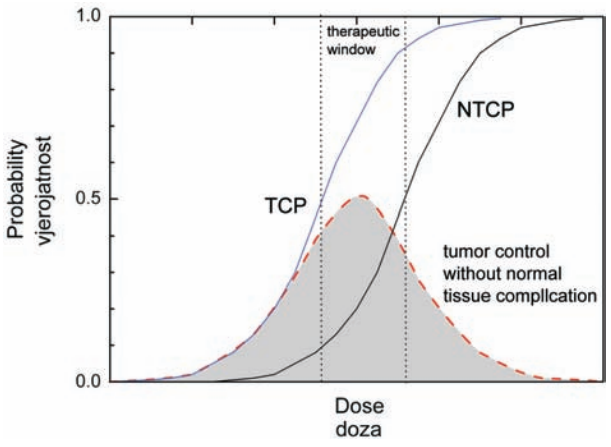
S l i k a 3 – *Raspodjela doze po dubini prodiranja zračenja u tkivo za x-zrake, protone, ugljikove ione dviju različitih energija, te prošireni Braggov vrh (SOBP). Krivulja raspodjele doze za protone i ugljikove ione pokazuje izraziti maksimum, Braggov vrh, koji se opaža na većim dubinama za veće ionske energije. Prošireni Braggov vrh dobije se kombinacijom iona različitih energija. Pripremljeno prema ref.*[10,11]

the surrounding tissue is much lower for photons than for heavy ions.[10]

Therefore, heavy-ion beams are excellent tools for the treatment of deep-seated tumors, because of the enhanced energy deposition at the end of the (heavy) particle range and the corresponding decrease of cell survival. Both model calculations and measurements show a considerable decrease in survival rate of cells irradiated by carbon ions at the depth corresponding to the position of the Bragg peak.[12] Similar Bragg curves with a maximum delivered dose at a certain energy-dependent depth are obtained also for protons (Fig. 3). By combining protons of different energy the SOBP can be produced, and proton therapy can be successfully applied for certain types, positions and sizes of tumor.[7]

Different kinds of radiation have different levels of effectiveness when it comes to ionizing molecules in living tissue.

The ratio of the absorbed dose of a reference radiation (normally x-rays or γ-rays of 200 keV) to the absorbed dose of a test radiation required to produce the same level of biological effects, all other conditions being equal, is called relative biological effectiveness (RBE).[6] (It should be pointed out that different RBE values can be assigned to different biological effects, such as single or double strand breaks of DNA, non-reparable DNA breaks, cell inactivation, etc, even for the same type of radiation.[6,13] In this paper we restrict the discussion to the RBE for cell inactivation/killing.) The RBE is also regarded as a measure of the benefit versus risk of radiotherapy – the higher the RBE, the lower the dose needed for the same biological effect. Namely, radiotherapy aims to irradiate tumor with sufficient dose to achieve local control while minimizing complication in normal tissue. However, probabilities of both these effects increase with increasing dose[6,10,14] (Fig. 4). The larger the distance between the tumor control probability (TCP) and the normal tissue complication (NTCP) curves, the easier it is to achieve the therapeutic goal, and the less likely the complications.[6] There is an optimum region of doses where TCP ≥ 0.5 and NTCP ≤ 0.5 (between dotted lines in Fig. 4) called a "therapeutic window", where the probability of tumor control without normal tissue complications (shaded area in Fig. 4) has its maximum (Fig. 4). Therefore, the lower the dose for the same radiation effect, the less the complication on healthy tissue.



F i g. 4 – *Dose-dependence of the tumor control probability (TCP) and the normal tissue complication probability (NTCP). Therapeutic window is defined as the dose region where TCP > 0.5 and NTCP < 0.5 (range between dotted lines). The probability of tumor control without normal tissue complication (shaded area) has a maximum in the therapeutic window. Prepared after ref.*[6,14]

S l i k a 4 – *Ovisnost vjerojatnosti kontrole tumora (TCP) i vjerojatnosti komplikacija zdravog tkiva (NTCP) o primljenoj dozi tijekom radioterapije. Područje doza za koje vrijedi TCP > 0,5 i NTCP < 0,5 (između crtkanih linija) naziva se "terapijski prozor". Vjerojatnost kontrole tumora bez komplikacija zdravog tkiva (osjenčano područje) najviša je upravo u terapijskom prozoru. Pripremljeno prema ref.*[6,14]

RBE depends on several variables, such as the particle type and energy, the absorbed dose and the biological system. Usually the RBE is correlated to the value of *LET* (Fig. 2). For low *LET* values, RBE is common for all particles and is close to 1. For protons the maximal RBE of about 1.3 is found at 25 keV/μm.[13] The RBE increases with *LET* reaching a maximum at a certain *LET* value depending on the ion. The position of the maximum RBE shifts to higher *LET* values for heavier ions:[15] maximum RBE for helium ions is observed at 100 keV/μm, and at 200–300 keV/μm for carbon ions.[13] The value of the RBE provides a quantitative index of the effectiveness per unit of absorbed dose of any radiation. For example, the RBE of 2.6 – 2.9 for neon ions[16] was determined at the Bragg peak, while for carbon ions of 13 keV/μm (*LET*) and 77 keV/μm the RBE of 1.0 – 1.3 and 2.0 – 3.0, respectively, were reported.[17] RBE varies also with the depth in the irradiated medium – RBE for C ions having energy 194 MeV/amu is calculated to be 1.7 at the entrance to the tissue, maximum value 3.6 at the depth corresponds to the Bragg peak, and is 1 beyond the peak.[18] Clinical experience and studies on human cells resulted in RBE of 3.0 for carbon ions having energy 290 MeV/amu (*LET* is about 80 keV/μm) in the region of SOBP.[19]

Therefore, the Bragg peak region is the most effective region for treatment by heavy ions, and hence detailed physics and chemistry occurring in the Bragg peak is essential for better planning and design of the treatment. In the existing facilities, heavy ions with about 300 MeV/amu-energy are used for irradiation, and they first lose their kinetic energy and momentum through elastic scattering with constituent atoms and molecules in a system. In the energy region of a few hundred keV/amu, the ionization and electronic excitation rapidly become dominant processes thus causing loss of large amounts of energy. This is the region where the Bragg peak begins, and these collision processes are in fact essential for it. For example, a beam of 290 MeV/amu carbon ions produces 5 times more ionizations (i.e. electron-ion pairs) at the maximum of the Bragg peak than at the entrance into a tissue.[20] Near the tail of the Bragg peak where the incident-ion energy is somewhere in the keV to high-eV region, all other collision processes are expected to play crucial roles, of which charge transfer, rotational and vibrational excitations, electron attachment (secondary electrons), and reactive scattering are important. Molecular ions produced through ionization and charge transfer, and those species produced by electronic excitations are often unstable undergoing fragmentation within a lifetime of less than 10^{-12} s. This fragmentation produces radicals and ions with appreciable kinetic energy sufficient to travel further out from the track of the incident ions. These products undergo a series of reactions with other surrounding molecules further producing different types of new chemical species. They all can eventually react with biological molecules causing biological damage. Therefore, the series of radiolysis events, i.e. initial ionization and excitation, production of fragmented species, secondary radical reactions, as well as the behavior of secondary electrons, as a whole, are the origin of the Bragg peak and hence of the radiation effect.

As discussed above, heavy-ions possess several advantages over low-*LET* radiations with respect to the OER and RBE, but the full physical and chemical picture is yet incomplete. It is usually thought that high-*LET* radiation is more efficient in producing direct hits to DNAs, while the effects of low-*LET* radiations are dominantly produced by radical reactions.[4,6] As it is well known, the dominant material constituting biological systems, including the human body, is the

water molecule – more than 70 % of the human body mass is water. Hence, upon irradiation, the majority of radiation energy is considered to interact with water molecules producing radicals $OH^{\bullet}$, $H^{\bullet}$, $O_2^{\bullet}$, etc, and these radicals interact rapidly with nearby DNA causing the indirect effect.

As a general example of an indirect radical – DNA reaction, we discuss here the following process involving water molecules. Direct dissociation of the electronically excited water molecule ($H_2O^* \rightarrow H^{\bullet} + OH^{\bullet}$) results in production of $H^{\bullet}$ and $OH^{\bullet}$ radicals, with relatively large kinetic energies allowing them to travel further. These fragments have very fast reaction rates and thus they almost immediately (within 10^{-12} s) react with the atoms and molecules they encounter while traveling. Dissociation through ionization of water molecule ($H_2O \rightarrow H_2O^+ + e^-$) results in unstable H_2O^+ ions that either undergo fragmentation producing H^+ ions and OH radicals, or react with other water molecule ($H_2O^+ + H_2O \rightarrow H_3O^+ + OH^{\bullet}$) producing H_3O^+ ions and $OH^{\bullet}$ radicals. On the other hand, electrons produced through ionization lose their kinetic energy in a series of collisions with various molecules, and within about 10^{-12} s become thermalized. Since water molecules are strong polar molecules, they orientate toward a thermalized electron and form energetically a stable state called a solvated electron, e_{aq}^-. The solvated electron is a transient species found in all systems where the charge is transferred through a medium.[21] It is highly reactive[22] and plays a key role in radiation chemistry in various aspects, e. g. in cancer radiotherapy or neutralization of toxic wastes.[21] In reactions of the solvated electron with water molecules ($e_{aq}^- + H_2O \rightarrow OH^- + H^{\bullet}$) and H^+ ions ($e_{aq}^- + H^+ \rightarrow H^{\bullet}$) $H^{\bullet}$ radicals are produced. Therefore, through ionization and electronic excitation of water molecules by incident radiation, a large amount of solvated electrons and various types of radicals (most important are $OH^{\bullet}$ and $H^{\bullet}$) and ions are produced. The distribution of radical species depends on the type of radiation – for high-*LET* radiation such a distribution is very dense, while for low-*LET* radiation it is sparse. When the density of radicals is high enough, they recombine and disappear, e. g. $OH^{\bullet} + OH^{\bullet} \rightarrow H_2O_2$, $H^{\bullet} + H^{\bullet} \rightarrow H_2$, $H^{\bullet} + OH^{\bullet} \rightarrow H_2O$). Finally, although heavy ions deposit more energy per unit length, the yields of free radicals per 100 eV absorbed energy are up to one or two orders of magnitude smaller for high-*LET* radiation than for x-rays.[23] Therefore, for high-*LET* radiations, the effects of radical reactions are considered to be of a secondary importance, while for low-*LET* radiations, they are the primary precursors of radiation effects. Modeling of DNA damage by electrons of various energies shows that between about 50 % and 70 % of DNA damage is caused by the indirect effect, mostly by interactions with the OH radicals.[24] However, the investigations aimed at elucidation of these phenomena are scarce when high-*LET* radiation is concerned, and the reason why it is so may be related to the paucity of well characterized heavy ion sources. Also a higher sensitivity of measuring devices is required, as well as their good spatial and temporal resolution. Consequently, further investigations of both direct and indirect effects of heavy ions on DNA are needed inside the Bragg peak.

The region beyond the Bragg peak consists often of healthy tissue, and this fact enhances the concern of a potential damage on a molecular scale caused by heavy ions after they have lost most of their energy or by low-energy (< 200 eV/amu) secondary ions. Until very recently, it has been widely believed that low-energy ions below a hundred or a few tens of eV/amu may have nearly null radiation effect since they do not possess sufficient energy to induce ionization, excitation and charge transfer upon interactions. A recent study,[5] however, indicates that beyond the Bragg peak more harm to the healthy tissue is caused by low-energy secondary particles than by heavy ions themselves. Hence, the effects induced by low-energy ions in the region beyond the Bragg peak should also be thoroughly investigated.

Ionization and *W* value

In radiation therapy, the clinicians must design a method of irradiation so that a desired dose may be delivered to a specific region of treatment, with a minimum dose delivered elsewhere. To optimize dose delivery to a tumor, one must know the energy deposition in a tissue or tissue-like material, and this is the central problem of accurate dosimetry. As mentioned earlier, the universal final products of an interaction of any ionizing radiation are free electrons, which are detected by various types of radiation detectors. The uncertainty of the measured energy deposited in a tissue depends on the quality of basic physical data, such as stopping powers and total ionization yields produced by incident particles of various charge and various energies.

The penetration depth (or a range) of a charged particle in matter is characterized by the mean energy loss per unit path length, or the stopping power. Stopping powers for electrons and positrons were critically surveyed in the ICRU Report 37,[25] while those for protons and alpha particles were presented in the ICRU Report 49.[26] Recent ICRU Report 73 presents a critical survey of the measurements and calculations of stopping powers for ions from lithium to argon (Z = 3 – 18) of energies from 1 keV/amu upward in condensed and gaseous matter.[27]

The other basic quantity for dosimetry is the ionization yield, i.e. the number of electrons produced by radiation in matter. The related quantity "average energy to produce an ion pair" (*W* value) is used more often. The *W* value is defined as the mean energy (expressed in eV) spent by the incident particle of energy *E* for the formation of a pair of an electron and a positive ion after complete dissipation of the initial energy, $W = E/N$, where *N* is the total number of produced electron-ion pairs. As it was the case for the stopping power, *W* value depends on the type and energy of radiation and on the irradiated material. The *W* value is defined after complete dissipation of the initial energy of the incident particle to matter. However, for high-energy particles in thin media, it is necessary to consider the differential *w* value, defined as $w = dE/dN$, where *dE* is the mean energy lost by a charged particle of energy *E* in traversing an absorber of thickness *dx*, and *dN* is the mean number of ion pairs produced when *dE* is completely dissipated in the gas. For sufficiently high incident energy $W = \text{const}$, and $w = W$ is a good approximation.

Accurate knowledge of the characteristics and values of *W* and/or *w* is required for conversion of the charge collected in the ionization chamber to deposited energy, and uncertainties in *W* values directly influence the overall uncer-

tainties in measured dose. For radiotherapy it is desirable to determine doses in tissue with overall absolute uncertainty of 5 % or better,[28–30] and it implies that the separate contributors to dose calculation (*W* or *w* values, stopping powers, etc.) should be known with absolute uncertainties of 2–3 %. However, available data on *W* or *w* are often fragmented, deficient, dispersed, and missing systematic. Since stopping powers for ions have been recently surveyed,[27] the current knowledge on *W* and *w* values for heavy ions will be discussed here in more detail.

The ICRU Report 31[31] and Chapter 8 in the IAEA TECDOC 799[28] provide a basis for assessing the present knowledge of *W* values for different charged particles in various gases. It should be pointed out that all *W* values are measured and reported for gases (N_2, CH_4, C_3H_8, CO_2, Ar, air) as irradiated material, although in radiation therapy one actually deals with the tissue as a complex material. Dosimetric measurements, including those of *W*, are often performed on gaseous tissue-equivalent (TE) mixtures. Most common TE gas mixtures, simulating the composition of tissue, are methane-based TE gas (64.4 % CH_4, 32.4 % CO_2, 3.2 % N_2, by volume), propane-based TE gas (55 % C_3H_8, 39.6 % CO_2, 5.4 % N_2), and butane-based TE gas (51.4 % C_4H_{10}, 42.3 % CO_2, 6.3 % N_2).[32] The TE gases are essential in measurements of radiation energy deposition in small spheres simulating human cells. The dose distribution curves on the cell-size level (0.1 – 10 μm sphere diameter) are indispensable in human radiotherapy, especially when neutrons and heavy particles are applied.[18,33,34] When complex substances are involved, an important practical and theoretical problem arises – the analysis of the validity of the additivity rule or how to derive *W* values for complex substances from the *W* values for their constituents. Experimental *W* values for heavy ions (C, O, N) and also other incident particles in TE gas mixtures were compared with the *W* values calculated from *W* values for pure components by applying various mixing models and the model giving the best agreement was identified.[32,35]

Dosimetry in heavy-ion therapy is performed by ionization chambers filled with air, and the measured values are then converted to doses in water or in tissue. Detailed description of the calculation method is beyond the scope of this review. The procedure of absorbed dose determination based on ionization chamber dosimetry is recommended by IAEA,[29] and this is currently the only international guideline for clinical dosimetry of ion beams. Additional details may be found elsewhere.[30,36,37]

High-energy heavy ions used in radiotherapy have a considerably different range of charge, mass, and velocity than the electrons and alpha-particles, for which there are extensive measurements of *W*. The heavy ions considered for use in radiotherapy include He, C, Ne, Si and Ar. The appropriate energies to obtain a sufficient beam penetration are typically 250 MeV/amu for He, 200 – 400 MeV/amu for C, 620 MeV/amu (Ne), 800 MeV/amu (Si), and 860 MeV/amu (Ar). The existing *W* or *w* data are fragmentary and most of them are measured for relatively low energies below 1 MeV where major variations in energy dependence are observed.[28,31] There is a lack of experimental data in the energy range above 1 MeV/amu, which is of interest for radiotherapy. Recently, two groups from the heavy-ion therapy centers (GSI and HIMAC) started a new series of *w* value measurements for high-energy carbon and some other ions.[38,39] The available *w* values for ions of interest at higher energies[38–45] are shown in Table 1. For comparison, some *W* values for high-energy electrons[28,31,35] (> 10 keV), high-energy protons[2,31,35,40–42] (> 100 keV) and 5–MeV alpha-particles[31,39] are also presented in Table 1.

T a b l e 1 – *W values for electrons, protons and α-particles, and w values for heavy ions*

T a b l i c a 1 – *W za elektrone, protone i α-čestice, te w za teške ione*

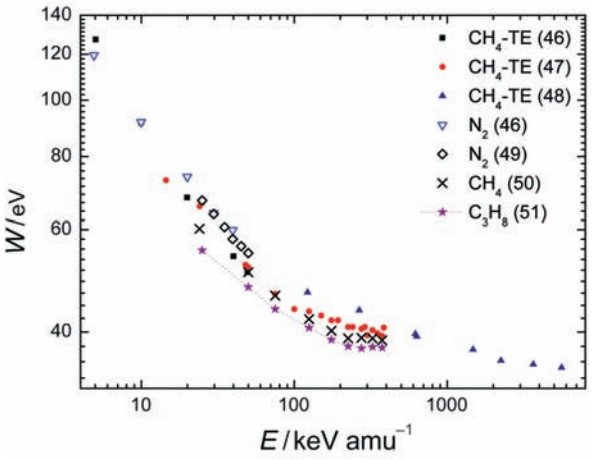
Particle Čestica	Energy Energija	Gas Plin	*W* or *w* (eV) *W* ili *w* (eV)	ref.
electrons	>10 keV	methane	27.3 ± 0.3	31
		methane-TE	29.4*	28
		propane	24.0 ± 0.5	31
			25.9 ± 0.7	28
		propane-TE	27.0 ± 0.3	35
		air	33.97 ± 0.05	28
		CO_2	33.0 ± 0.7	31
		N_2	34.8 ± 0.2	31
protons	100 keV	methane-TE	31.0 ± 1.5	31
		propane-TE	28.2 ± 0.3	35
	100 keV	methane	30.5 ± 1.0	31
	70 MeV	methane	27.9*	40
	100 MeV	N_2	36.5 ± 1.5	31
	>1 MeV	air (humid)	34.8 ± 0.7	2,41
	>1 MeV	air (dry)	34.2 ± 0.1	42
α particles	5.3 MeV	methane	29.1 ± 1.0	31
		methane-TE	31.1 ± 0.3	31
		N_2	36.39 ± 0.23	31
He^{2+}	3 MeV/amu	air	35.0 + 1.3	39
$^3He^{**}$	10.3 MeV/amu	air	34.5 ± 1.0	43
C^{6+}	2.5 – 4.5 MeV/amu	propane-TE	24.4*	39
C^{6+}	3 MeV/amu	air	32.7 ± 1.3	39
C^{**}	6.7 MeV/amu	air	36.2 ± 1.0	43
C^{**}	7.6 MeV/amu	air	34.2 ± 1.0	38
C^{**}	129 MeV/amu	air	33.7*	43
C^{6+}	250 MeV/amu	N_2	36.6 ± 0.7	44
C^{6+}	250 MeV/amu	N_2	36.4 ± 0.6	45
N^{7+}	3 MeV/amu	air	33.4 ± 1.3	39
Ne^{10+}	375 MeV/amu	N_2	35.4 ± 0.8	45
Ar^{18+}	479 MeV/amu	N_2	34.7 ± 0.5	45

* Errors not given in the original paper/
pogreška nije navedena u originalnom radu

** Ion charge not specified in original paper/
naboj iona nije naveden u originalnom radu

For carbon ions as incident particles a few sets of experimental data on *W* exist[46–51] (Fig. 5) covering a region of relatively low ion energies. The data show similar energy dependence in all gases. The constant high-energy *W* value has not been reached even at 5 MeV/amu in methane-based TE gas. The available *w* values in propane-based TE gas

(24.4 eV[39]) and in N_2 (36.6,[44] 36.4 eV[45]) are also significantly lower than the *W* in the same gas at the highest energy shown in Fig. 5. It can be noticed that for the presented gases the *W* is the lowest in propane, and the highest in N_2. Also, different sets of *W* for carbon ions in methane-based TE gases do not agree in the common energy range (100 – 400 keV/amu). When different ions are compared in the same gas, the *W* value at a particular energy in a given gas is generally higher for the heavier ion[28,35] and all data show similar energy dependence of *W*.



F i g. 5 – *Energy dependence of the W value (the mean energy required to form an ion pair) for carbon ions in several gases of interest for radiation therapy*

S l i k a 5 – *Energijska ovisnost srednje energije potrebne za stvaranje ionskog para (W) za ugljikove ione u plinovima od interesa za radioterapiju*

From the presented data it can be concluded that there is a need for new *W* value measurements for heavy-ion interactions with tissue and tissue-like materials for ion energies higher than ~10 keV/amu, and especially in energy ranges of several hundreds of MeV/amu that are of interest in therapy. Having in mind the recent study of the harmful effect of secondary low-energy particles in the region beyond the Bragg peak, it would be of interest also to study *W* for various ions in the low-energy region where significant energy dependence is expected.

Heavy-ion therapy

Radiotherapy by using protons and heavy ions was proposed as early as in 1946,[52] when the potential benefit of heavy ions was first brought to attention. Since then the physical and biological characteristics of various heavy particles have been studied. The heavy-ion therapy was first applied 1977 at the University of California Lawrence Berkeley Laboratory (LBL). Mostly neon ions were used.[19] In 1992 the LBL facility was entirely discontinued due mainly to financial difficulty. Currently, there are three heavy-ion therapy facilities: HIMAC (Heavy Ion Medical Accelerator in Chiba, Japan), HIBMC (Hyogo Ion Beam Medical Center, Japan) and GSI (Gesellschaft für Schwerionenforschung, Darmstadt, Germany).[53] The HIMAC construction and installation of all facilities were completed in 1993 and it was the world's first heavy ion accelerator complex dedicated to medical use in a hospital environment. Carbon ions were selected for clinical studies based on their high RBE in the Bragg peak region (3.0).[19] There are several new facilities under construction, e.g. in Heidelberg, Germany[54] (it will be the first clinical irradiation facility for heavy ions in Europe with the capacity of 1000 patients per year), and Pave, Italy,[7] and some more are in the planning stage (in France, Sweden, Austria).[7]

Over 2400 patients have been treated in the heavy-ion facilities since 1994 – more than 2100 patients were treated between 1994 and 2005 at HIMAC,[55] about 250 at GSI between 1997 and 2004,[7,56] and more than 50 at HIBMC in the period 2001 – 2004.[7] They all have shown impressive results of local control rates for some types of malignant, otherwise untreatable cases. The major obstacles of heavy-ion therapy facilities, despite their potential, are the costs for the construction, maintenance and treatment. As a measure, the construction cost of HIMAC was about 400 M$, while the photon facility (x-ray and γ-ray) may be constructed for about 20 M$. The cost and complexity of the exploitation of heavy-ion beams require often an international collaboration.

Before treating a patient, radiation oncologists have to identify the precise location of the tumor by imaging. This is often done using another physics-based technique – positron emission tomography (PET).[7] The energy of the heavy-ion beam – which is generally between about 300 and 400 MeV/amu –is then adjusted to match the tumor depth. Moreover, by combining ions with different energies in a single beam, the Bragg peak can be modulated into a plateau that dumps a high dose of radiation throughout the depth of the tumor (SOBP, Fig. 3). A recent attempt at HIMAC in Chiba was made to synchronize the beam irradiation timing with the body movement such as the patient breathing so that it increases the precision of irradiation making the pin-point shooting possible.

Increased biological effectiveness (RBE) of heavy charged particle beams (e. g. carbon ions) in the tumor in comparison to the lower RBE in the surrounding healthy tissue represents one of the major rationales for their application in tumor therapy. Although the production of x-rays is more economical and much easier in comparison with the production of heavy charged-particle beams, the available clinical experience with fast neutrons and protons justifies the heavy-ion therapy programs by four sets of arguments:

1. the radiobiology and clinical data indicate that, for the treatment of some tumor types and/or sites, high-*LET* radiations could bring benefit as compared to low-*LET* radiations
2. the attainability of high physical selectivity
3. the encouraging clinical results, although obtained on limited and selected groups of patients
4. less side effects than other radiations and chemotherapies.

To explain some of these arguments, summaries of clinical results at Japanese facilities are shown in Tables 2 and 3. The comparison of 1–, 2– and 5–year survival rates for heavy-ions and x-ray treatments (Table 2) clearly shows the advantage of heavy-ion treatment as could be expected

T a b l e 2 – *Comparison of survival rates after x-ray and heavy-ion treatments 1 year, 2 years, and 5 years after treatment*

T a b l i c a 2 – *Usporedba postotka preživjelih pacijenata podvrgnutih terapiji x-zrakama i teškim ionima godinu dana, 2 godine i 5 godina nakon tretmana*

		Survival rates (%) Udio preživjelih (%)		
	Radiation Zračenje	1 yr	2 yrs	5 yrs
Head-neck Glava i vrat	x-ray	90	75	58
	Heavy-ion	90	79	69
Lung Pluća	x-ray	78	55	22
	Heavy-ion	95	82	42
Bones Kosti	x-ray	15	-	-
	Heavy-ion	86	60	49

T a b l e 3 – *Local control rates of tumors by irradiation with heavy-ion and by conventional treatment (x-rays + chemotherapy)*

T a b l i c a 3 – *Postotak tumora pod lokalnom kontrolom nakon radioterapije teškim ionima i konvencionalne terapije (x-zrake i kemoterapija)*

	Heavy-ion (%) Teški ioni (%)	Conventional treatment (%) Konvencionalna terapija (%)
Salivary gland Žlijezda slinovnica	80	28
Nasopharynx Nosni dio ždrijela	63	21
Sarcoma Sarkom	56	28
Prostate Prostata	100	60 – 70
Lung Pluća	40	22 – 40
Brain Mozak	44	18

from the arguments above, although limited data are available for comparison.

The results of local control rates obtained by heavy-ion therapy in comparison with a conventional treatment (x-ray plus chemotherapy) are shown in Table 3. The local control rate means the percentage of the original cancer treated by any of these procedures and found to be well under control, although the patient might have died from the cancer at a different site. For most cases, again, it can be seen that heavy-ion treatment shows better results over conventional treatment, particularly impressive for treatments of salivary gland, nasopharynx and prostate malignancies. The LBL experience with heavy-ion therapy showed similar benefits for tumors of salivary glands and prostate, while for other localizations the results were poor.[2] Clinical experience at GSI since 1997[56] shows much better local control of patients having Chordomas when treated by carbon ions (local control after 3 years 81 %) than by photons (55 %). Also successfully were treated Chondrosarcomas (3–year local control rate 100 %).

The growing number of cancer patients treated by heavy-ion beams and the successful patient survival rates and local tumor controls have recently drawn attention to studies of potential late radiation effects in surviving patients. A radiotherapy treatment can be considered as successful when the balance between cure and unwanted late effects is found.[57] Potential late effects are associated with irradiated normal tissue. As mentioned earlier, at higher doses both the probability of tumor control and that of normal tissue complications increase. The dose-depth distribution, i. e. the Bragg peak, and higher RBE of carbon ions diminish the chance of normal tissue irradiation compared to irradiation by x-rays. However, if the normal tissue is irradiated, the high *LET* of carbon ions increases the risk of induced tumors and other enhanced late effects. Estimation of late effects has a further handicap in a relatively small number of treated patients and shorter follow-up time.[57]

Since more new heavy-ion facilities become available for clinical trials in the next years, more data for better comparison and illustration should become available making a better judgment possible. In addition, as discussed above, further deepening of our understanding of radiation physics, chemistry and biology of heavy-ion interactions is urgently required in order to enable clinical personnel to implement much better treatment plans and designs.

Concluding remarks

Heavy ions applied in radiation therapy combine the advantages of a high physical selectivity and high *LET* for some types of tumor. The higher RBE at the level of the Bragg peak or the spread-out Bragg peak and lower OER values further improve the advantage of the characteristic dose distribution. Having these properties, heavy ions are considered to be more effective than other types of radiation in treatment of hypoxic tumors, deep-seated tumors, or slowly growing tumors, generally of tumors that are resistant to low-*LET* radiation.

Understanding biological consequences of energy loss by charged particles, such as high-energy therapeutic ion beams requires access to a wide range of atomic and molecular data. The primary means of energy deposition of fast charged particles is ionization of a medium with the spatial pattern determined by subsequent energy transport by secondary electrons. The applications of high-*LET* radiations to radiation therapy and radiation research suffer because of the large gaps in our knowledge of atomic and molecular data for this type of radiation that can be related to the paucity of well characterized heavy-ion sources available for research. Very little is known about physical and chemical reactions occurring inside the Bragg peak after the incident high-energy heavy ion had deposited most of its energy in a small volume, particularly, the role of radicals and ions, in addition to the direct damage of DNA by densely ionizing

radiations is not well understood. The role of radicals and different ions formed there and their interaction with DNA should be carefully investigated. The need for new experimental data on the basic physical quantity of dosimetry, the mean energy required to form an ion pair (*W*) in tissue and tissue-equivalent materials, for high-energy heavy ions required in radiotherapy is especially emphasized.

Future advances in radiotherapy will depend considerably on a better understanding of the underlying mechanism of radiation actions on human cells. Contemporary biophysical models of radiation action now agree that biological effects are strongly influenced by radiation track structures on a scale of cellular dimensions down to nanometers or even smaller. However, the successful application of radiotherapy by heavy ions is going on, in spite of missing fundamental knowledge of detailed chemical and biological processes in tissue irradiated by high-*LET* radiation. The new heavy-ion facilities, both for basic research and clinical applications, will certainly result in a better understanding of various processes induced by heavy ions in both cancerous and healthy tissue.

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List of symbols
Popis simbola

LET – Linear Energy Transfer, keV/μm
– linearni prijenos energije, keV/μm

E – energy, eV or keV or MeV, for heavy ions: MeV/amu
– energija, eV ili keV ili MeV, za teške ione: Mev/amu

W – mean energy required to form an ion pair, eV
– srednja energija stvaranja ionskog para, eV

w – differential mean energy for an ion pair, eV
– diferencijalna srednja energija stvaranja ionskog para, eV

N – total number of electrons produced after complete dissipation of the initial energy of a charged particle
– ukupni broj elektrona nastalih nakon potpunog gubitka početne energije ionizirajuće čestice

d*E* – differential mean energy loss, eV
– diferencijal gubitka energije, eV

d*l* – differential path length, m
– diferencijal puta, m

d*N* – differential number of ion pairs
– diferencijal broja elektrona

dx – differential thickness, m
– diferencijal debljine, m

D – dose, Gy
– doza, Gy

Abbreviations
Popis kratica

RBE – Relative Biological Effectiveness
– relativna biološka učinkovitost

OER – Oxygen Enhancement Ratio
– omjer pojačanja zbog prisustva kisika

SOBP – spread-out Bragg peak
– prošireni Braggov vrh

TE – tissue-equivalent
– tkivu ekvivalentan

amu – atomic mass unit
– atomska jedinica mase

HIMAC – Heavy Ion Medical Accelerator in Chiba

HIBMC – Hyogo Ion Beam Medical Center

GSI – Gesellschaft für Schwerionenforschung

PET – positron emission tomography
– pozitronska emisijska tomografija

TCP – tumor control probability
– vjerojatnost kontrole tumora

NTCP – normal tissue complication probability
– vjerojatnost komplikacija zdravog tkiva

SAŽETAK

Fizika i kemija zračenja u terapiji raka teškim ionima

I. Krajcar Bronić[a] i M. Kimura[b]

Teški ioni, kao što su ioni ugljika i kisika, ubrajaju se u zračenje visokog linearnog prijenosa energije (*LET*) i prolaskom kroz tkivo stvaraju karakterističnu raspodjelu deponirane energije (doze) po dubini prodiranja koja se bitno razlikuje od raspodjele doze koju stvara zračenje niskog *LET*-a (γ-zrake, x-zrake, elektroni). Teški ioni gube manji dio energije pri ulasku u ozračeni biološki sustav, a zatim gube gotovo svu energiju u vrlo malom volumenu. Područje maksimalne deponirane energije naziva se Braggov vrh, koji ovisi o vrsti i energiji primijenjenog iona. Koristeći svojstvo Braggovog vrha, moguće je ozračiti samo područje tumora na nekoj dubini unutar tkiva, a istodobno izbjeći (štetno i nepotrebno) ozračenje okolnog zdravog tkiva. Postojanje Braggovog vrha nije jedina prednost teških iona pred zračenjem niskog *LET*-a – teški ioni naime pokazuju manji omjer pojačanja zbog prisustva kisika (OER) i veću relativnu biološku učinkovitost (RBE). Smatra se da je središnje područje dubinskog tumora slabo prokrvljeno te da je količina kisika u tom području stoga smanjena. Istraživanja su pokazala (slika 1) da je biološki učinak zračenja niskog *LET*-a znatno veći (OER = 3) u uvjetima dobre oksidacije tkiva, dok je razlika biološkog učinka zračenja visokog *LET*-a znatno manja (OER = 1,6, slika 1), pa su dakle teški ioni znatno učinkovitiji u uništavanju dubinskih slabo oksidiranih tumora. RBE je definiran kao omjer doze referentnog zračenja (x-zrake energije 200 keV) i doze danog zračenja potrebne za postizanje istog biološkog učinka. Viša vrijednost RBE znači da se manjom dozom postiže isti biološki učinak, te se tako postiže i bolji omjer korisnosti i rizika radioterapije. RBE ovisi o *LET* (slika 2), a za različite ione koji se primjenjuju u radioterapiji postiže maksimum na različitim vrijednostima *LET*-a. Slika 3 prikazuje raspodjelu deponirane energije po dubini u tkivu za protone i ugljikove ione kao primjer zračenja visokog *LET*-a. Karakterističan Braggov vrh postiže se na većim dubinama primjenom viših ionskih energija, a kombinacijom snopova iona bliskih, ali različitih energija može se postići prošireni Braggov vrh (SOBP), te se tako može jednoliko ozračiti cjelokupni volumen dubinskog tumora. Za usporedbu prikazana je i raspodjela doze po dubini za fotone, koja dosiže maksimum na maloj dubini ispod površine kože (zbog stvaranja sekundarnih elektrona), nakon čega slijedi gotovo eksponencijalni pad doze s dubinom. Omjer doze primljene u području tumora i doze izvan tumora znatno je manji nego u slučaju protona ili ugljikovih iona.

Na osnovi tih činjenica može se zaključiti da je područje Braggovog vrha područje u kojem je učinak terapije tumora teškim ionima najveći. Za bolje planiranje tretmana i postizanje boljih kliničkih rezultata potrebno je stoga detaljno poznavanje fizikalnih i kemijskih procesa koji se odvijaju u tkivu nakon ozračenosti teškim ionima energije oko 300 MeV/amu. Nakon ulaska u tkivo takvi ioni gube kinetičku energiju u elastičnim sudarima s molekulama. Kad energija padne na nekoliko stotina keV, prevladavaju procesi elektronskog pobuđenja i ionizacije uzrokujući nagli gubitak velike količine energije, i to je područje Braggovog vrha. Kad je energija iona pala u područje keV ili čak eV, a to je područje pri kraju Braggovog vrha, događaju se i drugi procesi, kao prijenos naboja, rotacijska i vibracijska pobuđenja, uhvat elektrona, razna raspršenja. Molekularni ioni nastali u tim procesima, kao i neki drugi produkti reakcija, vrlo su često nestabilni i brzo se raspadaju. Fragmentacijom nastaju različiti radikali i ioni koji mogu imati dovoljno energije da prijeđu značajnu udaljenost od mjesta svog nastanka i na udaljenom mjestu reagiraju s biomolekulama i izazivaju oštećenja. Međutim, ne zna se mnogo o detaljima svih ovih nabrojanih procesa koji čine ukupnost djelovanja zračenja visokog *LET*-a u području Braggovog vrha, ali i neposredno iza njega. Posebno je potrebno istražiti ulogu radikala i iona koji su nastali međudjelovanjem zračenja i vode, koja čini značajnu komponentu svakog biološkog sustava, te njihovo djelovanje na DNA.

Osnovni princip radioterapije je pronaći način da se predviđena doza preda području tkiva u kojem se nalazi tumor, dok je dozu u okolnom tkivu potrebno što više smanjiti. Slika 4 prikazuje vjerojatnosti kontrole tumora i komplikacija u zdravom tkivu u ovisnosti o dozi, te područje doza u kojem se postiže najbolji terapijski učinak bez komplikacija zdravog tkiva (terapijski prozor). Kako bi se ostvario najbolji mogući učinak radioterapije, potrebno je dakle poznavati i mjeriti dozu predanu tkivu, što je zadatak dozimetrije. Mjerenja se uglavnom zasnivanju na mjerenju elektrona koji nastaju međudjelovanjem svih vrsta zračenja i tvari. Nepouzdanost mjerenih doza ovisi o nepouzdanosti osnovnih fizičkih veličina, kao što su moć zaustavljanja i ukupni broj stvorenih elektrona. Broj elektrona najčešće se izražava pomoću veličine *W*, srednje energije potrebne za stvaranje ionskog para, koja se definira kao prosječna energija koju je upadna ionizirajuća čestica energije *E* utrošila na stvaranje jednog para elektron – pozitivni ion nakon što je čestica potpuno zaustavljena. *W* ovisi o vrsti i energiji zračenja te o ozračenoj tvari. Za čestice vrlo visokih energija, koje samo dio energije ostave u tkivu, koristi se diferencijalna srednja energija stvaranja ionskog para, *w*. Za dovoljno visoke energije vrijedi aproksimacija $w = W$. Dostupni podaci o *W* ili *w* u literaturi su nažalost nepotpuni i nesustavni, što pogotovo vrijedi za teške ione. Većina podataka odnosi se na relativno niske energije, kao što pokazuje primjer *W* za ugljikove ione u raznim plinovima (slika 5). Vrijednosti *w* za ione viših energija prikazani su u tablici 1, a za usporedbu dane su i vrijednosti *W* za druge vrste ionizirajućeg zračenja. Za potrebe radioterapije potrebna su nova mjerenja *W* ili *w* za ione visokih energija u tkivu ili tkivu ekvivalentnim smjesama.

Medicinska primjena ugljikovih iona u radioterapiji tumora počela je u Japanu i Njemačkoj 1994. godine i od tada je više od 2400 pacijenata podvrgnuto radioterapiji teškim ionima. Prvi klinički

rezultati pokazuju veliku uspješnost u terapiji dubinski smještenih tumora, te je tako opravdana visoka cijena gradnje takvih terapijskih centara. Tablica 2 pokazuje usporedbu postotka preživjelih pacijenata podvrgnutih terapiji x-zrakama i teškim ionima godinu dana, dvije godine i pet godina nakon tretmana, a tablica 3 prikazuje postotak tumora pod kontrolom nakon radioterapije teškim ionima i konvencionalne terapije (x-zrake i kemoterapija). U većini slučajeva bolji rezultati postignuti su terapijom teškim ionima. Radioterapija teškim ionima, uglavnom ugljikovim, nastavlja se i u novim terapijskim centrima unatoč visokom ulaganju i nedostatnom poznavanju osnovnih kemijskih i bioloških procesa u tkivu ozračenom zračenjem visokog *LET*-a. Nova saznanja iz područja radijacijske fizike, kemije i biologije pomoći će u daljnjem poboljšanju planiranja terapije teškim ionima te time i u postizanju još boljih kliničkih rezultata.

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