Overview of the use of radiotherapy in the treatment of cancer with a focus on Montenegro

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Abstract

The project examines the current state-of-the-art and use of radiation therapy in treatment of cancer patients. It surveys which modalities are currently available and how and when they are used, and the advantage and disadvantages of the various treatments used with a specific emphasis on Montenegro and South - Eastern Europe (SEE). This status has been looked at in terms of the current practices in Montenegro and SEE region. There is a detailed analysis of hadron therapy (HT) field both in terms of technology and the possible benefits since the idea is to explore the scope for HT in the SEE region and what is needed to make this a reality.

Introduction

The application of ionizing radiation has an important role in medical diagnosis and treatment. Ionizing radiation is used in radiotherapy, nuclear medicine and diagnostic techniques and interventional radiology.

Radiation can be defined as energy that travels through space, with either wave or particle properties depending on how it is measured and how it interacts with matter [1]. As it passes through matter, radiation interacts with the systems of which matter is composed, leading to various changes.

Ionization is the process of formation of charged particles, called ions, from electro-neutral atoms or molecules. It is a process in which an atom or a molecule acquires a negative or positive charge by gaining or losing electrons [2]. The resulting charged atom or molecule is actually an ion. Ionization can occur by the loss of electrons after a collision with subatomic particles or collision with other atoms, molecules and ions, or after an interaction with electromagnetic radiation [2]. The probability of ionization is highest for weakly bounded peripheral electrons and decreases towards the inner layers. The effects that ionizing particles will produce depend not only on the amount of energy they transmit to the body, but also on the location and volume of the part of the body exposed to radiation, as well as on the time interval for which that irradiation lasted.

Taking into account these properties radiation is of great importance when it is used for treatment of cancer.

X-ray (photon) therapy (RT, RTx or XRT) is a therapy that uses ionizing radiation to treat or control cancer by killing tumor cells [3]. It is carried out using X - rays, γ - photons, high - energy electrons [2]. X - ray radiotherapy, together with surgery, is one of the basic modalities for curative and palliative treatment of cancer in patients. This therapy can be curative for many types of cancer if they are localized on one specific-site of the body. It can also be used as part of adjuvant therapy to prevent tumor recurrence after surgery of the primary tumor.

Particle therapy with protons or heavier ions is currently the most advanced form of radiation therapy and offers new opportunities for research and to improve cancer treatment. Particles/hadron due to the Bragg peak deposit most of the dose/energy specifically at the end of the range so that normal tissue that is traversed receives a much lower dose than that by treatment using X-ray radiation [3]. The introduction of particle therapy globally has been slow, but the number of hadron therapy (HT) centers is growing, thus facilitating access to this treatment. The biological and treatment benefits of this therapy are considered very important.

Hadrons are directed to the target tumor site. They damage the DNA of tumor cells, which can ultimately causes their death. This method uses a hadron-focused beam to deliver the dose targetted to the tumor. It is especially important when a sensitive organ is nearby, since with precise focussing and targeted treatment, side effects are minimized. This method of treatment has been shown to be possible for pregnant women and is preferred choice over X-rays for tumor treatment in children when it is needed.

Cancer

Cancer is disease caused by mutations in the DNA that are mostly acquired spontaneous errors or by environmental factors. It can cause from abnormal cellular growth [1]. Normally human cells go through number of replications in the life-span – it grows and multiplies (cell division) in order for the tissue/organs to grow or repair tissues when necessary. With aging and many replications DNA damage can occur and can become mutated. Cells with damaged DNA can grow and multiply sometimes totally out of control resulting in malignant cells and eventually tumors. Cancer can start anywhere in the body and presents a disease in which some of the cells grow uncontrollably and can spread to other parts of the body resulting in the so called *metastatic disease* [4].

It is easy for cancerous (malignant) tumors to spread through the body, and consequently form new tumors (metastasis) [5]. Even though benign tumors do not spread through the body in order to form new ones, they sometimes can cause serious symptoms or be dangerous [5].

While normal cells grow when they receive certain signals, they stop dividing after receiving different signals and even die once through a process called apoptosis committing suicide in order to protect organism; cancer cells grow and they ignore process of programmed cell death (apoptosis) and so other control pathways [4]. Cancer cells invade into nearby areas and spread through the body while normal cells don't invade each other and they don't move through the surrounding tissues [4].

Errors that can happen while cells are dividing or the damage to DNA caused by substances from the environment can be reasons for genetic changes causing cancer [4]. Also they can be inherited from parents [4].

Even though body naturally reapir damaged DNA before the cells become cancerous, that ability decreases as the body becomes older. As disease it is different for each person, it doesn't always have the same symptoms for the same cells and the treatment is unique for every patient.

As one of the fundamental definitions the cell is the basic structural, functional, and biological unit of all known organisms. The main elements from which the cell is composed are cell membrane, cytoplasm and nucleus.

Nucleus contains all of the cell's genome (all genetic material of an organism). Nuclear DNA (deoxyribonucleic acid) is organized as multiple long linear molecules complexed with a large variety of proteins, such as histones, to form chromosomes [6]. DNA (Figure 1) is a molecule composed of two polynucleotide chains that coil around each other and form a double helix that carries genetic instructions for the development, functioning, growth and reproduction of all organisms. The two DNA strands are known as polynucleotides as they are composed of simpler monomeric units called nucleotides [7]. Each nucleotide is composed of one of four nitrogen-containing nucleobases (cytosine [C], guanine [G], adenine [A] or thymine [T]), a sugar called deoxyribose, and a phosphate group [7].

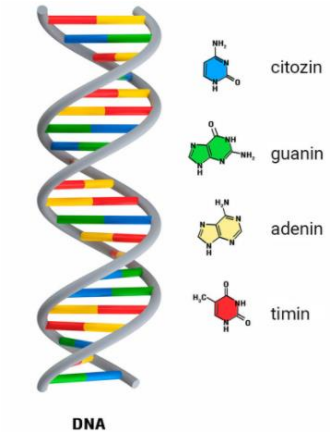

Figure 1: DNA chain [8]

DNA, located inside chromatin material of the nucleus, can be damaged by anything that can change the DNA sequence. Damage to DNA can be caused by exposure to radiation, chemicals, and other environmental sources, but mutations also accumulate naturally over time through uncorrected errors in DNA transcription. A change within the DNA chain can cause cancer.

Cancer cells have distinguishing histological features visible under a microscope. The cytoplasm may display abnormalities and the nucleus of a cancer cell is often large and irregular. In normal

cells, the nucleus is often round shape, while in cancer cells the outline is often irregular (Figure 2) [4]. Different combinations of abnormalities are characteristic for each cancer type [4].

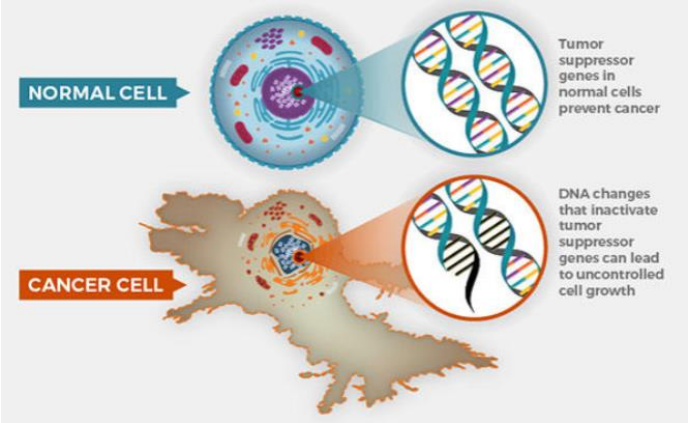

Figure 2: Comparison of normal and cancer cell [4]

Although it is contradictory, radiation (that can cause cancer) has a huge significance when it comes to treating this disease. Applying radiation precisely in an appropriate way has curative and palliative effect.

The goal of this kind of treatment (radiation therapy) is to deposit enough energy per unit of mass (radiation dose) in the tumor. This dose can be considered as the energy left by beam as a result of ionization, in a unit mass of tissue that is being radiated. As the water is the major component of the human body, most of the energy (about 70% of it) is being absorbed by water molecules resulting in production of simple molecules containing oxygen that are chemically very aggressive called reactive oxygen species or free radicals (oxidants) [9]. These radicals diffuse inside the cell and they can encounter DNA molecule and break it either on one strand (single strand break, SSB) or on both strands (double strand break, DSB) which produces damage (Figure 3) [9].

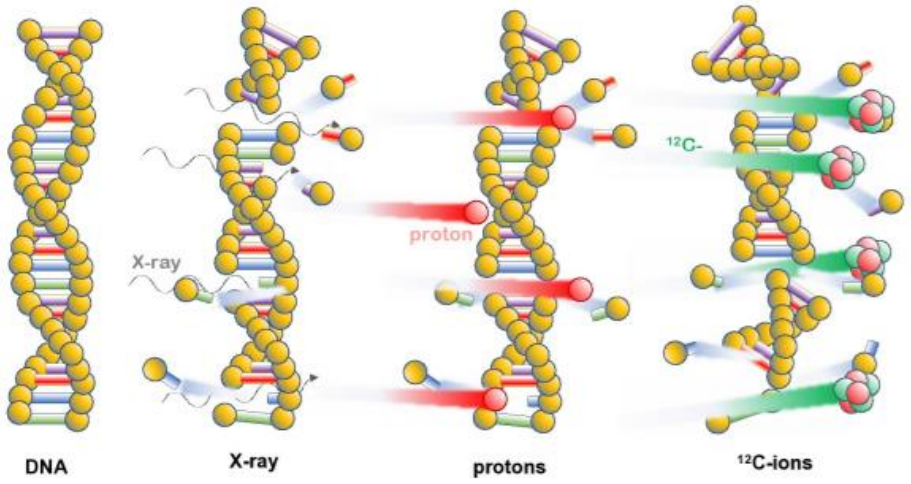

Figure 3: Simulation of DNA while being ionized with different kind of beam [10]

Unrepaired breaks of the DNA chain can cause the death of a cell (approximately one in every 50 DSB is lethal to the cell) [9]. Free radicals are activated in oxygenated tissues and deactivated in hypoxic ones (tissue being deprived of adequate oxygen supply) [9]. Hypoxic tumor cells tend to be radioresistant (they require larger dose of radiation in order to be damaged and thereby killed), but being hypoxic is not the only condition for tissue to be radioresistant [9].

Radiotherapy - historical overwiev

Contrary to expectations, the earliest evidence of cancer is found in ancient Egypt. In the mummies, growths that indicates the bone cancer (osteosarcoma) have been seen [4]. The origin of the word cancer is credited to the Greek physician Hippocrates ("Father of Medicine") but first descriptions of the disease date back to 3000 BC [4]. Hippocrates used terms *carcinos* and *carcinoma* to describe non-ulcer and ulcer forming tumors [4]. Another Greek physician, Galen, used word *oncos* to describe tumors and it presents the root of the word oncology [4].

The situation in medicine rapidly changed after the discovery of X-rays in 1895 by Wilhelm Conrad Röntgen. For this breakthrough he was awarded the Nobel Prize in 1901. Only after few months this invention found a purpose of huge importance in diagnostic and therapeutic appliance.

At that time, investigation of the radioactivity and natural sources of radiation was started by Antoine Henri Becquerel. Tree years later, Maria Sklodowska-Curie and her husband Pierre Curie discovered the radium as a source of radiation. In 1901, Becquerel and Curie reported on the physiologic effects of radium rays [11]. After that more and more scientists got interested and started researches related to this topic.

Discovery of nucleus inside the atom, made by Ernest Rutherford in 1911, and almost twenty years after that the discovery of neutrons, made by James Chadwick in 1932 were of a crucial significance for the further development of science in general, and especially medicine when it comes to field of radiation therapy.

Before the discovery of DNA, Claudius Regaud, a physicist and biologist, postulated that the chromatin is the target inside the cell [12]. Chromatin is noticable inside the cell nucleus while the cell is in the interphase (a period between two divisions during which the cell prepares for the division). Through his research and experimental work he concluded that subdividing the dose in subsets has less harmful effects on healthy tissue than when entire dose is applied at one time. These conlusions led the radiologist Henri Coutard to elaborate a fractination concept which uses the total dose divided into 30 separate fractions for laryngeal carcinoma which is the basis of modern radiation oncology [12]. He also began with curing various types of tumors with radium sources placed close to the tumor which presents the origin of brachytherapy [12].

One of thetechnology inventions that marked 20th century was definitely made by Ernest Lawrence in 1930 [2]. For the invention of the cyclotron, E. Lawrence won the Nobel Prize in 1939. The cyclotron provided synthetic radionuclides for nuclear medicine and radiation oncology. In 1936 the first artificial element, technecium, was created.

Following these important discoveries, in 1946, Robert R. Wilson, the founder of Ferimlab, proposed the idea of using high-energy protons for therapy [13]. He put the emphasis on the importance of the 'Bragg peak' because of which the maximum irradiation is placed inside the tumor while the healthy tissues are protected and preserved. This is considered as the beggining of hadron therapy [13].

Soon afterwards, in 1954, the Lawrence brothers and their team treated the very first patient with proton therapy in Berkeley [12]. The first patient treated with protons in the Europe was in Uppsala in Sweden in 1957 [12].

A large amount of research followed this scientific progress. Physicists experimented with a lot of different particles – ions (for medical uses) and found out the advantages that carbon and other ions possess.

The previously described discoveries (Figure 4) are not the only ones that lead to the discovery of hadron therapy, but they represent the main milestones. Recognition that ionization radiation can be used to control or kill cancer cells was revolutionary and enabled the birth of a completely new way of treatment – radiotherapy (RT) [13].

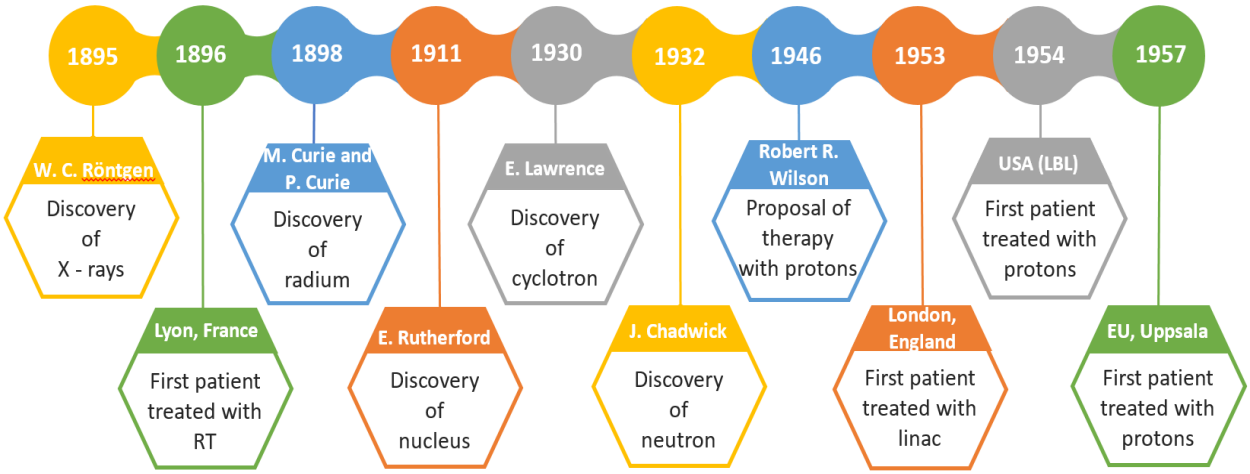

Figure 4: A chronological overview of important events that preceded and enabled the discovery of hadron therapy

X – rays

X-rays are part of the electromagnetic spectrum with frequencies from $3 \cdot 10^{16}$ to $3 \cdot 10^{19}$ Hz, or wavelengths from 0.1 to 10 nm [14]. Due to its high energy, this radiation is ionizing and is used in radiology as well as in crystallography to determine the structure of crystals. The application of X-rays is mostly based on the penetration of radiation through matter. As the atoms of a

substance are heavier, the stronger they absorb X-rays. Therefore, calcium in the bones absorbs X-rays better than carbon, oxygen and hydrogen in the muscles. This property is applied in diagnostics.

Electromagnetic radiation X and γ are more penetrating than α and β - particles but have less ionization ability [7]. When interacting with the electron shell, the incident electrons also cause deceleration, X – radiation which is a consequence of the action of the electric field of the nucleus on the electrons. This photon radiation has a continuous spectrum of energies that reaches the maximum energy of the incident electron [1,2].

X-rays produce a strong biological effect because they destroy the cells of the human body [15]. This is the basis of their healing effect. This radiation can cause the cells that cause the disease to break down and thus lead to healing [15]. However, excessive use of X-rays has a detrimental effect on healthy cells [15].

XRT

In order to increase the effect of ionizing radiation on tumors and reduce damage to healthy tissues, X-ray therapy uses methods based on radiobiological research and clinical experience, such as: radiation dose fractionation, use of radiosensitivity potentiators, application of biologically efficient radiation, combination of radiation and hyperthermia, air treatment in hyperbaric chambers with oxygen, etc [3].

X-ray radiotherapy has two equally important goals, which are to control the growth of the tumor and at the same time reduce the effect on (or protect) the surrounding healthy tissue. It is divided into EBRT (external radiotherapy) and brachytherapy [3]. In external radiotherapy, the radiation travels to the tumor from a device (linear accelerator), and in brachytherapy the radiation starts from a source that is introduced into the desired part of the body, a procedure in which radioactive material is placed inside the body near cancer cells [2]. Both techniques are currently used to treat tumors but brachytherapy is used only in specific cases.

This kind of radiotherapy uses a focused energy beam to damage cancer cells and at the same time have a minimal impact on healthy tissue [13]. It is a painless treatment that uses X-rays, emitted in a beam, which cannot be seen or felt [16]. Healthy cells have the ability to recover after irradiation, while cancer cells die after irradiation [17]. Due to genomic instability and errors in genetic control checkpoints, cancer cells avoid normal control of the cell cycle which allows damaged DNA to be passed on to daughter cells [17]. Dividing cells are especially radiosensitive and cancer cells divide more often which makes radiotherapy effective in killing cancer cells [17]. Cancer cells have reduced capacity to repair genomic lesions allowing DNA damage from other stages of the cell cycle to accumulate and be passed [17]. Contrary, healthy cells exposed to lower doses of ionizing radiation are capable of halting any ongoing replication and repairing the damage. If the damage is irreparable, appoptosis is being activated [17]. This is the concept that fractionated radiotherapy uses in order to allow normal cells to regenerate before additional doses are given [17].

Ionizing radiation acts by damaging the DNA of cancer cells leading to their death [18]. To spare normal tissue (such as the skin or organs through which radiation must pass to treat a tumor), the beam of radiation is directed from several different angles so that the beams of air intersect at the site of the tumor, causing it to be much higher absorbed dose than in surrounding healthy tissue [19].

As the tumor and surrounding normal structures are identified, small marks on the skin are marked on the patient [2]. Positioning the patient at this stage is crucial because the patient will have to be placed in an identical position during each treatment. If this is not the case and the patient is not in the same position during irradiation, negative effects can occur. Tumor response to X-ray therapy is also related to its size [2]. Due to complex radiobiology, very large tumors are less responsive to radiation than smaller tumors or microscopic diseases [3]. To overcome this, various strategies are used. The most common technique is surgery before radiation therapy [3]. Another method is to reduce the tumor with chemotherapy before radiotherapy [3]. The third commonly used technique is chemotherapy, due to increase in the sensitivity of cancer cells to chemotherapeutic drugs (such as Cisplatin, Nimorazole and Cetuximab) [3].

How cancer cells will react to radiation is dictated by their radiosensitivity [20]. Highly radiosensitive cancer cells are quickly killed by moderate doses of radiation. These include leukemia, most lymphomas (a primary tumor whose cells originate from lymphocytes, the immune system) and germ cell carcinoma [21]. Most epithelial cancers are only moderately radiosensitive and require a significantly higher radiation dose (60-70 Gy) to achieve a cure [22]. Some types of cancer are particularly radioresistant, so much higher doses are needed to achieve a significant killing effect than in normal clinical practice. Kidney cell cancer and melanoma are generally considered radioresistant, but X-ray therapy remains a palliative option for many patients with metastatic melanoma [23]. It is important to distinguish the radiosensitivity of a particular tumor (which is more of a laboratory value) from the curability of radiation in actual clinical practice. For example, although leukemia cells are highly radiosensitive, leukemia generally cannot be cured with this therapy because it spreads throughout the body [24].

Radiotherapy can be followed by certain side effects, usually caused by unavoidable damage to healthy cells during treatment. Side effects are mostly cumulative which means they can develop in the later stages of treatment [25]. They can be milder or stronger depending on the size and location of the tumor, the stage of the disease, the general health condition of the patient and the type of treatment being applied [25]. The two most common side effects of radiotherapy are irritation or damage to the skin on the part of the body being treated and fatigue [25]. Skin irritations may include dryness, itching, peeling, or flatulence [25]. Some patients may feel mild fatigue while some may feel severe exhaustion. Other side effects are usually related to the part of the body being treated, such as hair loss or dry throat when operating on the head and neck, or urinary problems when operating on the lower abdomen [25].

Thus, X-ray therapy can have a variety of side effects, such as skin thinning and sensitivity, hair loss, diarrhea, nausea, etc [25]. A very rare, worst form of side effect that radiotherapy can produce is the appearance of another cancer [9]. Although rare, there is a risk of developing secondary cancer.

There are strict procedures that reduce the risk of accidental overexposure to radiation therapy of patients. However, mistakes can happen occasionally. For example, the radiotherapy device

Therac-25 was responsible for at least six accidents between 1985 and 1987, where patients received a hundred times the prescribed dose and two people were killed directly due to radiation overdose. From 2005 to 2010, a Missouri hospital overdosed on 76 patients (most with brain cancer) over a five-year period because new radiation equipment was installed incorrectly [26]. Although medical errors are extremely rare, radiation oncologists, medical physicists, and other members of the radiation treatment team are working to eliminate them. Doctors and all professionals can learn from mistakes that have happened before and prevent them from happening again.

Doses used in XRT

The amount of radiation used in photon radiation therapy varies depending on the type and stage of cancer being treated. For curable cases, the typical dose for an epithelial tumor ranges from 60 to 80 Gy, while lymphomas are treated with a dose of 20 to 40 Gy [22].

Preventive doses are usually around 45-60 Gy in fractions of 1.8-2 Gy (for breast, head and neck cancer) [27]. Oncologists take many other factors into account when determining the dose, including whether the patient is receiving chemotherapy, the patient's general health, whether the radiation therapy is before or after surgery, and if so, the degree of success of the operation.

The parameters of the prescribed dose are determined during treatment planning [2]. Treatment planning is usually performed with the help of dedicated software [2]. The goal is to make a plan based on which the applied dose will destroy the cancer cells, and at the same time the dose to the surrounding healthy tissues will be reduced as much as possible in order to minimize side effects [2].

The total dose is fractionated for several important reasons. Fractionation gives normal cells the time they need to repair and recover, while tumor cells are unlikely to recover during that time. Also, fractionation allows tumor cells that were in the relatively radio - resistant phase during one treatment to move to the sensitive phase before the next fraction starts. Cells exhibit differential radiation sensitivity in the different phases of the cell cycle [28]. While they are in

mitosis, the cells are most sensitive to DNA damaging agents while cells in late S-phase (synthesis phase - the phase of the cell cycle in which DNA is replicated) are the most resistant [28]. Dose fractination allows redistribution of radioresistant S-phase tumor cells into more sensitive phase of the cell cycle which results in therapeutic benefit for slowly cycling normal cells [28].

There is no single and universal factional regime. In North America, Australia, and Europe, the typical fractionation schedule for adults is 1.8 to 2 Gy per day, five days a week, while for children, the typical dose per fraction is 1.5 to 1.8 Gy per day [22]. Sometimes two fractions are used daily towards the end of treatment [22]. Thus, there is no universal way of treatment.

One fractionation schedule that is increasingly used and is still being studied is hypofraction. This is a radiation treatment in which the total radiation dose is divided into large doses. Hypofractionated radiotherapy is the delivery of doses larger than 2 Gy of radiotherapy and presents potential strategy for improving dose intensity [29]. Typical doses vary significantly depending on the type of cancer, from 2.2 Gy per fraction to 20 Gy per fraction. This approach enabled decreasing radiotherapy volumes and because of that became more feasible, which allow for more conformal radiotherapy delivery and limit the dose delivered to normal tissue [29]. Higher physical or biologic dose is associated with better local control and with better survival, but currently, 60 Gy to 66 Gy in daily fractions of 2 Gy remains the most common schedule [29].

Hadrons

Hadrons are subatomic particles made up of quarks connected by a strong nuclear force [2]. They are divided into baryons and mesons [30]. Baryons are hadrons composed of three quarks and are characterized by a half-whole spin (protons, neutrons and others), while mesons consist of a quark and an antiquark, so their spin is an integer (pion, kaon and others) [30]. Only protons are stable, while neutrons are stable within the atomic nucleus (free neutrons have a half-life of about 880 seconds) [7]. All other hadrons are unstable [7].

Hadrons have a slight lateral scattering [7]. The loss of energy per unit of path (LET) increases with the deceleration of the hadron, and the range of the particles is directly proportional to the energy [7].

Unlike X - radiation, hadron radiation during energy loss through the body shows a Brag peak which speaks of delivering the maximum dose of radiation in or near the tumor, while damage to the surrounding normal tissues is minimized [31].

Hadron therapy

Hadron therapy is a therapy for the treatment of cancer using the radiation beam of hadrons - protons, neutrons and ions. Photons demonstrate a high initial dose that declines with penetration into the depth of the absorbing material of the body [32]. In contrast, the proton and carbon particle beams demonstrate superficial low initial energy deposition that is maximally absorbed at depth in a Bragg peak of energy absorption where the primary ions dump their energies as they stop with significantly reduced energy deposited beyond the stopping peaks (Figure 5) [12].

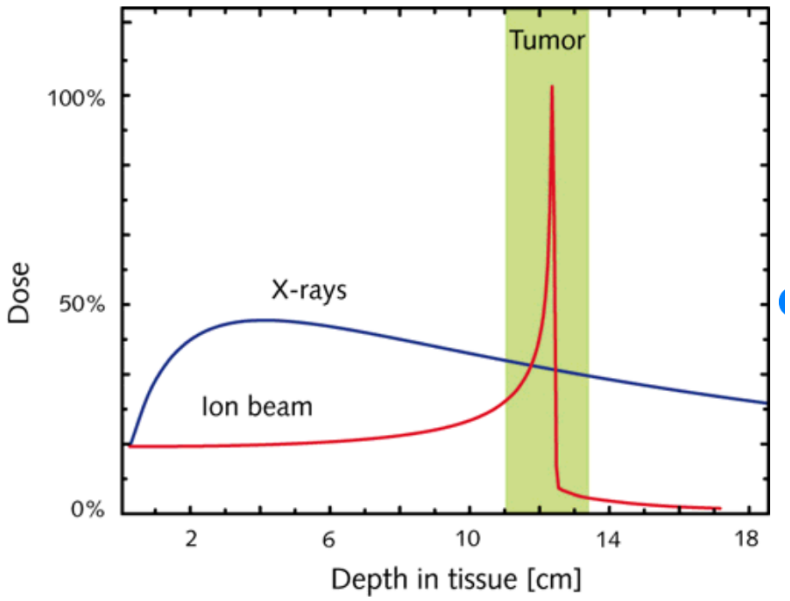

Figure 5: Dose distribution in the tissue for
beam of X-rays (blue line) and ions (red line) [33]

The idea of using an accelerated proton beam to treat cancer was proposed by the physicist and founder of Fermilab, Robert Wilson, in 1946. Protons and light ions have unique physical properties. They penetrate with minimal lateral diffusion, and most of the energy is released at the end of the range (in the so-called Bragg peak) without detrimental effect on healthy tissues in the environment. In addition, they can be directed in narrow beams, which allows great precision when it comes to radiation dose distribution and cancer-consistent treatment [34].

Advances in accelerator technology, along with improved medical imaging and software, made proton therapy a viable option for routine medical applications in the 1970s [12]. However, it was not until the 1990s that patients began to be treated in a clinical setting [12]. When proton radiation is observed, they have almost no "tail" behind Brag's top. Once a proton interacts, it will generally no longer interact, while this is not the case when ions are involved.

The main advantage of proton therapy over other types of therapy is that the dose of protons is distributed over a narrow range, resulting in a minimal dose of radiation in healthy nearby tissues [13]. Therefore, protons can be used to treat tumors that are close to a sensitive and vital organ, such as the eyes, brain, spinal cord, kidneys, and reproductive organs [12].

On the other hand, ions have a sharper Bragg peak and thus a lower total dose for healthy tissue in the environment. Carbon ions have less lateral scattering than protons, which can provide better protection for normal tissue. Also, carbon ions have a higher linear energy transfer (LET) compared to protons and photons which directly affects the higher value of relative biological efficiency (RBE) [32]. The linear energy transfer of the beam of carbon ions is constantly increasing as they pass through the body, reaching a maximum in the region of Bragg peak. This property is an obvious advantage in the treatment of deep-seated tumors. Carbon ions are also more effective in hypoxic tumors that are resistant to both photon and proton radiation [35]. Weaker acute or late toxicity of carbon ions compared to protons leads to improved quality of life during and after cancer treatment.

Beams of protons used for therapy have maximum energies of 200 – 250 MeV and range of 25 – 35 cm in water. When it comes to carbon ions, the maximum energy used for medical purposes is 400 – 450 MeV [12].

Protons have similar biological and clinical effects as X-rays thanks to the fact that they are both rarely ionizing radiations. For the same probability of cure while treating with protons, doses in the nearby tissues are much more less than while using X-rays. That is the reason why radtiotherapy with protons is more preferred for children in comparison with radiotherapy with X-rays. When six electrons are removed from the carbon atom, a carbon ion is being obtained. Carbon ions present a completely different type of a radiation because despite penetrating to the same depth in the patient's body as protons do, in a traversed double helix carbon ions produce twenty times more ionization. Even thought carbon ions behave as sparsely ionizing radiations (just like X-rays and protons) when they enter the tissue, by slowing down, at the last 3-4 centimeteres of their path they become densely ionizing why they produce clustered DNA damages that the cell can not repair by itself. More concentrated dose inside the tumor is not the only advantage of carbon ions, but also that their dose is much more effective in comparison with X-rays and protons when it comes to controlling radioresistant tumors [9].

Construction needed for HT

Accelerators are needed to realize any type of radiotherapy.

When the radiotherapy with X – rays is being applied, linear accelerators ('linacs') are needed. Particles pass the accelerator only once, they acquire energy moving on the linear path and the final energy is limitted by length of accelerator [36]. Mostly 'linacs' used for radiotherapy (Figure 6) are 1-metre long copper tubes with a diameter of about 10 centimeteres [9]. The reason why this kind of radiotherapy is more presented in the world is precisely because of the simplicity of the apparatus required for its application. Accelerators needed for proton and ion therapy are much larger, more complex and more expensive in comparison to those for therapy with X – rays [9].

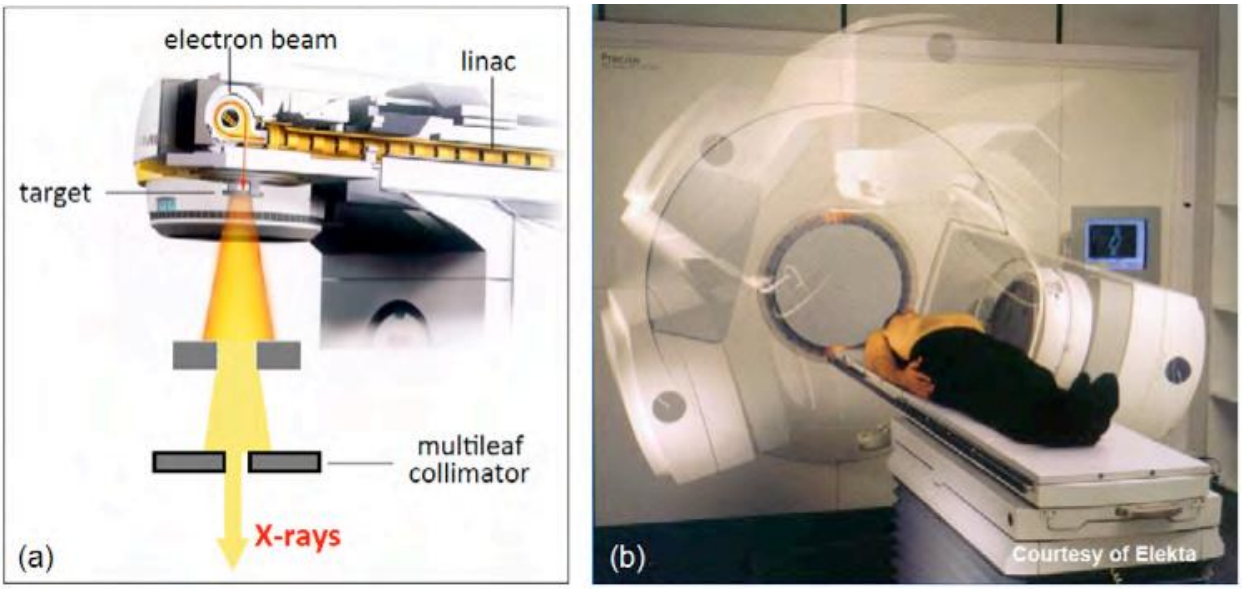

Figure 6: The linac (a), the magnets that deflect the electron beam by 270°, the target and the collimators are mounted on a "gantry" that rotates around the patient (b) [9]

The linear accelerator used for XRT is small and light. It is mounted on a gantry that rotates around the patient table. Because of this the beam produced when accelerated electrons hit heavy metal target can be directed towards the solid tumor from any direction.

Since the proton and carbon ions are 2 000 and 24 000 times heavier, respectively, than an electron has to be accelerated to about 200 MeV for protons, and 5 000 MeV when it comes to carbon ions, instead of 10 MeV, to treat 30-centimetre deep tumor [9].

Especially, for particle therapy cyclotrons and synchrotrons are commonly used. For treatments with protons, it is possible to work with synchrotrons or cyclotrons, but also with synchro-cyclotrons [12].

A cyclotron (Figure 7) is a type of circular accelerator invetned by Ernest Lawrence [2]. It accelerates charged particles outwards from the center of a flat cylindrical vacuum chamber along a spiral path [2]. The particles are held to a spiral trajectory by a static magnetic field and accelerated by a rapidly varying (radio frequency) electric field. For this invention, the first 'cyclic' accelerator, Lawrence was awarded the Nobel Prize in Physics [2].

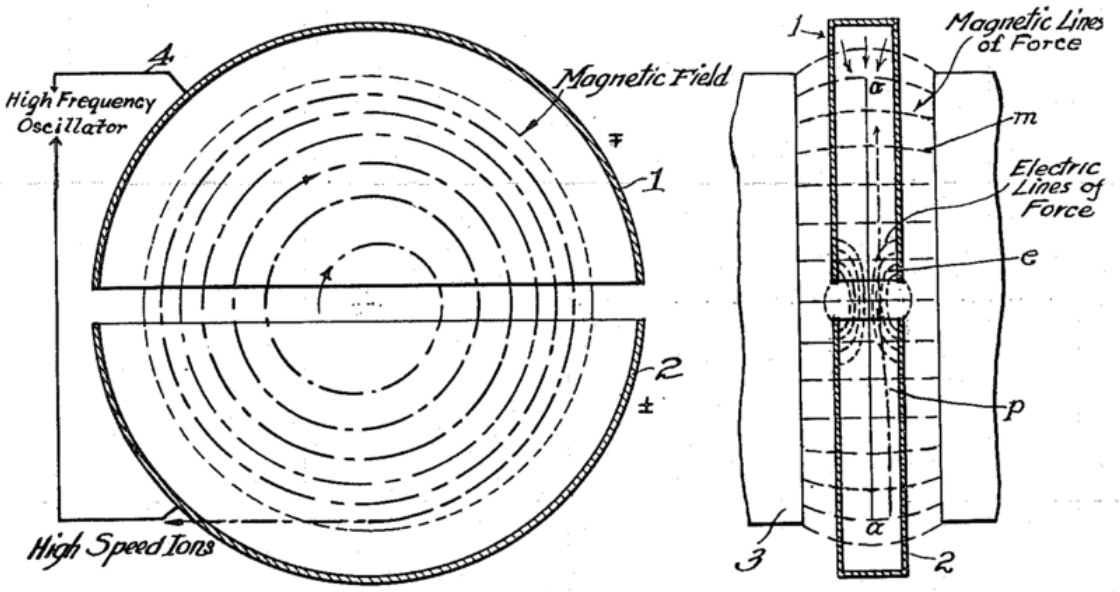

Figure 7: Diagram of cyclotron operation from Lawrence's 1934 patent [37]

A particle source is placed in the middle. Acceleration gap is connected to the RF source between two D-shaped magnets (Dees). The "D" shaped electrodes are enclosed in a flat vacuum chamber, which is installed in a narrow gap between the two poles of a large magnet. Because of that, dees are in the constant vertical magnetic field that is perpendicular to the electrode plane. The magnetic field causes the particles' path to bend in a circle due to the Lorentz force perpendicular to their direction of motion. A radio frequency (RF) alternating voltage of a several thousands volts is applied between the “Dees”. It creates an oscillating electric field in the gap that accelerates the particles. The radius of particle trajectory becomes larger as the energy increases. In this case RF field has constant frequency and magnetic field is constant.

Althought particles with higher energy are circulating at a larger radius in the cyclotron all particles have the same revolution frequency. In order to reduce the size of the cyclotron, a stronger magnetic field is needed. Cyclotrons used for proton therapy are single-magnet machines with a diameter of 5 meters and a weight of about 200 tons [12].

A synchrotron is particular type of cyclic particle accelerator. Unlike the cyclotron, in the synchrotron particle beam travels around a fixed closed-loop path (Figure 8). The magnetic beam bends the particle beam into its closed path and increases with time, while the kinetic energy of the particles is also increasing.

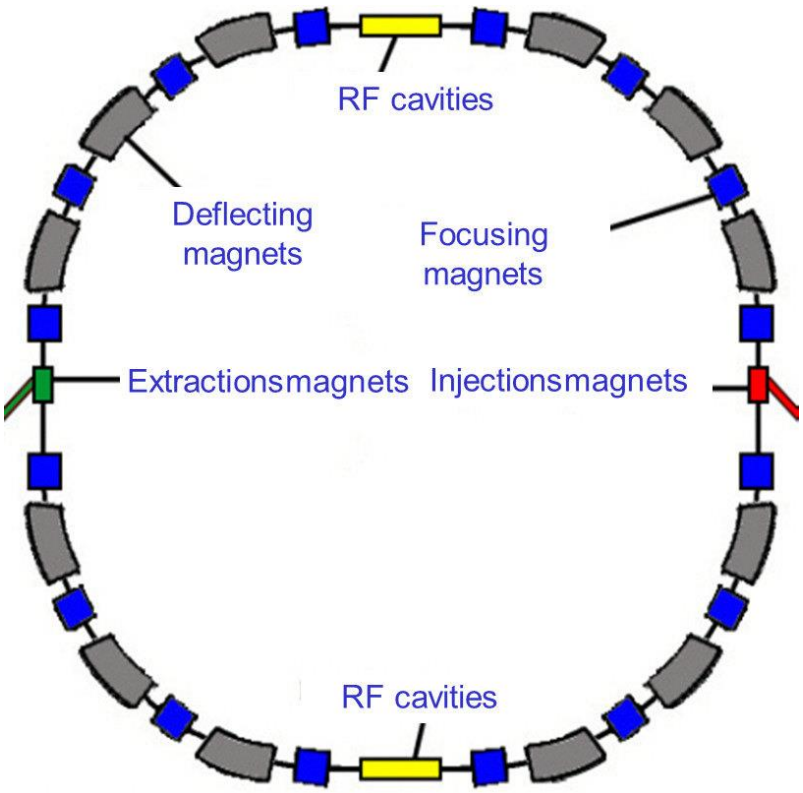

Figure 8: Components of the cyclotrons [38]

Synchrotrons are composed of a preaccelerator which injects protons into a ring of 4-8 bending magnets with quadrupole and sextupole in between them [12]. One circular orbit is defined and magnetic field vary while the energy rises [12]. RF frequency is constant [12]. After being accelerated in the synchrotron, particles are mostly extracted to next accelerator or to some target in order to do some experiments and research [12].

For protons, the ring has a typical diameter of about 6 – 8 meters and for the ions around 25 meters. The preaccelerator is a seperate 6-10 meters long chain of an ion source followed by accelerators – usually a radio frequency quadrupole (RFQ) accelerator followed by a linac [12].

The gantry of an external beam radiotherapy is a mechanical structure that supports a beam transport and can rotate around the patient. Strong and large magnets are needed when hadron therapy is being applied for beam transport [12]. For protons the gantries have a diameter of up to 12 meters and mass of 100 – 200 tons. The gantry used for carbon therapy at HIT (Heidelberg Ion Therapy) has a diameter of 13 meters and a mass of 600 tons [12].

Doses applied in HT

The linear energy transfer of hadrons increases with the deceleration of hadrons [7]. Hadrons are characterized by low lateral scattering, and their range is directly proportional to energy [7]. When the dose distribution using hadron is observed, it has a slow increase - plateau, then a sudden jump and a sharp maximum almost at the very end of the range (Bragg peak) and a sharp drop at the end of the range (Figure 5) [13].

If the linear energy transfer (LET) is small for small doses, damage will occur to the DNA strand, followed by its recovery [39]. Conversely, if the LET value is high, more damage occurs to the DNA strand after which there is no recovery [39].

If the LET value is high, the efficiency of killing cancer cells will be higher, but also collateral damage, there will be acute and delayed effects in healthy tissue cells, with the risk of developing another cancer [17].

Modulation of hadron energy or hadron's range is achieved by gradually reducing the initial hadron energy, which leads to the superposition of a series of monoenergetic hadron beams of close energies [40]. In this way, as the energy decreases, the position of the Bragg peak moves towards the source of the beam (Figure 9) [40]. Bragg peak and extended, so called spread out Bragg peak (SOBP) have a higher LET than the bundle at the entrance to the tissue [40].

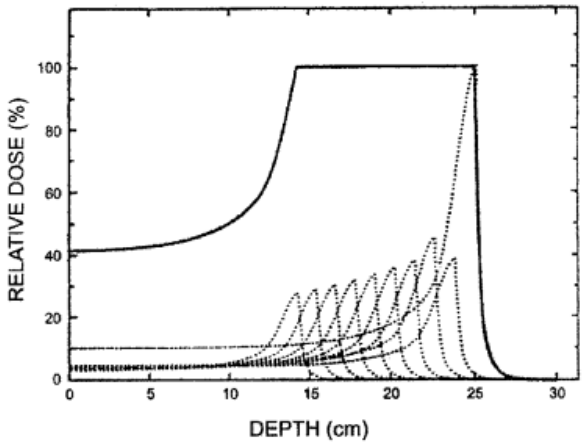

Figure 9: Modulation of hadron energy or range due to a slight increase in the input radiation dose [41]

Precisely directing the radiation dose into the tumor volume and thus sparing the adjacent healthy tissue are the essential advantages of hadrons over conventional radiation [13]. Figure 10 shows the advantage of using hadron therapy during the treatment. The dependence of the effective relative dose of the radiation range in the tissue for different types of radiation is shown. For the needs of treatment, the prescribed doses, the treatment plan is best suited to carbon ions and protons of modulated energy in the presence of extended Brag peak so called spread – out Bragg peak (SOBP).

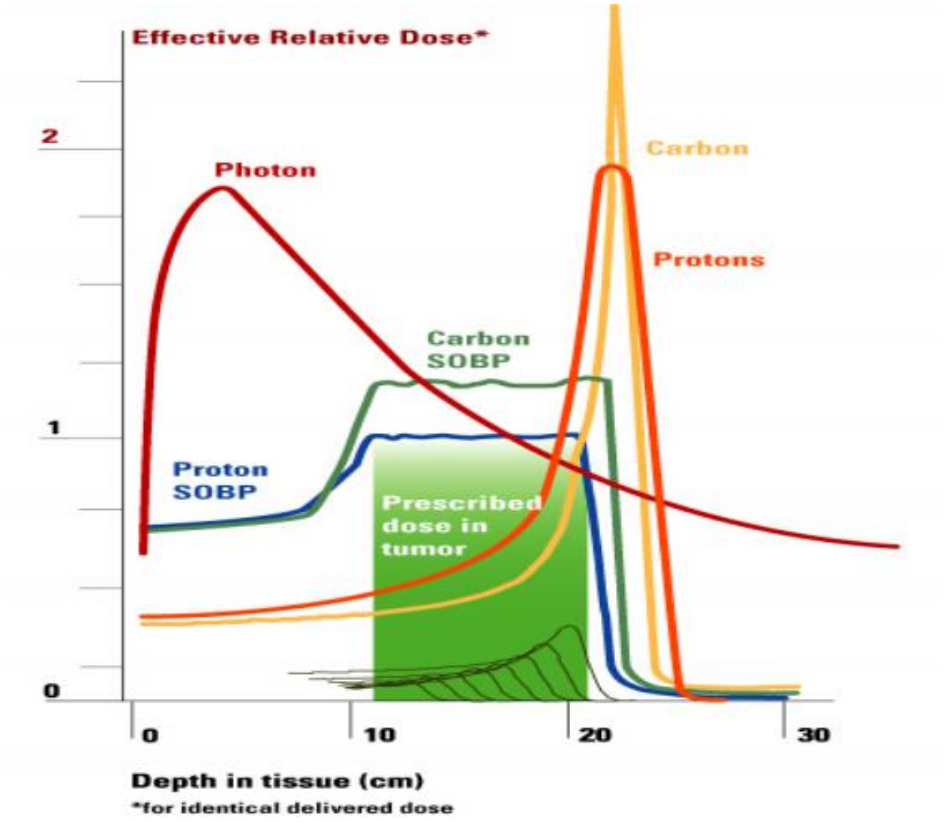

Figure 10: Dependence of (effective relative) dose of radiation range in tissue for different types of radiation [42]

Statistics

About 45-50% of all cancer can be treated by surgery and/or radiation therapy.

Cancer is the second leading cause of death globally and was responsible for 9.6 million deaths in 2018 [43]. Approximately 1 in 6 deaths is due to cancer. Only in 2018, there were 17 million newly diagnosed people with cancer, of which 33% of cases were related to smoking and the consequences of tobacco consumption [43]. The most common cancers are:

- lungs;
- breast;
- colon;
- prostate;
- skin and
- stomach.

It is projected that by 2040, there will be 27.5 million new patients each year facing the disease [43].

In 2015, 16 200 patients were treated with proton therapy. It is estimated that this number will rise to 300 000 in 2030 [43].

In the period from 1954 to 2019, 260 150 patients were treated with hadron therapy worldwide [44]. As expected, the largest proportion of patients were treated with proton therapy (222 425), and a much smaller number of patients were treated with carbon ions, followed by helium ions, pawns, and other ions [44].

Currently, around 110 hadron therapy centers are active worldwide (Figure 11), and the number of clinics is increasing rapidly [44]. Around 30 of these facilities are located in Europe (Figure 12).

Figure 11: Particle therapy facilities in the world (red flags mark the proton facilities and blue ones mark facilities operating with carbon ions) [44]

Figure 12: Particle therapy facilities in the Europe (red flags mark the proton facilities and blue ones mark facilities operating with carbon ions) [44]

From the figure it is clear that the Southeastern Europe, more precisely, the Balkan Penninsula, which encompasses ten countries, does not have any particle therapy facility for this kind of treatment. It is easy to understand why a hadron therapy facility is needed in this region.

Montenegro and SEEIST

Montenegro is a country in Southeastern Europe (Figure 13). It is located on the Adriatic Sea and is a part of the Balkans, sharing borders with Serbia to the northeast, Bosnia and Herzegovina to the north and west, Kosovo to the east, Albania to the southeast, and the Adriatic Sea and Croatia to the southwest. Montenegro's territory is equal to 13 812 square kilometers, and in previous year (2020) in Montenegro lived 621 720 citizens [45].

Figure 13: Position of Montenegro in the Balkan Peninsula [46]

The South East European International Institute for Sustainable Technologies (SEEIIST) was proposed in late 2016 by Prof. Herwig Schopper and received first official political support by the Government of Montenegro in March 2017 [47]. Thanks to Dr Sanja Damjanović, Minister of Science of Montenegro at the time, this initiative was brought to the political level for the countries of South – Eastern Europe (SEE) [9]. After the signing of the Declaration of Intent in October 2017 at CERN, the Initiative was transformed into a regional project gathering: Republic of Albania, Bosnia and Herzegovina, Republic of Bulgaria, Kosovo, Republic of North Macedonia, Montenegro, Republic of Serbia and Republic of Slovenia [9].

In spring 2017, an Editorial Committee was established whose goal was to prepare the conceptual design report of a 'Facility for Tumour Hadron Therapy and Biomedical Research' (HTR) [9]. In parallel, similar committee was organized for "4th Generation Synchrotron Light Source for Science and Technology" (SRL) [9]. According to the plan, about 500 patients each year will be treated [9]. At the same time, half of the beam produced will be used for cancer research with wide range of different ions, not only protons and C-ions that are currently used clinically [9]. This project has a capacity for about 1000 researches, which brings positive changes in all aspects for the SEE region [48].

In 2018 Europe had a population of 751 million of citizens, of which 42 million live in the SEE region [50]. In 2018 in Europe were 2 300 000 new cancer patients, while in the SEE region around 222 000 from which 1000 were children younger than 14 [43]. During this year in the SEE region the most frequent cancer was the lung cancer (14.3%), colorectum cancer (12.1%) and breast cancer (11.5%) [49].

Analyzing these data for Europe and SEE region, the comparison can be made. In Europe 0.29% from the whole population got cancer, while in the SEE region (in the same year, 2018) 0.53% of the whole population got cancer. These statistics are worrying since in this part of Europe there is much more poverty and the standard of life is much lower in comparison with the rest of Europe.

Conclusion

The use of ionizing radiation in the treatment of tumors is based on the possibility of killing of the tumor. At the same time, there is a reversible damage to the cell population of normal tissues, since irradiation of the tissues surrounding the tumor cannot be avoided.

Despite that X-ray therapy is a fairly painless treatment and has already helped and cured a huge number of people, it produces plenty of side effects and therefore ways of optimising X-ray therapy or looking at more targetted RT is beginning to be considered. Even though protons have almost the same biological effects as X-rays, they deliver energy more precisely to the tumor - site while sparing surrounding tissues more effectively. Because of that, side effects are reduced in comparison to other types of radiotherapy which represents the most important advantage of hadron therapy. Thanks to this property of the Bragg peak the hadron therapy treatment is realized with minimal effect to the healthy tissue/organ.

Dose distribution due to the existence of Bragg peak (and its modulation) is responsible for the development of hadron therapy. Due to the reduction of the dose and the volume of normal tissues that are irradiated during hadron therapy, the patient's tolerance to radiation is increased, which enables the distribution of a higher dose hence more effective killing of the tumor. By delivering a higher dose of radiation during particle therapy, in combination with increased hadron precision, the impact on normal tissues is avoided, toxicity is reduced and local cancer control is better.

There is no single way to treat cancer. Hadron therapy has advantages over other radiotherapy treatments. Providing more people with treatment with this therapy is a big step forward in the fight against cancer, given that the direction of hadron radiation is very precise, side effects are minimized and the probability of developing secondary cancer is lower.

Data statistics presented for SEE region is not very extensive but it is sufficient to realize that even though this region is relatively small it has a significant rate of cancer incidence. When comparing data from the SEE region with rest of the Europe it shows a great need for a hadron therapy center in this region.

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