Particle Accelerators and Gamma-therapeutic Devices - an Effective Tool for Cancer Treatment

VLADIMIR KRASILNIKOV
Department of Nanomaterials
Belgorod State University
St. Pobeda 85, Belgorod, 308015
RUSSIA
EDUARD KUPLENNIKOV
Department of Nuclear Physics
National Scientific Center "KIPT"
St. Akademicheskaya 1, Kharkov, 61108
UKRAINE

Abstract: - The review is based on the analysis of the state and the concept of modernization of world radiation oncology. The material contains brief information about the reasons for the use of radiation therapy for the treatment of cancer foci; active sources of particles; achieved results of therapy, etc. The role of accelerator technology, innovative related equipment and nuclear physics methods for the treatment of oncological diseases is described. The main characteristics of linear electron accelerators with the energy E_e = 6 MeV, the parameters of multifunctional installations with E_e = (4 - 25) MeV generating several photon and electron beams and accelerators of protons and carbon ions are given. It is shown that to date, the treatment of malignant foci with beams of protons and carbon ions has surpassed all existing methods in terms of efficiency.

Key-Words: - particle accelerators, ionizing radiation, malignant neoplasms, (e,γ)-treatment, hadron therapy.)

Received: April 12, 2022. Revised: November 9, 2022. Accepted: December7, 2022. Published: December 31, 2022.

1 Introduction

Over the past hundred years, cancer incidence and mortality in the world has moved from 10th to 2nd place, second only to diseases of the cardiovascular system. Specialists of the International Agency for the Study of Malignant Tumors have reviewed the situation with the disease in 185 countries of the world in recent years [1]. Data were analyzed only in those regions where medical care is at a sufficiently high level and it is possible to make at least rough estimates. The forecast of scientists is disappointing. According to oncologists, by 2040 the number of annual cases of malignant localizations will increase by 47% and reach 28.4 million. The research results show that the number of diseases is increasing from year to year and so far, no changes in this trend are visible in the near future. Therefore, the search for the causes of the appearance of malignant tumors, promising technologies for diagnosis and treatment continues.

The emergence and development of oncological localizations in initially healthy tissues have not been sufficiently studied. It is only known that the growth of cancerous foci in peacetime is observed primarily in industrial centers and regions with unfavorable environmental conditions; when people are employed at enterprises with the impact of harmful production factors, with works related to the creation and operation of nuclear materials, etc. The situation becomes especially critical in places of local and large-scale radiation accidents. The most important condition for the successful treatment of cancerous tumors is their early detection. Tumors of the 1st and 2nd stages of growth are most often painless, there are no pronounced symptoms.

Therefore, the primary task of physicians, aimed at reducing the mortality and disability of potential cancer carriers, is to regularly conduct mass preventive examinations of the population as is done in some countries. So, in the United States, on average, 40 people per thousand of the population undergo diagnostic radioisotope examinations per year, in Japan - 25, in Austria - 19, in Russia - 7. In

Russia, almost 60% of diseases are first registered in the third or fourth stages of the disease [2].

Currently, in practical medicine, the main methods of treating various forms of tumors and metastases are: surgery ~ 49%, radiation therapy (RT) with ionizing radiation ~ 40% and chemotherapy ~ 11% [3]. RT of cancer foci is carried out by exposing the tumor to various types of radiation (α-particles, β-particles, electrons, protons, neutrons, pi-mesons, heavy ions, X-rays and γ-radiation). This direction of treatment, the so-called radiotherapy (RT), has become widespread in all developed countries. Modern technologies using RT have proven to be one of the most advanced ways to combat the disease.

Paying tribute to the past, we note that active research work on the use of radiation in science, industry, and especially in medicine [4] began almost immediately after the discovery of electromagnetic (X-ray) radiation with an energy of ~ (30 – 250) keV by V. Roentgen in 1895, and phenomena of radioactivity (spontaneous emission of uranium salts) by A. Becquerel in 1896. Later, both types of radiation were called ionizing radiation (IR). During the first experiments on the use of RT for the treatment of various diseases, including malignant tumors, it was noticed that severe burns and ulcers occurred on the skin of the testers with sufficiently long work and the healing process lasted in several months. Moreover, it turned out that radiation not only affects the skin, but can also cause radiation damage to internal organs and tissues, or even lead to the death of living organisms.

Further medical and biological experiments showed that the ability of photons and elementary particles or atomic nuclei to ionize a substance can result to the observed consequences, i.e., strip an electron (electrons) from neutral atoms or molecules, as well as capture electrons, creating negative ions in the process of interaction. It has been proven that the cause of damage of organs and tissues due to ionization is the cessation of cell division mainly due to: a) single or double strand breaks of DNA helices; b) ionization damage to intracellular membranes and other important cell structures; c) radiolysis of water [5,6] which in biological objects is ~ (60 - 70) %. The latter process leads to the formation of chemically highly active free radicals and peroxides interacting with protein molecules, enzymes and other structural elements of living tissue that results in disruption of the normal functioning of cells.

As shown by the experiments that were started by the French physicians E. Besnier and A. Danlos in 1901, the most sensitive to radium radiation, as well as to X-rays, are young, rapidly growing, multiplying cells. Irradiation causes them serious damage up to complete destruction and death. Thus, it became possible in principle to use ionizing radiation to destroy malignant tumors consisting of just such cells.

The purpose of the work is to acquaint the reader with the development of charged particle accelerator technology for RT of neoplasms. Also, to show that modern accelerators, high-tech auxiliary equipment and nuclear physics treatment technologies have the qualities and technical capabilities of successful treatment of a wide range of cancerous localizations.

2 Progress of accelerating technology

Researchers at the turn of the 19th - 20th centuries worked, relying mainly on knowledge related to chemical elements, and therefore much of the IR phenomenon remained incomprehensible. Only in the 1930s, scientists began actively to study the phenomenon of IR and realize the prospects that promise its application in science, technology, and medicine. It became clear that for the further scientific and practical development of this direction, sources are needed that are capable of generating streams of charged particles of different energies and intensities in particular. The number of accelerators of various modifications and directions began to grow rapidly [7]. In the late twenties - early thirties of the last century, the following were developed and launched: the Wideröe linear accelerator (1928), the cascade accelerator (1929), the Van de Graaff electrostatic accelerator (1931), the proton cyclotron (1931). In 1937, a linear electron accelerator (LEA) with an energy of ≤ 1 MeV was put into operation in London which was first used to treat oncological localizations of various nature. In the fifties, e-accelerators competed with γ- therapeutic devices using radioactive nuclides ^{226}Ra, ^{137}Cs and ^{60}Co as a radiation source. In the early seventies, more than 300 accelerators of various types: 157 betatrons, 118 LEAs, 22 Van de Graaff accelerators and 9 resonant transformers were already operating in medicine. In general, out of ~ 40 thousand accelerators operating in the world in 2015, about 25 thousand worked in industry, about 1200 units in fundamental science, and about 35% did in medicine. The world leadership in the number of medical accelerators was held by the USA 36.1%, EU countries 26.8%, Japan 7.9%, China 9.4%, Russia 1.3%, and other states 18.5%. Manufacturers planned to increase the number of medical units to 21,000 units [7] in 2020. As an example, Fig. 1 shows a typical view of a modern radiotherapy LEA for RT [8].

Fig. 1. Ellus-6M [8]

In the eighties, mass production of LEA for RT was begun taking into account the requirements of practical medicine. They began to crowd out other types of sources. Only the companies Varian, Elekta, IBA, Siemens, Philips increased the annual production of installations from 700 to 1000. All accelerators have the qualities and technical capabilities to carry out treatment with the least negative impact on surrounding tissues, maximum comfort for the patient and effective treatment of a wide range of cancerous locations. The company's products are successfully operating in 117 countries. In recent decades, public and private specialized medical institutions in different countries have been actively purchasing therapeutic accelerators and auxiliary equipment from well-known companies. The range of accelerating devices offered on the market is distinguished by the maximum electron beam energy, intensity, radiation dose rate, main directions of therapy, etc. An additional attraction for potential customers is that the accelerators are supplied with ready-made diagnostic, therapeutic, radiological equipment; medico-physical technologies for radiation treatment planning; clinical dosimetry; guarantee of quality and radiation safety, etc.As for γ-therapeutic devices using radioactive sources, their number in the leading countries, according to the IAEA, decreased to 2046 (the sum of γ-devices of the first 15 countries with the largest number of them) in 2019. In the last century, the number of such devices reached tens of thousands [6] in the world, not counting the X-ray machines numbered by several million [7]. To a large extent, this was facilitated by the mass production of LEA which could successfully replace obsolete γ-devices in many cases. However, LEA cannot yet completely replace these γ-installations since modern devices have changed a lot structurally and outwardly. They are automated, computerized and able to effectively treat a certain class of malignant tumors. Due to the relatively high photon energy and specific activity, the distance from the source to the patient's body can vary from 80 cm or more. The head of the device rotates in a plane around the axis making it possible to irradiate the tumor at different angles thereby increasing the sparing effect for nearby organs. While revolving around the patient, the source remains "pointed" at the pathological formation. The therapy table on which the patient is located has three degrees of freedom allowing the patient to be positioned in the beam field of γ-installation using radioactive cobalt ^{60}Co. All of this allows us to solve extraordinary medical problems. As an example, let us cite the Gamma Knife (Cyber-knife) stereotaxic surgical system [6] which literally burst into practical medicine quite recently.

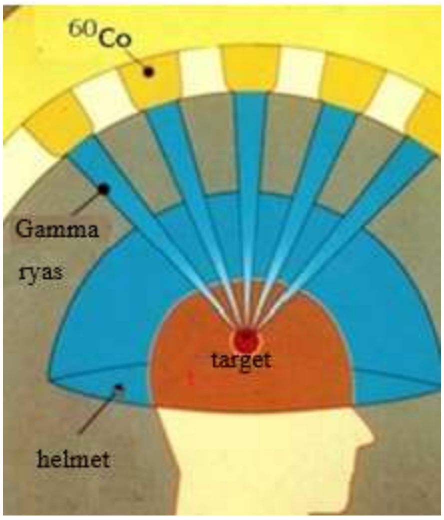

Fig. 2. Radiation with Gamma Knife [6]

The concept of the method was proposed in 1951 and finally implemented in 1968. The essence of surgery lies in the fact that γ radiation from about two hundred of tiny ^{60}Co γ - sources of high specific activity is focused on the tumor from the outside with collimators (see Fig. 2) [6]. Pointing accuracy is 0.3 mm. A high concentration of energy at the intersection of the beams (dose up to 10 Gy) destroys cancer cells and adjacent healthy tissues receive minimal radiation exposure. "Gamma Knife" allows you to treat vascular neoplasms, brain tumors including metastases without surgery and weeks of brain irradiation. In many cases, one treatment session is sufficient. So far, the application of the method is limited by the size of the cancerous tumor measured by a size ≤ 3 cm. In 2019, there were ~ 314 such systems in the world.

Initially a significant role was played by therapeutic LEAs with an energy of $E_e \leq 6$ MeV in the successful treatment of oncological localizations. The use of low-energy installations was beneficial not only in terms of physical and technical characteristics, but also from an economic point of view which is extremely important in conditions of clinics that did not have sufficient funding. Thus, LEA with $E_e \leq 6$ MeV is a kind of compromise between the energy, the efficiency of treating a certain class of tumors, the cost of the accelerator and related equipment. And nowadays, many specialized firms are engaged in the development and production of more advanced LEAs with a maximum energy of 6 MeV. There are developments of similar installations in the Russian Federation. So, the ELLUS-6M automated radiotherapy complex was developed and put into operation at NIIEFA, St. Petersburg [8]. Since the 1980s, NIIEFA has been producing LEA SL-75-5-MT under license from PHILIPS [9]. To date, ~ 60 copies have been released. The main operational characteristics of two foreign accelerators of the latest generation with a maximum energy of 6 MeV are described below. These are the Clinac 600C radiotherapy LEA and the Cyber-Knife radiosurgical complex.

Clinac 600C. Maximum energy is 6 MeV, manufactured by Varian (USA). Dimensions ~ 272x127x269 cm, weight ~ 6.7 t, dose rate 250 IU/min (1 IU = 10^{-2} Gy) for energy 4 MV and 400 IU/min for 6 MeV. Possible therapeutic procedures: photon radiotherapy, including "Photon-arc Therapy", "3D-CRT", "IMRT", full body irradiation. The accelerator is equipped with Portal Vision, Portal Dosimetry, Portal Imagine systems. There is a 120-leaf collimator for the formation of static and dynamic fields of complex shape. The deviation of the beam center from the isocenter during rotation is less than ± 1 mm. The system is mounted on a turntable rotating around a horizontal axis in the range of ± 180°.

Cyber-knife - radiosurgical complex. The first operation was carried out with its use in 1999. The setup consists of a compact LEA with a photon energy of 4 or 6 MeV and a mobile robotic manipulator with 6 degrees of freedom for RT at an energy of 6 MeV. The unit allows one session to irradiate the tumor and many metastases from 1200 possible directions. The accelerator generates a photon beam on a target, including one of an asymmetric shape, regardless of its position in the body, with an accuracy of 0.5 mm. In this case, the edge of the tumor practically coincides with the irradiated area. Treatment is carried out during one session. The installation allows irradiating a large number of malignant foci in different parts of the human body. Currently, ~ 326 robotic systems are operating in the world [6] (153 of them in the USA, 9 in Russia).

Science and practice in this segment of medicine has shown that bremsstrahlung energies of more than 6 MeV are required for the treatment of many forms of cancer. The list of diseases that can be treated by high-energy beams is noticeably wider than one does by low-energy beams. There is a higher quality of therapy. It turns out, for example, that the likelihood of recurrence of prostate cancer decreases with increasing radiation energy. In the range (8 - 20) MeV, the probability of recurrence is constant and equal to ~ 10% (at an energy of 6 MeV, the probability is ~ 18%). The survival factor of patients treated with high-energy beams is (2–4) times higher than when exposed to kilovoltage X-rays [10]. These and other similar results encourage the use of high-energy photons for therapy. At the same time, such installations have a more complex design, large dimensions and weight, require increased radiation protection, are much more expensive and require appropriately qualified personnel. Despite the "shortcomings" described above, specialized companies develop and create multi-profile facilities with Ee = (4 - 25) MeV which have several photon and electron beams. They are capable of operating both with a current of up to 100 μA for the formation of bremsstrahlung photons and with a low intensity current of up to 500 nA for direct electron irradiation (about 10% of patients) [11]. To date, in medical practice, the main tool for RT of cancerous tumors is the beams of bremsstrahlung photons of the LEA. At the same time, more than 97% of LEAs have an energy of (4 – 25) MeV.

Due to the large number and variety of multifunctional models with several beams only a small part of the installations is presented below for review. As an example, innovative models of Mobetron and Novak7 accelerators [6, 7], as well as multi-profile LUEs with several electron and photon beams, were chosen. The latest systems such as SL-20, Primus and Clinac-2100C [9] are used in the clinical oncology of the Russian Federation, as well as Elekta Synergy is used in Ukraine. The presented samples are the developments of the latest generation of well-known companies.

Mobetron. The main task of the accelerator is to destroy the tumor cells remaining in the tissue after a surgical operation, and its bed is irradiated with an electron beam once. That’s what this complex is used to generate electrons in modern clinics. It can work directly in the operating room without special protection and does not provide for special requirements for the equipment of the room. This procedure is due to the fact that there is a possibility of infection of the wound during the transportation of the patient from the operating room to the experimental room of the traditional accelerator and back. The installation consists of an accelerator, a power supply modulator and a control panel. The maximum dimensions are 250 cm high and 290 cm long. Weight is 1140 kg. The possibility of installation is electron beams with energies of 4, 6, 9 and 12 MeV with a therapeutic range of up to 4 cm. The system provides a dose of (10 - 25) Gy per fraction with a dose rate of 10 Gy / min and allows you to deliver a high dose of radiation to the patient once.

Novak7 is a miniature LEA mounted on a robotic arm with four rotating "joints". The facility generates electrons with energies of 3, 5, 7 and 9 MeV with a pulsed dose of (2 - 9) cGy/pulse. The repetition rate is 5 Hz, the pulse duration is 4 μs. The irradiation time for the prescribed dose of 20 Gy is (1 - 2) min. Application, dimensions, weight, placement in the operating room is about the same as the Mobetron system. Mobetron and Novak7 installations are shown in Fig. 3. [6].

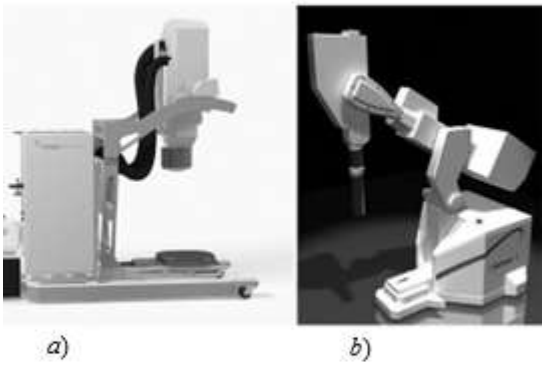

Fig. 3. Installations: *a*) Mobetron, b) Novak7 [6]

By the way, there is a project of a more advanced device based on a split microtron with a beam energy of 4 to 12 MeV [7]. The unique accelerator is placed in a container measuring 24×13×48 cm. The weight of the microtron is ≤ 120 kg. Power consumption is about 1 kW.

SL-20. The radiotherapy complex manufactured by Philips (England). It has two photon energies and eight electron ones. It is operated in "RONTS RAMS". St. Petersburg. RF.

Primus. The radiotherapy complex manufactured by Siemens (Germany). It has two photon energies and six electron ones. It works in “RONTS RAMS”. St. Petersburg. RF.

Clinac-2100C. The radiotherapy complex manufactured by Varian (USA). It has two photon energies and five electron ones. It operates in the oncological center "Innovation". Kyiv. Ukraine.

Elekta Synergy. The radiotherapy complex manufactured by Elekta (Sweden). It has three photon energies and six electron ones. It is operated in the Spizhenko Clinic, Kyiv. Ukraine.

3 (e,γ)-Therapy of cancer foci

The successful practical application of remote (e,γ)-therapy of malignant localizations, relapses and metastases has advanced this technique to a leading position in the treatment of the disease. Suffice it to say that therapeutic LEAs have amounted to more than 13 thousand out of 14,000 operating accelerators in 2015 [7]. Moreover, γ-radiation received a clear priority. A wide range of energies of existing γ-emitters provides high penetrating power and is used to treat deep-lying localizations. In addition, bremsstrahlung is fairly well collimated and has low radiotoxicity. The latter circumstance allows the use of large doses of radiation which guarantees the reliability of the results obtained and reduces the treatment time. All of the above explains the fact that the bulk of radiation therapy procedures used in the world is implemented by photon irradiation. About 70% of the total number of patients need traditional types of RT (electrons, gamma, X-rays). γ-therapy is the decisive factor providing a positive outcome of the procedure in approximately 40% of all cases [6].

A radical dose of radiation (55 - 70) Gy (1Gy = 100 rad) is required for the complete destruction of a malignant neoplasm. Such a dose is detrimental for healthy tissue. An effective means of protecting the patient's healthy cells is to irradiate the focus from different directions and use the fractionation technique (the course of therapy is carried out daily in small doses until the required total value is reached). Standard fractionation involves 5 exposures per week once a day for 2 Gy. The positive effect is due to the fact that healthy cells, when receiving a relatively small dose, will recover much faster than cancer cells [12]. Apparently, the fact that increasing the energy of γ-quanta leads to a shift of the position of the maximum dose deep into the biological object can be considered as a certain disadvantage of the technique. Deeper penetration of radiation leads to a high dose at the outlet of the tumor volume. This means that healthy tissues, including "critical organs", receive practically comparable dose loads behind the irradiated area.

As for electrons, therapy is carried out in ~ 20% of patients from the number of people with recommended RT. A free particle travels a certain distance in tissues spending energy on ionization acts and excitation of atoms. Electrons with energies up to tens of MeV pass several centimeters deep into the tissue and have a maximum ionization density close to the surface of the tissue/air interface. Therefore, they are used to treat tumors located close to the skin surface or at the level of the patient's body [13,14]. Since the mass of electrons is small, they scatter strongly increasing the volume of the irradiated tissue. The absorbed dose falls off rapidly after reaching its maximum, preventing damage to underlying important biological organs. The maximum absorbed dose is at different depths depending on the energy of the electrons. The maximum absorbed dose is at a tissue depth of ~ 10 mm at E_e = 6 MeV. Then the dose gradually decreases.

In connection with the appearance of compact LEA, the quality of treatment of neoplasms with intraoperative RT (IORT with electrons) has noticeably increased [6,7]. This is discussed in more detail above.

4 Formation of hadron therapy (HT)

Despite the successes achieved in the treatment of cancers with electromagnetic radiation, it turned out that a fairly large number of patients have tumors that are resistant to photon therapy. Therefore, it is advisable to use densely ionizing particles, mainly protons, neutrons, pimesons, heavy ions for ~ 20% of patients with heavy radioresistant forms [15,16]. This is due to a more pronounced damaging effect of cancer cells compared to electrons, X-rays and γ radiation.

With regard to light and heavy ions, their use for medical purposes has begun much later than the use of electrons and γ-quanta. Only in 1946, the medical journal “Radiology” published an article by R. Wilson where the author noted that proton and heavy ion beams would be ideal for the treatment of malignant tumors, since their inertial characteristics predict releasing of most of an energy in immediate vicinity of the end of a particle path. It is possible to set with a high accuracy of ~ 1 mm the place where the particles must stop and give up their energy by smoothly changing the energy. It should be noted that increasing the maximum energy of the particles is needed with increasing a ion mass which is associated with technical difficulties, increasing energy consumption and the cost of the accelerator complex.

Fig. 4 [17] shows the actual ratio of the dose to the depth of tissue penetration by protons, π-mesons and carbon ions. The same figure shows the dependence of the dose on the tissue penetration depth for photons with the energy of 18 MV. Narrow maxima, the so-called Bragg peaks, correspond to the release of the greatest energy in the region of the finite path of particles. It can be seen that the dose increases with increasing the ion mass; the destructive effect of radiation is growing. The relative biological efficiency is ~ 3 at the peak for carbon ions and it is for protons ~ 1.1 for protons, i. e. the damaging effect of carbon ions in tumor cells is several times higher than that of protons. In practice, to irradiate the tumor throughout its depth, the sharp Bragg peak is modified into a distribution that is uniform over a certain area. The dose ratio at the peak to the dose at the tissue entry is the best for carbon nuclei among ions from He to Fe [6]. A “fragmentation tail” is visible behind the peak. When an ion interacts with a substance the nucleus breaks up into fragments which leads to the appearance of a dose after a peak where, in principle, a “critical biological organ” can be located and subjected to unwanted irradiation. The contribution of the "tail" increases with increasing mass of the ion, for comparison, it is ~ 1 - 2% for protons, ~ 15% for carbon, ~ 30% for neon [15]. For a number of objective reasons, practical medicine prefers carbon therapy as the best treatment option.

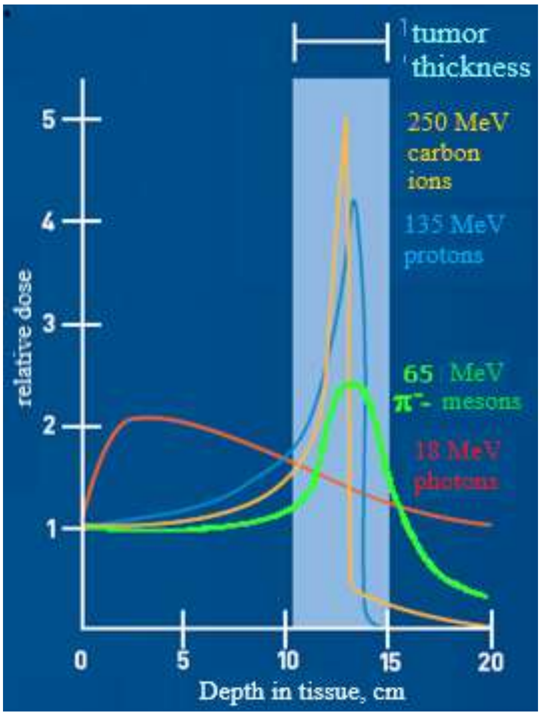

Fig. 4. Dose dependence on tissue penetration depth [17]

Biomedical research on beams of protons, deuterons and alpha particles of the synchrocyclotron at Berkeley (USA) was first performed by Tobiash and Lawrence in 1952. The first patient using proton therapy was cured in 1954 [18]. Clinical experiments on the use of high-energy protons in RT were started by Kilberg in 1959 at the synchrocyclotron with an energy of 160 MeV. Later, it turned out that at proton energies > 10 MeV the deviation of the particle trajectory from a straight line is statistically insignificant. Ionization processes are dominant and the absorbed energy is concentrated along the track for the proton energies which are used in RT. As a result of ionization, a "coat" of secondary electrons most of which have an energy of less than 100 eV is formed. The mechanism of heavy particle interaction with atoms and molecules of living tissue is fundamentally the same as for protons [6]. The optimal parameters for therapy were determined by the analysis of radiobiological experiments: proton energy (70 - 250) MeV which corresponds to the path of particles in the tissue (5 - 30) cm; size of the extracted beam on the target (3 – 5) mm; particle intensity on the tumor ~5·109 s^{-1}; position stability on the object 1 mm; exposure time (1 - 3) min.

“Gantry” units including superconducting are one of the key elements of the equipment of modern centers for both proton and ion therapy. This mechanical design is intended to rotate the transport device and form the beam around the patient in the range of angles (0-180)°. The independent rotation of the "gantry" in combination with the rotation of the patient at an angle of (0-180)° allows irradiation from any direction. The systems are very complex, expensive and cumbersome (for proton RT, the length of the "gantry" is ~ 10 m, the height is ~ (10 - 15) m, the weight is ~ 100 t; for the carbon beam, the length is ~ 20 m, the diameter is ~ 12 m, the weight is from ~ 200 to ~ 600 t) [6]. However, their use allows: a) to ensure the conformity of irradiation, when the maximum of the generated dose distribution with an accuracy of 1 mm corresponds to the shape of the target when irradiated from several sides; b) increase the number of locations recommended for irradiation from 7 to 30%.

To date, there are 71 proton therapy centers in the world, 44 ones are under construction, and it is planned to build 21 more centers in the near future [18]. Linear accelerators, cyclotrons, synchrotrons, synchrocyclotron, as well as superconducting synchrocyclotron, synchrotrons, and cyclotrons can be used to obtain beams of protons and ions (see, for example, [19]). However, linear accelerators have not found wide practical application due to their large length.

Studies have begun on the clinical application of beams of various ions after the launch of the Phasotron at the Lawrence Laboratory (LBL, USA), and the BEVALAC synchrotron [15, 20] later in 1975. The construction of the world's first heavy ion accelerator laboratory HIMAC (Heavy Ion Medical Accelerator in Chiba) began in Japan in 1984. Two heavy ion synchrotrons were launched at HIMAC to carry out radiotherapy of neoplasms with ions from helium to argon at the end of 1993. The first session with a beam of carbon ions was carried out in 1993. It turned out that approximately 30% of patients require protons for treatment, and only carbon ions can help for 10-15% of patients in the course of clinical studies. To date, about 20,000 patients have been treated with carbon ion beams in the world (5 centers in Japan), Germany (2 centers), Italy (1 center), China (2 centers) [20].

It should be noted that so far radiotherapeutic complexes for HT (treatment with protons and carbon ions) are less than 1% of the total number of medical accelerators [6]. However, the positive aspects of this technology prevail over all other radiation techniques. In particular, a) fluxes of protons and heavy ions satisfy the requirement of irradiating only the zone of the pathological site to a greater extent than other types of ionizing particles (electrons, γ-radiation, neutrons), and living tissues located nearby are practically not affected; b) the particles can be easily formed into well-directed narrow beams that penetrate the tissue almost without scattering to a depth determined by the choice of energy; c) HT significantly reduces the radiation load on the surrounding organs, the duration of exposure, the risk of adverse reactions, is better tolerated by patients and does not require mandatory hospitalization which allows ambulatory treatment; d) the number of sessions of irradiation with protons and carbon ions can be reduced up to 10 or more times instead of (30 - 40) procedures used in traditional radiotherapy today; e) HT has surpassed all existing methods of treatment in terms of efficiency. In practice, up to 90% of cancer patients are cured. As for the side irradiation of living tissue, protons allow you to halve the radiation load on healthy tissues surrounding the tumor compared to γ-rays. Carbon ions, on average, activate normal tissues 4 times less than X-rays at the same dose in the tumor and half as much as protons. Protons are the most effective for tumors located near critical organs; when a sharp drop in radiation dose is needed.

The number of HT centers in the world is continuously growing. And this is despite the fact that the construction of a modern clinical complex for proton therapy takes (3 - 4) years; it takes (3 - 5) years to master the equipment, and its cost reaches $200 million. The creation of an ion therapy center requires more time for construction and commissioning and costs twice as much. To date, there are about 70 HT complexes in the world. Only eight of them use beams heavier than proton ones [6]. It is predicted that there will be ~ 300 centers in the world by 2032. Two of the AT complexes under construction and those being prepared for operation will use a superconducting cyclotron with a proton energy of 250 MeV and six will use a superconducting synchrocyclotron with the same energy [16].

There is development of promising HT projects all over the world including Russia. Compact, high-field, medical accelerators are becoming more widespread in modern conditions. This also applies to the creation of superconducting cyclotrons and synchrocyclotron and "gantry" systems. This does not require the creation of a specialized cryogenic infrastructure. Such technologies can be implemented within oncological hospital centers [16]. Since the 1990s, only multi-cabin clinical centers have been built; there is one proton or ion accelerator which allows splitting the beam into several treatment cabins with "gantry". A project was proposed in [20] to create an irradiation center with carbon beams at the National Research Center "Kurchatov Institute" (RF) based on elements of the IHEP U-70 accelerator complex and existing infrastructure facilities. Projects of a superconducting carbon synchrotron [21] and a cyclotron [22] have been created at JINR (RF) which also include the gantry system. In INP named after G.I. Budker, the project was developed for a proton-ion therapeutic complex based on a fast-cycling booster and an ion synchrotron with electron cooling [23], etc.

It should be noted that a necessary condition for the successful implementation of all stages of RT is the provision of specialized clinics with qualified personnel, and not only with modern radiotherapy accelerator complexes, high-tech devices and mechanisms. It takes about 10 years to educate high-class specialists according to leading Western scientists. For example, medical physicists undergo at least (5-7) years of postgraduate medical-physical and clinical training, internships at research and educational centers, and only then are they certified in the United States. Table 1 shows the main staffing of accelerators and radiotherapy centers in Europe, the USA and Russia per 1 million population [24].

5 Conclusion

This review is based on the methodology of nuclear medicine, which is based on radiation therapy (RT). In particular, RT of cancer foci implies exposure of the tumor to various particle flows, such as α-particles, β-particles, electrons, protons, neutrons, π-mesons, heavy ions, X-rays and gamma

Table 1. Staffing of radiotherapy centers and accelerators in Europe, USA, RF [24]

	Europe	USA	RF
Radiotherapy centers	2.5	8	1
Medical physicists and dosimetrists	10	33	2
Radiation oncologists and therapists	11	49	8
Medical technologists	13	17	7
Accelerators	5	14	0.7

radiation. Malignant tumors are destroyed by such an exposure. At the same time, it is important to prevent damage and even destruction of cells of nearby healthy tissues which imposes certain requirements on the methods of influencing particle flows on the neoplasm area. It has become clear since the time of Becquerel and Roentgen that radiation not only affects the skin but can also cause radiation damage to internal organs and tissues or even lead to the death of living organisms. The formulated direction has become widespread in developed countries around the world.

Here we come to an important element of the methodology of nuclear medicine, namely to accelerator technology which provides the generation of beams of various particles for the treatment of oncological diseases. Modern accelerators with associated innovative equipment have proven to be one of the most advanced means of combating the disease. The review consistently acquaints the reader with the development of accelerator technology for RT of neoplasms from the days of the discovery of ionizing radiation by Roentgen and Becquerel to the present, passing through such important milestones as the creation of a linear accelerator, Van de Graaff electrostatic accelerator, gamma-therapeutic apparatus, cyclotron, phazotron, and so on. The methodology of nuclear medicine required each time an increase in the energy of the generated particle beams used by RT in the creation of a new accelerator facility starting from kilovolt values to tens of megavolts at the modern level. Modern accelerators, high-tech ancillary equipment and nuclear physics treatment technologies have the qualities and technical capabilities to successfully treat a wide range of cancer sites as shown in the review.

RT can be used not only as an independent method but also in combination with chemotherapy or with surgical methods. Moreover, a significant contribution to the methodology of nuclear medicine was made by a γ-installation using radioactive cobalt ^{60}Co, called the “Gamma Knife” (Cyber-knife), for performing radiosurgery in the brain described in section **2 the Progress of accelerating technology** of this review.

The success of radiation therapy is also associated with the emergence of new designs of devices such as "gantry" mounted in modern centers for both proton and ion therapy (see section **4 Formation of hadron therapy (HT)** of this review). It has been demonstrated that the treatment of malignant foci with beams of protons and carbon ions is currently the most effective since the dose for pathological tissues increases and the dose for normal tissues decreases in this case. Irradiation with protons and heavy ions is called by hadron therapy (HT).

It should be noted that so far there are quite a few radiotherapeutic complexes for HT in the total number of medical accelerators. But the number of HT centers is constantly growing in the world due to the clear predominance of the positive aspects of this technology over all other radiation techniques. There is development of promising HT projects all over the world including in Russia. There is a rapid growth and complication of radiotherapy and radiosurgical equipment and technologies in order to improve the quality of radiation therapy.

Compact, high-field, medical accelerators have been widely used recently. However, for the future development of this work, it is required to carry out the development of large (expensive) projects for the creation of superconducting cyclotrons, synchrocyclotron, and "gantry" systems in the field of radiation medical physics including new methods of clinical radiotherapy, a network of educational and service structures. The latter circumstance is due to the fact that a necessary condition for the implementation of RT is the provision of specialized clinics not only with modern radiotherapy accelerator complexes, high-tech devices and mechanisms but also with qualified personnel since the maintenance of medical accelerator complexes requires special training. Only in this case it is possible to bring closer the solution of the priority task of physicians to reduce the mortality and disability of potential cancer carriers.

References:

[1] UN news. December 15, 2020. Healthcare. News.un.org/ru/story/2020/12/1392562

[2] A.A. Vorobyov, E.M. Ivanov, A.G. Krivshich et al. Center for Proton Therapy of the St. Petersburg Institute of Nuclear Physics, *Questions of atomic science and technology, Series "Nuclear Phys. Research"*, Vol. 59, No. 4(80). 2012, pp. 146-150. (In Russian).

[3] R. Soukhami, J. Tobias. *Cancer and its treatment.* M.: Binom, 2009. (In Russian)]

[4] G.E. Trufanov, G.M. Zharinov, M.A. Asaturyan. *Radiation therapy.* Vol.2. 2010. (In Russian)

[5] M.T. Maksimov, G.O. Odzhagov. *Radioactive pollution and their measurement,* M.: Energoatomizdat, 1989. (In Russian)

[6] A.P. Chernyaev, E.N. Lykova, A.I. Popadko. *Medical equipment of modern radiation therapy*. M. PEP of the Faculty of Physics, Moscow State University 2019. (In Russian)

[7] A.P. Chernyaev, M.A. Kolyvanova, P.Yu. Borshchagovskaya. Medical accelerators, Part 1. *Moscow University Bulletin. Series 3. Physics. Astronomy*, No 6, 2015, pp.28-36. (In Russian)

[8] M.F. Vorogushin, A.P. Strokach, O.G. Filatov. NIIEFA accelerators for applied purposes, *ECHAYA Letters*, Vol. 13, No 7(205), 2016, pp. 1251-1256. (In Russian)

[9] I.M. Lebedenko, O.V. Staroverov, Yu.V. Zhurov et al. Electron accelerators of the SL75-5-MT series with a photon radiation energy of 6 MeV. Dosimetric, clinical and operational characteristics, *Medical Physics*, No 1. 2009, pp. 15-20. (In Russian)

[10] H.S. Kaplan. Radiotherapeutic advances in the treatment of neoplastic disease, *Israel J. Med. Sci.* Vol. 13. 1977 pp. 808-814.

[11] A.V. Agafonov. Accelerators in medicine, *15th conference on charged particle accelerators*, Protvino, Russia. Part 2, 1996 pp. 366-373. (In Russian)

[12] I.N. Backman. *Radiochemistry. Radiation and nuclear medicine.* Vol. VII, M.: ONTO PRINT, 2012. (In Russian)

[13] V.N. Vasiliev, A.A. Kokontsev, S.P. Tyurnin, V.M. Sotnikov. Large-field electron irradiation of the skin, *Medical Physics*, No. 4. 2011 pp. 11-19. (In Russian)

[14] V.A. Lisin. Calculation and analysis of the total distribution of the dose of electrons and γ-radiation when intraoperative radiation therapy is combined with remote γ-therapy. *Medical Physics*, No 4. 2012 pp. 36-40. (In Russian)

[15] *Review of the use of proton and ion therapy.* Feasibility study for the construction of a proton-carbon complex for cancer therapy in Khanty-Mansiysk. Part 1. INP named after G.I. Budker SB RAS. Novosibirsk. 2008. pp. 1-70. (In Russian)

[16] S.A. Kostromin, E.M. Syresin. Trends in accelerator technology for hadron therapy, *ECHAYA Letters*, Vol. 10, No 7(184), 2013, pp. 1346-1375. (In Russian)

[17] Accelerators for therapy and diagnostics. http://nuclphys.sinp.msu.ru/nuc_tehn/med/accelerators.htm (In Russian)

[18] Pryanichnikov A.A., Chernyaev A.P., Khoroshkov V.S. *Introduction to the physics and technology of proton therapy: Proc. allowance - M.: OOP of the Faculty of Physics of Moscow State University*, M.: PEP of the Faculty of Physics, Moscow State University, 2019. http://nuclphys.sinp.msu.ru/mpf/Proton_therapy.pdf (In Russian)

[19] O.V. Karamyshev, K.S. Bunyatov, A.L. Gibinsky et al. Research and development of the superconducting cyclotron SC230 for proton therapy // *ECHAYA Letters*, Vol. 18, No 1(233), 2021,
pp. 73-85. (In Russian)

[20] Federal State Budgetary Institution National Research Center "Kurchatov Institute", IHEP. Center for ion beam therapy based on the U-70 accelerator. Protvino. 2017. (In Russian) http://www.ihep.su/files/Journal_2017_Final_2_05_02_2018.pdf

[21] E.M. Syresin, V.A. Mikhailov, A.V. Tuzikov et al. Project of a superconducting medical synchrotron for hadron therapy, *ECHA Letters*, V. 9. No. 2 (172), 2012, pp. 328-344. (In Russian)

[22] Jongen Y. et al. Compact Superconducting Cyclotron C400 for Hadron Therapy, *Nucl. Instr. Meth. A*, Vol. 624, No 1, 2010, pp. 47-53.

[23] E.B. Levichev, V.V. Parkhomchuk, S.A. Rastigeev, A.N. Skrinsky, V.A. Vostrikov (BINP SB RAS, Novosibirsk, Russia), M. Kumada (NIRS, Chiba, Japan). Carbon Ion Accelerator Facility for Cancer Therapy, *Proceedings of RuPAC 2006, Novosibirsk, Russia*. pp. 363-365.

[24] M.I. Davydov, A.V. Golanov, S.V. Kanaev et al. Analysis of the state and the concept of modernization of radiation oncology and medical physics in Russia // *Problems in Oncology*, Vol.59. No 5, 2013, pp. 529-538. (In Russian)

Contribution of Individual Authors to the Creation of a Scientific Article (Ghostwriting Policy)

Vladimir Krasilnikov carried out the editing, formal analysis, and data curation.

Eduard Kuplennikov has implemented the selection of references, formal analysis, and written the original draft.

Sources of Funding for Research Presented in a Scientific Article or Scientific Article Itself

The article was written with self-funding.

Creative Commons Attribution License 4.0 (Attribution 4.0 International, CC BY 4.0)