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INSTRUMENTS AND METHODS OF INVESTIGATION

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Nuclear physics technologies in medicine

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Contents

Abstract. The review is devoted to the physical foundations of nuclear technologies in medicine. Physical ideas used in high-tech medical devices and systems, as well as key milestones in the progress of 'nuclear medicine,' are considered. The history of the emergence of such systems in Russia and worldwide along with healthcare demands are traced, and current development trends are discussed. The system of training relevant personnel is described.

Keywords: accelerators, radiation technologies, medical physics, nuclear technologies, nuclear medicine, tomography, CyberKnife, Gamma Knife

1. Introduction

Currently, there are a great many devices, instruments, and technologies in medicine based on physical methods. They range from simple mechanical devices, thermometers, and hygrometers to high-tech radio-wave, acoustic, laser, X-ray, and nuclear physics technologies in medical diagnostics, therapy, and surgery.

Thus, the use of physical methods based on direct electric current began in the clinics of Moscow University at the end of the 18th century (in the 19th century, F. Belyavsky introduced the concept of galvanoionotherapy), and the effect of alternating current on the body was carried out at the end of the 19th century by the French biophysicist J.A. d'Arsonval.

Physical methods in medicine are conventionally divided into nonionizing and ionizing methods. Nonionizing methods include electrotherapy, acoustic, laser, and magnetic resonance.

Electrotherapy uses electrical energy for treatment, i.e., direct and alternating currents, radio waves up to microwave frequencies, forming a wide range of physiotherapeutic procedures [1].

Acoustic methods include ultrasound devices and technologies for diagnosing internal organs and tissues without surgical intervention, and nonlinear acoustic methods in both diagnostics and the use of high-power acoustic pulses in medicine for the destruction of kidney stones (lithotripsy), sonic booms, etc. [2, 3].

Laser technologies are successfully used not only in diagnostics and the creation of implants, but also in surgery for cutting tissues with a laser, for vision correction, and in photodynamic therapy for the destruction of cancer cells (see, e.g., [4, 5]).

Magnetic resonance systems and technologies are unique achievements of the joint work of physicists, chemists, and medical doctors.

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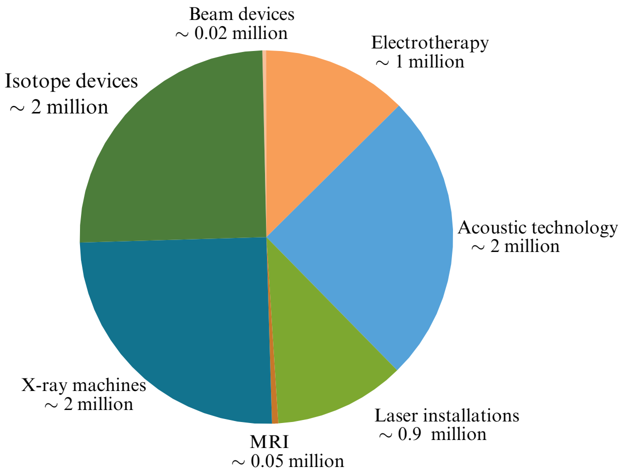

Figure 1. Medical equipment in the world.

Ionizing methods and technologies include X-ray, radionuclide, and particle beam methods. We will consider them below.

The above-mentioned methods formed the basis for the creation of many devices, instruments, and large diagnostic and therapeutic systems for medical purposes.

Based on data about medical equipment purchases, this paper attempts to at least roughly estimate the ratio of the total volume of medical equipment based on the above-listed physical methods [1] from different branches of physics, which is presented in Fig. 1.

This review considers one of the components of the spectrum of physical methods in medicine: technologies using ionizing radiation.

Fundamental research in the second half of the 19th century led to the discovery of sources of ionizing radiation: X-rays (W. Röntgen, 1895 [6]) and radioactivity of uranium salts (A. Becquerel, 1896 [7]). In 1898, M. Sklodowska and P. Curie isolated a new chemical element that emits alpha particles, which they called polonium [8]. In the same year, they discovered another radioactive chemical element, radium [9].

As a result of these discoveries, an X-ray tube was created, as was a prototype of a radioisotope device.

X-rays were used in the USA as early as January 1896 to diagnose bone fractures, and in February in Russia, physicists A.S. Popov and S.S. Kolotov created an X-ray tube based on their own designs and took a number of pictures, including of a hand. In November 1897, with the participation of A.S. Popov, the first marine X-ray room was opened [10].

In 1901, P. Curie first proposed the idea of using radioactivity to treat cancer [11].

In the same year, the French scientist A. Danlos used radioisotopes to treat a patient with tuberculosis [12], and, in 1903, A. Bell began to place radium sources directly in or near a tumor [13].

Russian science found itself in the thick of these events. In 1900, the properties of radioactive radiation began to be studied at the University of St. Petersburg, and Professor A.P. Sokolov of Moscow University studied the radioactivity of mineral waters in the Caucasus. He also created the first practical course on radioactivity in the country. In 1902, the famous scientist A.S. Popov created a device for measuring "the voltage of the atmospheric electric field using the ionizing effect of radium salts."

In 1903, in St. Petersburg, radionuclide sources were used to treat an oncological disease, basal cell carcinoma [14]. That same year, Marie and Pierre Curie visited the oncology institute that opened at Moscow University on the initiative of Moscow University professor L. Levshin and with donations from the Morozov merchant dynasty. They donated several radium needles to the institute, which began to be used to treat oncological diseases.

During the Russo-Japanese War of 1903–1904, the famous cruiser *Aurora* and the hospital ship *Mongolia* had X-ray rooms that made it possible to diagnose fractures and wounds from shrapnel and bullets in battle participants. In 1918, a few months after the October Revolution, when the country was experiencing famine, devastation, virtual anarchy, and civil war, the State Roentgenology and Radiological Institute with a physical-technical department was created in Petrograd, headed by A.F. Ioffe (now the world-famous Radium Institute). In 1921, a radium laboratory was organized at the Academy of Sciences. In 1922, V.G. Khlopin obtained the first domestic radium preparation at the Radium Institute [15].

At the turn of the 1930s, a whole range of unique physical facilities — accelerators — were created for the experimental study of the structure of atomic nuclei: a cascade accelerator (1929), a Wideröe linear accelerator (1928) [16], a Cockcroft–Walton generator (1924) [17], an electrostatic Van de Graaff accelerator (1931) [18], and a cyclotron (1931) [19]. In 1937, an electron accelerator was built in London at St. Bartholomew's Hospital [20] for the treatment of cancer patients. The energy of the bremsstrahlung gamma radiation obtained with it did not exceed 1 MeV, and the dimensions of the unit reached 10 m. The use of accelerators in medicine has evolved over time into the largest area of applied nuclear physics technologies to date, remote radiation therapy.

The creation of the cyclotron by E. Lawrence and S. Livingston [19] predetermined the conditions for the production of artificial radioisotopes using it. Many artificial radioactive isotopes used in nuclear medicine and radiation therapy were obtained by this method. Among them, one of the first was the radionuclide ^{60}Co, synthesized in 1937 at the cyclotron in Berkeley by D. Livingood and G. Seaborg [21], as well as ^{99}Tc, discovered in 1939 by G. Seaborg and E. Segrè [22]. These achievements of nuclear physics became the threshold of the nuclear medicine era [23], which plays a significant role in the development of radionuclide diagnostics and therapy, primarily for the treatment of tumors.

The radionuclides radium ^{226}Ra and cesium ^{137}Cs obtained at cyclotrons became the basis for the development of another major nuclear-physical avenue in medicine, contact radiation therapy with sealed radioactive sources [14] (currently, this method is called brachytherapy). With these radioactive sources, intracavitary and intratissue methods were developed for the treatment of various neoplasms.

The launch of the first nuclear reactor in 1942 [24] significantly expanded the therapeutic and diagnostic use of radionuclides, since it became possible to intensively produce a variety of radioactive isotopes and supply them to consumers. The beginning of such regular supplies of radionuclides to medicine in 1946 is considered the birth date of nuclear medicine. One of the first examples of the implementation of nuclear medicine methods is the successful experience of using the isotope iodine ^{131}I for the treatment of thyroid cancer [25].

[1] The assessment was based on an analysis of medical equipment purchases over several years.

The emergence of radionuclides served as the basis for the development of methods for visualizing human organs using radiopharmaceuticals. In 1948, point-by-point registration of an image of the thyroid gland was carried out, and, in 1949, D. Copeland and E. Benjamin [26] proposed the idea of the first diagnostic device based on open radioactive sources — a gamma camera, which is a two-coordinate scanner with scintillation counters.

Thus, humanity has discovered, in addition to X-ray radiation, a second unique method for examining human internal organs without surgical intervention. X-ray radiation has become the basis for two areas of application in medicine: X-ray diagnostics and X-ray therapy, and nuclear physics has become the basis for the emergence of three large areas in medicine: radiation therapy, radiation diagnostics, and nuclear medicine. [2]

2. X-ray radiation in medicine

X-ray instrumentation and examination methods using it have firmly entered our understanding of a medical institution. The history of the emergence of X-ray diagnostic and therapeutic devices and technologies begins practically with Röntgen's discovery. They are widely used in the diagnosis of and therapy for various diseases. X-ray examination allows determining the state of human internal organs and diagnosing their diseases.

What is the physics of the X-ray radiation effect on biological tissues? The main mechanism of its action is the photoelectric effect, which is the dominant mechanism of interaction of photons with matter in the energy range from 30 eV to approximately 200 keV. The contribution of inelastic and Compton interactions in this energy range is negligibly small. The cross section of interaction of photons with electrons on the K-shell is

$$(\sigma_{\text{phot.}})_{\text{K}} \sim \frac{Z^5}{E_\gamma^{3.5}} \,. \tag{1}$$

A good approximation of the photoelectric effect cross section is the expression $\sigma \sim Z^3/E_\gamma^3$. It is due to the strong dependence on the charge of the medium's atoms, and the energy of photons, different tissues, vessels, bones, cavities, etc. are clearly visible in an X-ray image. Bones contain more calcium than soft tissues, so they are darkened in the images, and cavities are lighter areas. The discovery of this physical effect became the basis for the development of X-ray diagnostics. X-ray radiation is also used in therapy. As can be seen from Eqn (1), more photons will be absorbed at their low energies. The technique of X-ray therapy is based on this principle. When designing it, another important law is taken into account, the exponential decrease in the intensity I of the beam in a substance:

$$I = I_0 \exp(-\mu x) \,, \tag{2}$$

where μ is the linear attenuation coefficient, and I_0 is the radiation intensity at $x = 0$ at the entrance to the medium.

These great discoveries laid the foundation for the modern X-ray field, encompassing industry, medicine, agriculture, and a broad range of scientific research, and have become key elements of medical diagnostics. There are several million (according to some estimates, ~ 4 million) X-ray devices, units, and systems in the world. Moreover, the devices differ significantly from each other; many technical advances have been developed to solve specific problems. But they are united by the basic laws of physics. X-ray systems are manufactured by about a hundred companies in many countries around the world, which annually produce more than 200 thousand X-ray units.

Currently, several basic diagnostic methods using X-rays (X-ray diagnostics) are used: fluoroscopy, fluorography, radiography, and X-ray computed tomography.

The most high-tech of the X-ray diagnostic methods is X-ray computed tomography (CT) [27]. The essence of the method is to solve the inverse problem. Since the exponential law is satisfied with a high degree of accuracy for X-ray radiation, this made it possible to develop mathematical algorithms for restoring tissue density based on measuring the intensity of X-ray radiation. They were used in X-ray computed tomography. [3] Using mathematical methods for solving inverse problems, the structure of tissues through which X-rays pass is reconstructed. Images from different sides are added together, creating an image of one tissue slice.

With the translational displacement of the table with the patient, a set of such images is constructed. An integral volumetric image is constructed from them. The main thing in computed tomography is the speed of image processing by the computer. The more slices, the less radiation load on the patient. Thus, 7 generations of CT have been created, and in the latest models up to 320 slices are performed simultaneously with one rotation of the X-ray tube. At the same time, the speed of information processing began to exceed 30 images per second.

What is happening with the development of X-ray technology in our country? There are about 80 thousand X-ray devices in Russia, more than 60 thousand of which are in medicine [28]. There are about fifteen manufacturers that supply medicine with $\sim 2-4$ thousand X-ray devices, which generally meets the needs of medical institutions. The main types of X-ray devices are stationary and mobile X-ray diagnostic systems, fluorographs, C-arm X-ray machines, mammographs, and CT scanners. Russian companies [4] supply healthcare institutions with about 70% of fluorographs, $\sim 40\%$ of stationary and mobile X-ray diagnostic systems, $\sim 30\%$ of C-arm X-ray machines, and $\sim 24\%$ of mammographs. All this makes up about 50% of all X-ray equipment used in the country's medical institutions [28].

Complex X-ray equipment is mainly imported from abroad, with angiographs and CT scanners being entirely foreign-made.

The number of X-ray machines operating in medical institutions in our country is presented in Table 1. Approximately 80% of these devices are used for medical purposes. Over 15 years, their number has grown by 1.65 times, and by 6% in other sectors of the country's economy.

Table 2 shows the share of operating X-ray machines in Russia in the global number. The number of operating CT scanners and medical X-ray machines, including therapeutic ones, in our country corresponds to the world level. Our country is provided with mammographs and therapeutic machines at the

[2] Nuclear medicine is currently understood as radiation radionuclide diagnostics and therapy with open radioactive sources.

[3] Such algorithms for absorbing media were developed by the Austrian mathematician I. Radon in 1917.

[4] Leading manufacturers with their own R&D and production base include, in Moscow: CJSC Amiko, LLC PMP Proton, LLC Mosrentgenprom, Gelpik, SpektrAp, and Medical Technologies; and in St. Petersburg: CJSC NIPK Elektron.

Table 1. Medical X-ray units in Russia [28–31].

Types of units	2007	2012	2017	2022
X-ray units in medicine	36,722	43,835	52,079	60,669
X-ray units in the whole economy	44,025	54,477	66,018	78,556
Share of X-ray medical devices (%)	0.83	0.8	0.79	0.77

Table 2. Medical X-ray equipment in Russia and the world [28, 32, 33].

	In the world	In Russia	Russia's share, %
Computer tomographs	93,773	2222	2.37
X-ray medical devices	$\sim$ 4,000,000	60,669	$\sim$ 1.5
Mammographs	57,913	3714	6.4
X-ray therapy units	732	86	11.7

level of highly developed countries. It is necessary to increase the share of CT machines of the latest generations. The most urgent task is to launch production of our own CT, angiographs, mammographs, and other modern high-tech X-ray units. Several decades ago, we had a good situation with the use of X-ray therapeutic devices. There are a number of effective Russian methods of therapy using X-ray machines.

3. Radionuclides in medicine

As noted above, the history of using radionuclides in medicine in our country is very rich and begins in 1903. Of the more than 3000 isotopes currently known, including 271 stable ones, approximately 300 types of nuclides can be used in the world economy. In practice, approximately 100 radioactive isotopes are used. At present, the main method of obtaining radionuclides is their production in reactors or proton accelerators. More than 230 research reactors in 56 IAEA member countries and 1268 cyclotrons are used to produce isotopes [34, 35]. In most cases, they are cyclotrons with an energy of 4–70 MeV, which can produce up to 50 radionuclides. More than 45 types of radionuclides are produced for medicine: $\sim$ 27 types of radionuclides for diagnostic purposes, $\sim$ 37 for therapeutic purposes; 20 types are obtained by the generator method (with β^+- and β^--decays, and with electron capture and isomeric transitions).

In recent years, radionuclides have also been produced in electron accelerators as part of pilot projects. For many isotopes, the cost of such production is comparable to that of production in proton accelerators. However, the possibility of using medical electron accelerators located in the radiotherapy departments of oncological institutions for these purposes makes this approach very attractive, since it opens up the possibility of using short-lived radionuclides for medical purposes. For example, in recent years, work has been actively carried out on the production of ^{131}Cs $(\gamma, 2n)$, ^{89}Zr, ^{177}Lu (γ, p) and ^{179m2}Hf, and ^{180m}Hf (γ, γ') using the photonuclear method [36–38].

The physical meaning of the action of radionuclides on biological tissues in diagnostics and therapy is as follows. A radionuclide in a cancer cell decays with the emission of one photon or simultaneously with a charged particle. Within the cell volume, the photon and the charged particle perform ionization and the cell dies. The emitted photon leaves the human body and enters the detector, transmitting information about the location of the cancer cell. This approach is based on an important experimentally established fact that radionuclides are absorbed differently by healthy and tumor cells. Radionuclides accumulate more strongly in some organs, less strongly in others, and not at all in others. To deliver a radionuclide to a cell, chemists and biologists create radiopharmaceuticals (RPs) that deliver the radionuclide proposed by the physicist to the cell.

When selecting a radionuclide, first, it is important that its half-life be longer than the time during which it is distributed in a certain organ or tissue area, and the doctor will have time to conduct an examination. Second, the radionuclide must be such that its concentration in the tumor is higher than in healthy tissues. Then, the volume and shape of the pathology can be seen on the diagnostic device. Third, the half-life of the radionuclide and the activity should not be too long so that the healthy tissues of the patient do not receive an additional dose load. Fourth, the radionuclide should quickly decay and be easily and completely eliminated from the body.

Radionuclides that emit high-energy photons are used for diagnostics. The higher their energy, the greater their penetrating ability. Then, more photons will fly out from the internal tissues and be registered by the detector.

In essence, radionuclide diagnostic tomographs (GC, SPECT, and PET) work by measuring the distribution density of the radionuclide in pathological areas.

Technologies using radioactive isotopes are very diverse, primarily in industry and nuclear medicine (in radionuclide diagnostics and therapy).

3.1 Radionuclide diagnostic devices

Physicists have created a number of unique tomographs based on radionuclides: gamma camera (GC), single-photon emission computed tomograph, and positron emission tomograph. They are all united by a common physical idea to determine the point from which the photons fly out and count their number.

3.1.1 Gamma camera. The physical idea of this unique device was proposed in 1949 [26]. The two-coordinate device created is based on the fact described above — the nonuniform distribution of radionuclides in organs and tissues, and above all in pathological foci. Photons emitted by radionuclides are registered outside the patient's body. For the gamma camera, such radionuclides are selected that emit single photons with a sufficiently high energy of more than 150 keV. Physicists have created a unique collimator that allows photons to pass through only in one direction (Fig. 2). Large scintillation crystals are grown especially for gamma cameras and are used to create a scintillation NaI(Tl) detector, a single crystal 10–12 mm thick and up to 500 mm in diameter. Photons hitting it produce flashes. At photon energies of about 150 keV, 90% of the photons are absorbed in it. Then, the flashes from the interaction of photons with the crystal are collected by a photomultiplier, where the signal is amplified and accumulated in a computer.

Currently, two types of emission computed tomography are used in radionuclide diagnostics:

• single-photon emission computed tomography (SPECT), which uses radionuclides that emit gamma radiation (^{99m}Tc, ^{123}I, ^{67}Ga, ^{111}In, and ^{201}Tl);

• positron emission tomography (PET), which uses radionuclides that emit positrons (^{11}C, ^{13}N, ^{15}O, ^{18}F, ^{68}Ga, ^{82}Rb).

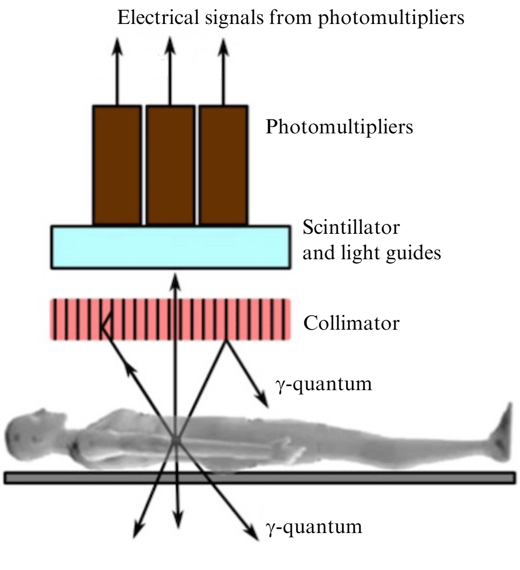

Figure 2. Gamma camera configuration.

3.1.2 Single-photon emission computed tomography. The use of gamma cameras does not provide high-quality information on the third spatial coordinate, which is obscured by the superposition of data along the selected direction. The purpose of creating SPECT was to obtain a three-dimensional diagnostic image[5] [39]. This idea could be realized with the advent of high-speed computing technology. Based on gamma cameras, physicists and mathematicians created the single-photon emission computed tomograph, a new type of device for radionuclide diagnostics. In this device, unlike a gamma camera, the detector (two large scintillation crystals, usually mutually perpendicular) rotates around the table with the patient. In this case, many images are taken from different directions, using which a three-dimensional image of the object is constructed. Usually 30 images are processed per second (Fig. 3). But the creation of a better diagnostic radionuclide device, the PET scanner, was yet ahead.

[5] The development of SPECT began in 1963–1964. At the turn of the 1970s–1980s, physicists and mathematicians created a new type of device for radionuclide diagnostics — a single-photon emission computed tomograph.

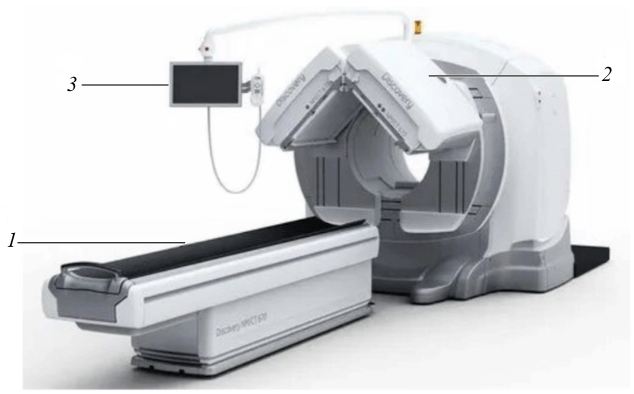

Figure 3. General view of single-photon emission computed tomograph: *1* — movable table; *2* — two detectors located at right angles to each other; *3* — computer monitor.

3.1.3 Positron emission tomography. One of the most modern examples of the use of nuclear physics in medicine[6] is the positron emission tomograph[7] [39]. Whereas X-ray and magnetic resonance tomography reveal the structure of an organ at the stage of its morphological change, PET is capable of registering changes in the metabolic processes that precede this, helping with the earliest recognition of pathological features long before the appearance of morphological changes.

The operation of the device is based on the following basic physical ideas. First, in accelerators, β^+-active radionuclides are obtained in nuclear reactions that emit positrons. Second, during the decay of β^+ radionuclides, positrons are formed, which annihilate when interacting with electrons. As a result, two photons are emitted in strictly opposite directions. Third, coincidence schemes developed in nuclear physics experiments are used, registering those photons that simultaneously hit NaI (Tl) crystals. Fourth, crystals with high efficiency of photon detection ($\sim 80\%$) are used.

The physical mechanisms in PET look like the following. During β^+ decay, radionuclides emit a positron, which travels a distance of 1–3 mm in the surrounding tissues, losing energy when colliding with molecules and atoms of biological tissue. As its energy decreases, the probability of annihilation increases proportionally to $\sim 1/v$. When the positron velocity is close to zero, it interacts with an electron and annihilates in the reaction

$$e^- + e^+ \to 2\gamma\,, \qquad (3)$$

transforming into two photons with an energy of 0.511 MeV each, which fly apart in opposite directions. These photons are registered by crystalline scintillation counters. When photons hit the scintillation crystals, a flash of light occurs, which is recorded by photodiodes, and then the signal is amplified by a multiplication circuit. Among all the flashes, special electronic circuits select those pairs of photons whose signals arrive simultaneously (such circuits are called coincidence circuits). The operating principle of a PET scanner is illustrated in Fig. 4.

The key element of a PET scanner is a detector consisting of a large number of scintillation crystals, among which every two oppositely located crystals are included in a coincidence circuit in pairs.

A set of detectors forms a ring with a diameter of 80–100 cm and a width of 10–20 cm. To reduce the influence of external radiation, the outer surface of the detector ring has a lead screen. A positron emission tomograph is a complex for producing radionuclides, consisting of a PET scanner and a cyclotron. The resolution, i.e., the accuracy of determining the point from which a pair of photons flies out, reaches 1–3 mm. These systems, created by physicists, currently represent the most accurate diagnostic device operating in medicine. There are about 6000 such systems in the world, and 60 are in Russia. Unfortunately, the plans for Russian positron emission tomographs were not completed due to the Russian economic situation in the nineties.

[6] The first use of the radioisotope ^{131}I for the diagnosis of thyroid disease dates back to the late 1930s. Early developments in imaging devices in the 1950s included two-dimensional scanners and scintillation cameras. These types of devices became widely used in clinical practice by the mid-1960s. It was from this period that the Eiger camera (gamma camera) became one of the main technical means of imaging with isotopes.

[7] The first multi-detector PET scanners were developed in the early 1960s at several research centers and were systems with a ring of 32 sensors and a resolution of more than 2 cm.

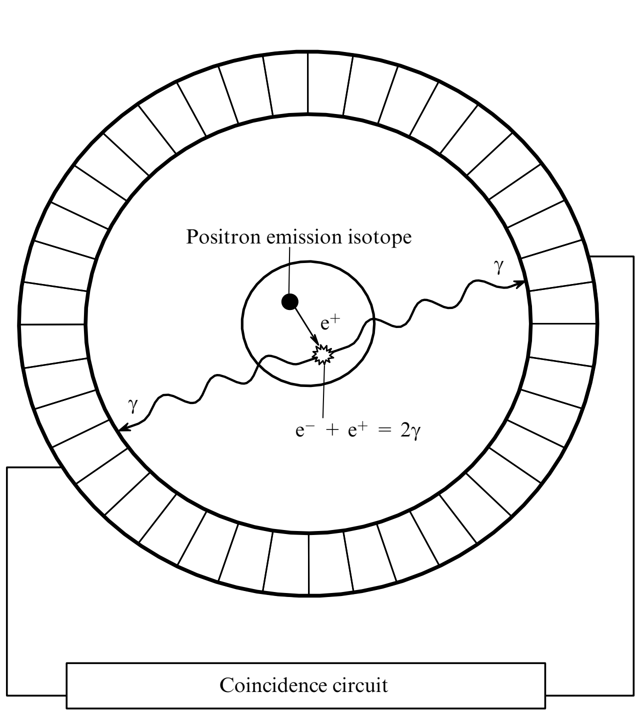

Figure 4. Operating principle of PET tomograph.

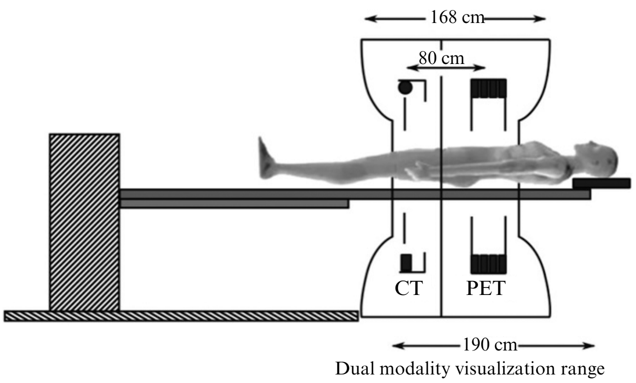

Figure 5. Schematic diagram of combined PET–CT tomograph.

Finally, let us address the problem solved by each of the CT, SPECT, and PET tomographs:

CT is a method of structural visualization of tissue; it determines the size and shape of the pathological process and the degree of involvement of surrounding tissues in it;

SPECT determines the blood supply of tissues by their ability to accumulate in pathological foci in a three-dimensional image;

PET tracks the distribution of biologically active compounds in the body and allows studying such processes as metabolism, transport of substances, and gene expression.

One of the latest achievements of modern physics is the combination of two types of tomography, for example PET–CT. As can be seen from the above, the use of such a combined tomograph allows realizing the capabilities of two tomography methods: CT and PET. At the same time, doctors can not only see the size and shape of the pathological focus, but also study the dynamic processes occurring in and around it: metabolism, transport of substances, gene expression, etc. In this setup, shown in Fig. 5, two rings of the PET and CT are mounted on the same axis. The examination is carried out either on one of them or on both at once.

In addition to radionuclide diagnostic units, other nuclear physics methods based on radionuclides in contact and remote radiation therapy are widely used in oncological institutions: brachytherapy, remote radiation therapy with cobalt units and gamma knives, as well as boron-neutron capture therapy. Let us consider the physical ideas of these methods.

3.2 Brachytherapy

Brachytherapy or contact radiation therapy[8] is a type of radiation therapy in which a small, hermetically-sealed radiation source is placed inside or near the area requiring treatment. In this case, the radioactive substances do not enter the body directly but irradiate the surrounding tissues through the walls of the capsule.

The advantage of brachytherapy is that the sources are placed in close proximity to the tumor (and sometimes directly into it), so that a very high dose can be delivered to the tumor cells (the dose rate near the sources can reach hundreds of Gy/h), which is guaranteed to kill them. The rapid dose drop due to geometric attenuation with distance from the radioactive source allows protecting critical organs and tissues from high doses. However, tumors that can be approached without surgery are quite rare. Therefore, the distribution of the method is quite limited. The dose rate in brachytherapy varies from 0.4 to 12 Gy/h.

In brachytherapy, physicists have proposed using a number of radionuclides: ^{226}Ra, ^{137}Cs, ^{198}Au, ^{60}Co, ^{192}Ir, ^{125}I, ^{103}Pd, ^{131}Cs, ^{252}Cf, ^{204}Tl, ^{90}Sr/^{90}Y, ^{106}Ru, ^{169}Yb, ^{32}P, ^{145}Sm and ^{182}Ta, ^{177}Lu, ^{188}Re, and ^{170}Tm. Table 3 presents the physical characteristics of some of the radionuclides used. It can be seen that they are mainly sources of gamma-quanta with energies below 1 MeV, with the exception of ^{60}Co, and two sources of electrons with energies greater than ^{90}Sr and ^{106}Ru. Research work is underway with a number of isotopes.

Brachytherapy has a long history of development. It allows treating tumors that can be reached nonsurgically. There are approximately 3500 brachytherapy units in the world, including 153 that operate in Russian medical institutions [32]. Russia has its own developments of such devices. The AGAT-VT device is successfully operating in oncological institutions of the Russian Federation. By 2013, the Open Joint-Stock Company MSM had developed the NUCLETRIM gamma-therapy complex for brachytherapy [40], comparable to the best foreign counterparts. In Russian oncology centers, five such complexes were installed and put into operation in 2013–2014. In 2021, the Research Institute for Technical Physics and Automation (NIITFA), a division of the Rosatom State Corporation, developed another fully domestic gamma therapy device for brachytherapy, BRACHIUM, with minimal dependence on imported components [41]. At present, about ten such complexes are operating in medical institutions. Its key feature is that the device uses the first Russian planning system, which provides the ability to solve a full range of problems in planning irradiation procedures.

Recently, electron brachytherapy has become increasingly popular. The main idea is to use miniature X-ray diodes with a maximum energy of 50 keV[9] as radiation sources [42].

[8] Radionuclide sources were first used to treat oncological diseases in 1903 in St. Petersburg to treat basal cell carcinoma.

[9] The MSU Research Institute of Nuclear Physics is developing similar types of ionizing radiation sources.

Table 3. Physical characteristics of some radionuclides used in brachytherapy.

Source	How to obtain	$T_{1/2}$	Emission
^{226}Ra	occurs in nature	1620 years	γ 0.83 MeV (average)
^{137}Cs	fission product	30.17 years	γ 0.662 MeV (average)
^{60}Co	neutron activation	5.26 years	γ 1.17; 1.33 MeV
^{192}Ir	neutron activation	74 days	γ 0.38 MeV (average)
^{125}I	neutron activation	59.9 days	characteristic + γ 27.8 keV (average)
^{103}Pd	neutron activation	17 days	characteristic + γ 20.9 keV (average)
^{198}Au	neutron activation	2.7 days	γ 0.412 MeV
^{90}Sr	fission product	28.7 days	β 2.27 MeV (max.)
^{106}Ru	fission product	1.02 days	β 3.54 MeV (max.)
^{169}Yb	neutron activation	32 days	γ 93 keV
^{131}Cs	neutron activation	9.7 days	γ 30.4 keV
^{170}Tm	neutron activation	128.6 days	γ 66 keV

Compared to the use of radionuclide sources, their advantage is that the source generates low-energy X-rays and does not require the construction of canyons. In addition, such a source can also be used for intraoperative brachytherapy, which expands the indications for use.

3.3 Cobalt gamma units

In the early 1950s, units for remote radiation therapy based on a ^{60}Co source were created [43]. Physicists were led to this idea by the fact that, at that time, electron accelerators with low energies of 1–5 MeV were operating in medicine, and irradiation was carried out with beams of bremsstrahlung photons. Their average energy was approximately half of this energy, ~ 0.5–2.5 MeV. During the decay of the ^{60}Co nucleus, photons with an average energy of 1.25 MeV (or more precisely, two close photon energies of 1.18 and 1.33 MeV) are produced, i.e., almost the same as in the accelerators used. These circumstances, as well as the simplicity of controlling cobalt devices, made them quite competitive with the existing accelerators. Other isotopes, ^{226}Ra, ^{137}Cs, were also tested, in which photons with energies of 0.19 and 0.66 MeV, respectively, are produced. Figure 6 shows the decay diagram for ^{137}Cs and ^{60}Co.

However, ^{60}Co turned out to be the most suitable of these radioactive sources for external beam radiation therapy. Its advantages over ^{226}Ra and ^{137}Cs sources are its high average photon energy and the possibility of obtaining a higher specific activity (curie/g). The maximum dose when using ^{60}Co γ radiation is shifted from the body surface to a depth of ≈ 0.5 cm, which reduces skin irradiation. The ^{60}Co source is obtained by irradiating the stable ^{59}Co isotope with neutrons from a reactor in the reaction $^{59}Co(n,\gamma)\ ^{60}Co$. Currently, clinics widely use gamma-therapeutic devices with a ^{60}Co source with an activity of about 5000 Ci, which allows for various irradiation geometries and modes.

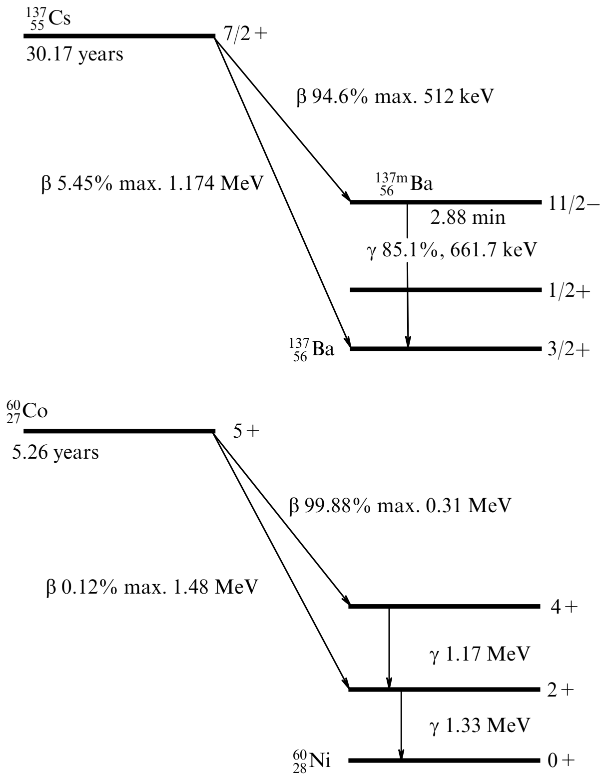

Figure 6. Simplified diagrams of decay of ^{137}Cs and ^{60}Co.

The source is usually a small solid cylinder or several disks contained in a sealed steel capsule. This capsule, in turn, is inserted into the next one and welded shut to prevent radioactive leakage.

The electrons that are produced during the radioactive decay of ^{60}Co nuclei are absorbed by the steel capsules, producing X-rays with an energy of about 0.1 MeV. These photons do not make a significant contribution to the dose, since they are reabsorbed by the capsule or scattered in the medium. On the other hand, high-energy photons can interact with the housing of the device or the collimator, which leads to the creation of low-energy photons outside the source capsule. They have a significant effect on the dose distribution in the patient (about 10%). In addition, secondary electrons are formed, usually called electron beam contamination, which also increase the dose on the surface of the patient's body.

In the 1950s and 1960s, cobalt installations were serious competitors to accelerators. They had not only photon energy but also a beam intensity comparable to an accelerator and were also much smaller. They are easier to operate than accelerators and are more common in countries where there is a shortage of qualified specialists capable of operating and servicing accelerators. In the seventies, the number of cobalt installations in the world exceeded 13 thousand. However, in recent decades, they have been replaced by compact linear electron accelerators. There are currently ~ 1000 of them left in the world and ~ 100 in Russia. Hundreds of thousands of cancer patients undergo treatment with these systems every year. It can be said with certainty that cobalt units will not be completely displaced from radiation therapy.

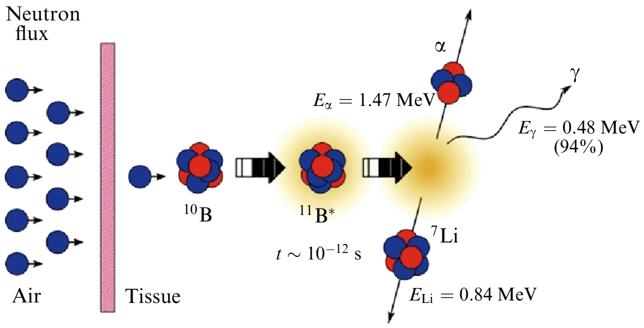

Figure 7. Schematic diagram of interaction of neutrons with boron isotope in patient's tissues.

3.4 Physics of neutron capture therapy

Neutron capture therapy is a method of radiotherapy using nuclear reactions under the influence of neutrons with radiosensitive drugs [44]. The essence of the method is that, before irradiation, to increase the sensitivity of the tumor to the radiation of the neutron flux, boron, gadolinium, or cadmium are introduced into it and exposed to a thermal neutron flux. The cross section of thermal neutron absorption by the ^{10}B isotope is 3837 barns, while the absorption cross section of neutrons by most elements is of the order of a few barns. As a result of the absorption of a neutron by the nucleus of a ^{10}B boron, a nuclear reaction occurs with a large release of energy in the cell. An excited nucleus of ^{11}B is formed, which decays in 10^{-12}s into a nucleus of ^{7}Li, an alpha particle, and a gamma quantum (Fig. 7):

$$^{10}_{5}\mathrm{B} + \mathrm{n} \rightarrow {}^{11}_{5}\mathrm{B}^* \xrightarrow[10^{-12}\,\mathrm{s}]{\alpha} {}^{4}_{2}\mathrm{He} + {}^{7}_{3}\mathrm{Li} + \gamma\,. \quad (4)$$

In 6% of cases, their total energy is 2.8 MeV, and in 94%, it is 2.3 MeV, with 0.48 MeV carried away by a photon. These charged particles quickly lose energy. Accordingly, the lithium nucleus is slowed down on a path of 5 μm, the alpha particle, on a path of 8 μm. Since the size of the cell is about 10 μm, if there is a boron nucleus inside it that has absorbed a neutron, then 80% of the energy of the nuclear reaction is released in the cell and it dies.

In neutron capture therapy, substances containing ^{6}Li, ^{115}Cd, or ^{159}Gd are also used. If they are selectively accumulated in a tumor and irradiated with thermal neutrons, then the tumor cells are affected by the decay products of the above nuclei, and the degree of damage to healthy cells is small.

This original method has not yet received wide distribution in the world and is mainly a subject of research projects, but with the improvement in radiopharmaceuticals that deliver nuclides to tumor cells, its use in nuclear medicine is very promising. In our country, such a project has been implemented at the Novosibirsk Institute of Nuclear Physics. Currently, Novosibirsk physicists are introducing this method at the N.N. Blokhin Russian Cancer Research Center.

3.5 Gamma Knife

Back in the 1940s, ideas for oncological operations were being developed in which the role of a scalpel was to be performed by gamma rays emitted by radioactive sources. In 1948, the Swedish neurosurgeon L. Leksell proposed a stereotactic frame for high-precision neurosurgical oncological operations. This proposal marked the beginning of stereotactic surgery.

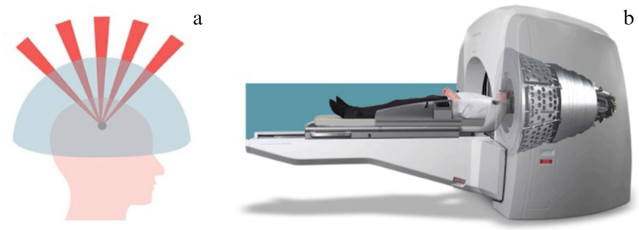

Figure 8. Gamma Knife: (a) schematic representation of device in action; (b) general view of device.

In 1951, Leksell proposed the concept of stereotactic surgery without opening the human skull using radioactive ^{60}Co sources with a half-life of 5.2 years and an average photon energy of 1.25 MeV [45]. This concept was implemented in an apparatus called a Gamma Knife. In it, many beams of γ-radiation from ^{60}Co sources are directed at one point. As a result, the dose in a small target volume increases many times over. Leksell, together with radiobiologist B. Larsson, created the first model of the Gamma Knife (Leksell Gamma Knife) with 179 ^{60}Co sources, and in 1968 in Stockholm, the first Gamma Knife operation was performed [46].

The operation of this system, created for stereotactic radiosurgery, is based on the following physical principles. An artificially synthesized radioactive isotope Co^{60} is used, which is obtained in reactors, as for cobalt units. Radioactive sources up to 3 mm in size are made of it. Physicists have developed a method that allows collimation to obtain thin radioactive photon beams, which in a Gamma Knife are precisely concentrated in a small volume (Fig. 8a).

High target irradiation accuracy (up to 0.3 mm) is achieved due to the static arrangement of the sources and a relatively small distance to the isocenter, located at a distance of 400 mm from each of the sources. In modern systems, a given small volume is irradiated by 201 beams from Co^{60} radioactive sources with an activity of each source of 30 Ci.

The totality of sources provides a dose rate at the isocenter of about 3 Gy/min. The dose delivered to the tumor causes the death of cancer cells. In fact, the tumor is burned out. That is why the device was called a Gamma Knife. The dose accumulated in the target is many times greater than the dose on the surface of the human body, and healthy tissues receive a dose of radiation many times less than the volume of the tumor. Each beam of ionizing radiation is formed by a stationary collimator located on a helmet. The general view of the Gamma Knife device and the schematic principle of its operation are presented in Fig. 8.

The patient's head is kept motionless inside the helmet, due to which the photon beams passing through the helmet channels converge on the target volume. A specific set of beams is selected to irradiate different structures of the brain in order to minimize the irradiation of brain areas that cannot tolerate high doses of radiation. The Gamma Knife allows treating vascular neoplasms, tumors, mainly in the brain, including metastases, without surgical intervention and long-term multi-week irradiation on linear accelerators. So far, the use of this method is restricted to tumors with a diameter of no more than 3 cm.

The results of implementing the considered physical ideas for the medical use of radionuclides and the creation of high-tech medical units, systems, and devices based on them are presented in Table 4. Moreover, their development in Russia

Table 4. Number of medical units using radionuclides [32, 34, 48–50].

	In the world	In Russia	Russia's share, %
Gamma cameras and SPECT	27,180	220	0.81
PET scanners	5671	60	1.06
Boron Neutron Capture Therapy	33	2	6.06
Gamma Knife	396	7	1.8
Brachytherapy	3470	153	4.41

and the world is compared. Hundreds of millions of therapeutic, radiosurgical, and diagnostic procedures are implemented on their basis without surgical intervention. In all developed nuclear physics methods based on radionuclides, not a single radionuclide is used; instead, a medical preparation into which it is incorporated is employed. This is a very difficult radiochemical and radiobiological task. It is necessary that the cell or the entire organism not reject this preparation or solution. The radionuclide must be delivered to the appropriate organ or cell. Based on radionuclides used for medical purposes, more than 200 types of radiopharmaceuticals (RPs) have been created in the world. This makes it possible to carry out more than 50 million procedures and 100 million laboratory tests and to create more than 50 thousand therapeutic doses annually [47].

A significant share of the radionuclides used in the world is produced in our country [47]. But, unfortunately, we barely have a complete closed cycle. Most of the radionuclides are sent abroad, and ready-to-use RPs return to us. In Russia, only 22 types of RPs are used, including 6 types of RPs for PET.

Table 4 shows that the use of diagnostic radionuclide systems in our country, gamma cameras, SPECT, and PET (which, by the way, are not produced in our country) accounts for a share of about 1% of their total number in the world, which is low, as shown by an analysis of data over many years and for different units. The analysis leads to the conclusion that, if in our country the number of high-tech installations of a certain type is significantly higher than 1% of their total number worldwide, then the situation is quite satisfactory. From this point of view, we have a good situation only with brachytherapy.

In Novosibirsk, scientists are actively developing the method of boron neutron capture therapy at the Budker Institute of Nuclear Physics of the Siberian Branch of the Russian Academy of Sciences [34] and implementing it in medical practice at the Federal State Budgetary Institution, the Blokhin National Medical Research Center of Oncology. But this is still an interesting pilot project.

4. Charged particle accelerators in medicine

Accelerators, like reactors and any isotopic device, are unique creations of nuclear physicists of the 19th–21st centuries. They have become not only a tool for scientists to study the microworld, but also an integral part of many technological processes in industry, agriculture and medicine. Achievements of the development of accelerator technology are the development of scientific research in related fields of science and technology, e.g., electronics, forevacuum technology, microwave physics, and materials science, and the creation of new devices, instruments, and technologies based on them. There are currently more than 46 thousand charged particle accelerators in the world, and more than a third of them are in medicine.

The active penetration of accelerator technology into medicine is associated with the 1970s. By this time, more than 300 accelerators of various types were already operating in this field (157 betatrons, 118 linear accelerators, 22 Van de Graaff accelerators, and 9 resonant transformers). Trial experiments were conducted with proton accelerators — 4 of them were in operation, including 2 in our country. In 1955, a linear resonance electron accelerator was launched for medical purposes [51]. By the 1980s, linear electron accelerators had significantly decreased in size (about 1 m in length) and became convenient for use in radiation therapy. They began to displace the previously dominant betatrons and cobalt units.

To date, joint research by physicists and physicians has led to the development of a whole range of effective nuclear physics methods of remote radiation therapy based on accelerators of charged particles (electrons, protons, ions): linear electron accelerators, cyber knives, intraoperative and tomotherapy units, and proton and ion accelerators.

What is the physical meaning of the effect of such a diverse set of methods on a tumor? All of the listed irradiation methods have one thing in common: cancer cells survive worse than healthy cells.

Cancer cells grow faster. Therefore, they require more nutrition and, as a result, a large number of blood microvessels pass through cancer tissues. More oxygen is consumed to provide nutrition to diseased cells. The cross section of interaction of photons with oxygen is greater than with lighter nuclei ^{12}C, ^{14}N. Moreover, the number of oxygen nuclei in biological tissue is much greater than that of any other element (except hydrogen). Oxygen entering the tissue with blood must be added to this. Healthy tissues have less of this additional oxygen supply. This may explain the higher probability of cancer cell death compared to healthy cells.

To describe this fact, radiobiologists have proposed the term 'therapeutic interval' or 'therapeutic window.' It is understood as the 'dose distance' between the survival curves of tumor cells and normal tissues. Figure 9a shows the dependence of the degree of damage to the tumor and normal tissue on the total absorbed dose. The difference in dosages for a given degree of damage to the tumor and normal tissue, indicated by the segment with arrows, is the therapeutic interval. In Fig. 9b, the arrows determine the 'difference in radiosensitivity' of the tumor and normal tissue. The therapeutic interval is not a constant value. It differs for different tumors, values of transmitted doses, degrees of dose fractionation, etc. But the main thing is that all remote radiation therapy with beams of photons and electrons, and protons and ions is based on this concept.

4.1 Electron accelerators in medicine

In remote radiation therapy using electron accelerators, physicists have solved the following main problems:

— creating a compact medical accelerator with variable energy from 4 to 25 MeV;

— achieving maximum correspondence of the dose transmitted to the tumor to its size and shape, taking into account its displacement because of the patient's breathing;

— together with radiologists, determining the best fractionation for the maximum possible suppression of tumor cells;

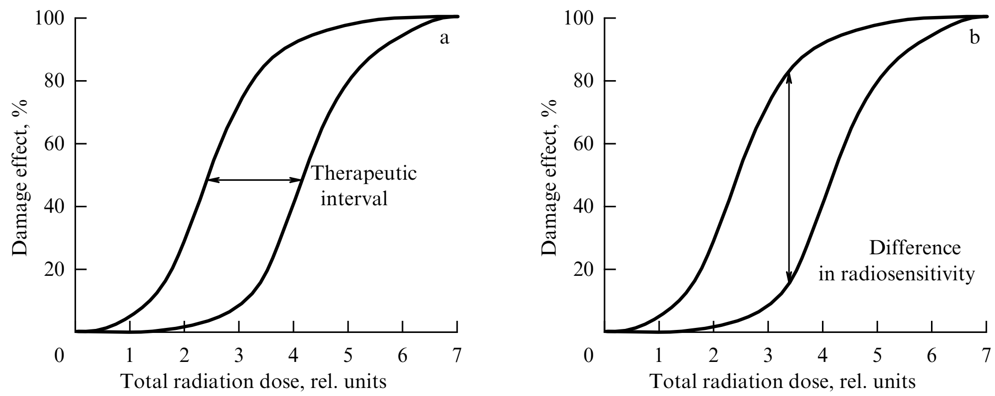

Figure 9. (a) Therapeutic interval — difference between doses at which healthy and cancer cells survive, (b) difference between 'radiosensitivity' of tumor and normal tissue.

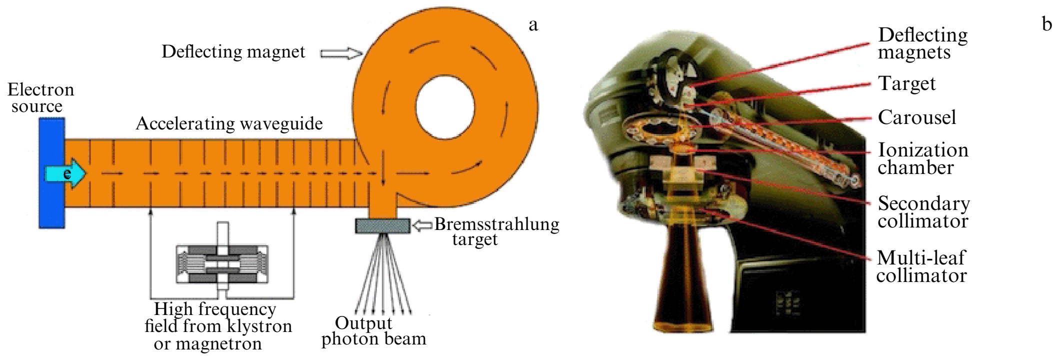

Figure 10. Design of medical accelerator: (a) schematic diagram of electron acceleration and (b) accelerator head.

— together with engineers, creating a complex and bulky device (called a gantry) on which to place an accelerator, which allows the accelerator to rotate around the patient and irradiate the tumor from different sides in order to ensure uniform irradiation of the tumor volume with a minimum dose load on healthy tissues.

The design of a medical accelerator is shown in Fig. 10. Inside the gantry, there is an accelerating section, in which the beam is accelerated by a microwave electromagnetic field with a frequency of about 3 GHz to an energy of 4–25 MeV. Electrons are accelerated in the accelerating section by standing high-frequency waves. At the end, there is a ring in a magnetic field. In this ring, under the action of the magnetic field, the accelerated electron beam turns by 270° and is directed perpendicularly to the target to form a beam of bremsstrahlung photons (Fig. 10a). The target consists of a heavy material, for example, tungsten or an alloy of heavy materials. If it is necessary to irradiate directly with an electron beam, the bremsstrahlung target is removed and the electron beam comes out. The photon beams pass through the patient's body, reducing their intensity, and therefore can affect organs and critical tissues behind the tumor, i.e., having a lower maximum radiation dose. Electron beams stop a few centimeters from the object surface and allow irradiation of only closely located tumors.

Therefore, to achieve maximum compatibility of the planned dose and the shape of the irradiated tumor, physicists and mathematicians have created radiation therapy planning systems based on the theory of interaction of radiation with matter. In these systems, the beam must irradiate the tumor from many directions, and the accelerator for this purpose is located on a gantry, which carries out its rotation around the patient. The shape of the photon beam is changed using a special mechanical device — a multi-leaf collimator. It consists of many metal plates that constantly change the shape of the photon beam so that it coincides with the outlines of the tumor from each direction of irradiation (Fig. 11).

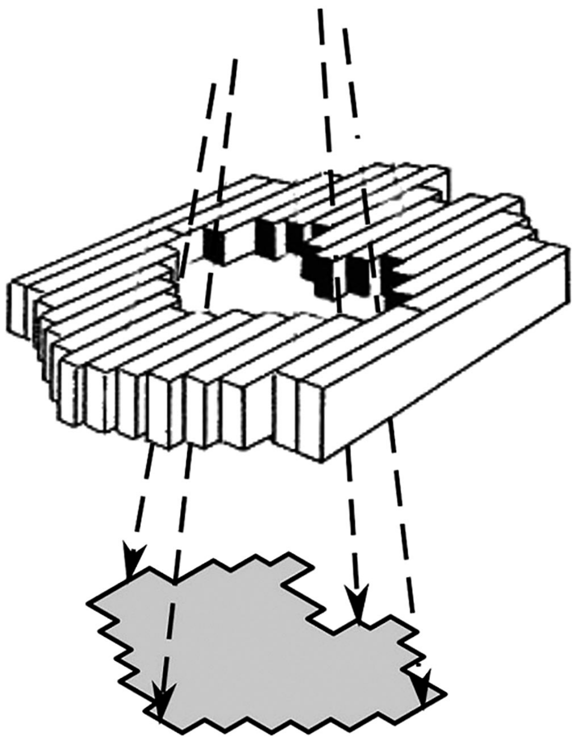

Figure 11. Shape of tumor in MLC collimator.

Formation of the irradiation field maximally close to the shape of the tumor is called three-dimensional conformal radiation therapy (CRT).[10] This nuclear physics method made it possible to increase the radiation dose to the lesion tissues and reduce the load on the surrounding healthy tissues. Later, physicists made several fundamental improvements to the planning systems.

Radiation therapy planning is based on direct and inverse mathematical methods. In the direct planning method, the intensity and shape of the incident beams are specified, and the resulting doses are calculated using numerical algorithms. Manually or semi-automatically, the beam characteristics are selected to ensure that the dose distribution conforms as closely as possible to the specified one. Inverse planning specifies the desired dose distribution, and the software algorithm independently (or with limited human assistance) finds the optimal characteristics and numbers of beam directions from which irradiation is carried out. Inverse planning is more convenient and effective, but more complex from the point of view of mathematical implementation. Therefore, inversion planning methods appeared later, using modern high-power computers.

The development of computed tomography (CT) and magnetic resonance imaging (MRI) scanners, which made it possible to visualize volumetric tomographic images and include them in the planning system, contributed to the improvement of the quality of radiation treatment planning.

The next step in the development of radiation treatment planning systems was the creation of image-guided radiation therapy (IGRT) systems, i.e., planning in the dynamics of the treatment process. For this purpose, the relative positions of the tumor and various human organs through which the beam can pass were clarified. To obtain images in real time, additional dosimetry devices were created — flat panels with solid-state amorphous silicon detectors. The principle of their operation is that the scintillator converts hard gamma radiation into photons of visible light, which is recorded by an array of photodiodes and processed by a computer. This made it possible to increase control over the course of radiation treatment.

Further development of complementary methods of radiation therapy included:

— taking into account the patient's respiratory function when irradiating moving organs;

— taking into account the heterogeneity of pathological tissue by varying the intensity of beams from different directions during irradiation (IMRT, Intensity-Modulated Radiation Therapy);

— stereotactic radiosurgery (SRS), when multiple beams are directed to one point;

— volumetric modulated arc therapy (VMAT), in which the gantry rotates 360° in one session.

The physics of the beam impact on a cancer cell using new additional mathematical methods is the same. The problem solved by physicists and mathematicians when creating new packages of complex programs is improving the accuracy of the beam's hit on the tumor and reducing the number of such hits on healthy cells.

Thus, a modern medical accelerator is not just a physical device, but a whole complex of systems, including diagnostic and treatment planning systems, positioning systems, collimator systems, and others.

[10] This type of therapy is understood to imply the formation of a radiation field that is as close as possible to the shape of the tumor.

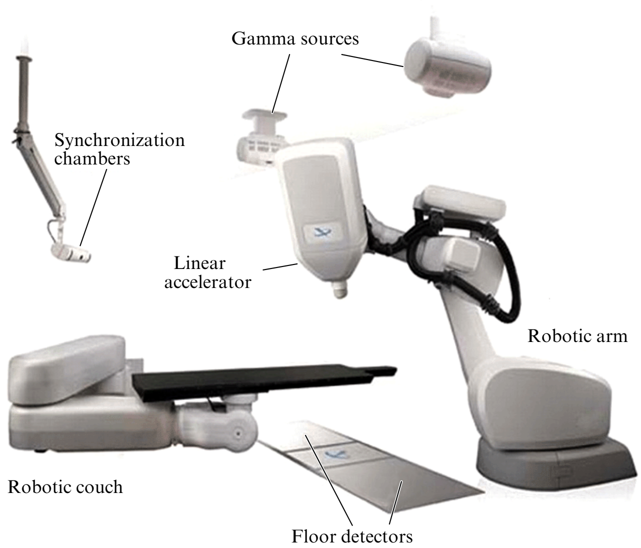

Figure 12. CyberKnife equipment in treatment room.

4.2 Stereotactic radiosurgery

For a long time, stereotactic radiosurgery could only be performed for brain tumors using a Gamma Knife. However, in 1992, the CyberKnife was created in the USA under the leadership of D. Adler. The CyberKnife became the first and only radiosurgical system available to patients that combined image control and computerized robotics. Thus, a new generation of intelligent robotic radiosurgery was born. The system (Fig. 12) consists of a lightweight linear accelerator mounted on a mobile robotic arm with six degrees of freedom and tracking systems (X-ray and infrared) for movement and breathing.

The energy of the linear accelerator used in the CyberKnife is 6 MeV, and its mass is about 120 kg. Bremsstrahlung is generated on a tungsten-copper target. The radiation is collimated using tungsten collimators, which set circular radiation fields of different radii from 5 to 60 mm. The dose rate in modern models is 8–10 Gy/min.

4.3 Tomotherapy

At the end of the last century, physicists and physicians began to think about developing technologies that would allow combining two or three tomography methods or radiation therapy methods simultaneously with diagnostic methods. One of the most rapidly developing areas is tomotherapy, which involves combining CT and a linear accelerator to perform radiation therapy[11] [52]. Similar ideas were implemented much earlier, but with a cobalt gamma apparatus.

The essence of the method is that, instead of an X-ray source used in a CT scanner, a compact electron accelerator with a low energy of 6 MeV is used. The method combines the capabilities of a CT scanner for diagnostics and radiation therapy using bremsstrahlung photon beams. When performing CT diagnostics, a reduced beam intensity is used, while during radiation therapy it is increased. The tomotherapy method allows monitoring the process of radiation treatment in the dynamics. The electron accelerator moves around the patient in a spiral (Fig. 13). The detection system is located

[11] The tomotherapy technique was developed by University of Wisconsin professors Thomas Mackie and Paul Reckerdt, and the first treatment was performed in 1994.

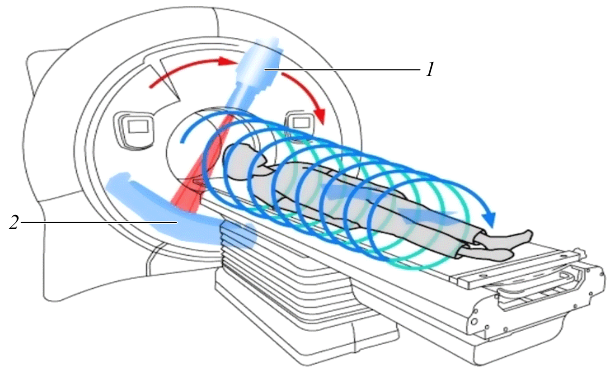

Figure 13. Tomotherapy technique: *1* — electron accelerator, *2* — detector unit, movable table.

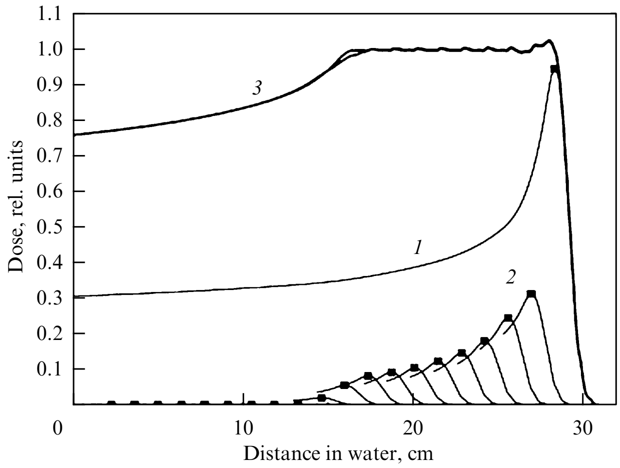

Figure 14. Bragg peaks: *1* for proton energy of 250 MeV, *2* after passing through comb filter, *3* modulated Bragg peak.

opposite it. This approach allows irradiation of both the entire body and large tumors (up to 1.5 m).

4.4 Proton and ion accelerators in medicine

First of all, it is necessary to note the reasons why physicists continued to search for radiation therapy methods. The use of photon and electron beams did not solve the entire set of problems set by oncologists. First, some tumors turned out to be radioresistant, i.e., resistant to high doses of radiation. Second, irradiation with bremsstrahlung photons, as noted above, always occurs 'through and through,' i.e., the tissues located behind the tumor still receive a dose, although in planning systems it is reduced as much as possible. But the dose limit for some critical organs and tissues turned out to be quite strict. Third, as early as 1903, the physicist Bragg [53] established an experimental fact: the deceleration trace of an alpha particle in a photographic plate had an increased blackening at the very end of its path. Furthermore, the dose was not transferred to the substance. This fact was called the Bragg peak. Fourth, for protons and ions, the average angle of multiple scattering is small and is less than 4°, which increases the accuracy of hitting the target.

Such a peak was observed for various heavy charged particles and ions [54]. In 1946, R. Wilson wrote in the medical journal *Radiology* that beams of protons and heavy ions would be ideal for treating cancer patients, because most of the energy release and hence biological damage occurs in the immediate vicinity of the end of the particle's path [12] [55].

The reason for its appearance is as follows. Heavy charged particles lose energy in the medium as a result of ionization losses, inelastic scattering, and nuclear reactions. Ionization energy losses are proportional to the square of the particle charge and approximately inversely proportional to the square of its velocity. In addition, they are proportional to the density of the substance and do not depend on the mass of the incident particle. Therefore, with an increase in the depth of penetration of heavy ions and protons into the substance, the energy losses per unit path (i.e., the dose absorbed by the substance) increase insignificantly almost along the entire path in the substance and only at the end of the path do they begin to increase rapidly and create a sharp maximum (Fig. 14).

[12] K. Tobias and J. Lawrence were the first in 1952 to use beams of protons, deuterons, and alpha particles from the synchrocyclotron at the Berkeley Laboratory (USA) for medical and biological research. In 1954, the first patient was treated with a proton beam at Berkeley. In 1967, such a beam was launched at JINR (Dubna), and in 1969, at ITEP (Moscow).

The main reason for the emergence of the Bragg peak is

$$\left(-\frac{\mathrm{d}E}{\mathrm{d}x}\right)_{\mathrm{ion}} \sim \frac{1}{v^2}\,. \qquad (5)$$

The presence of a maximum in the depth distributions of the dose at the end of the path allows concentrating a large dose inside the target volume and reducing the dose in the healthy tissues surrounding it.

To irradiate a tumor throughout its depth, the sharp Bragg peak (see Fig. 14) is modified into a distribution uniform in a certain region (see Fig. 14). It is practically impossible to vary the energy of heavy charged particles at the accelerator output. Therefore, this is achieved using special filters installed in the beam path. Comb, rotating, spiral, and other filters are usually used. Their operating principle is reduced to the transformation of the original monoenergetic beam into one with a wide energy spectrum (see Fig. 14). The proton beam passes through a different layer of the filter material and, as a result of ionization losses, a spectrum of protons with different energies and their own Bragg peaks is formed. In the target region, these dose distributions are added together and a total, modulated Bragg peak is formed.

In experimental use, proton therapy has shown advantages over using photons, e.g., in irradiating malignant tumors near critical structures, such as chordomas and chondrosarcomas of the skull base and spine.

In radiation therapy, ring accelerators of protons and ions, cyclotrons and synchrotrons, are mainly used. Note that, to obtain a modified Bragg curve in a synchrotron, the beam is removed from different orbits and the corresponding Bragg curves are summed up, and in a cyclotron, as was said above, a comb filter is used for this purpose. In this case, the flux of secondary particles and, first and foremost, the fluxes of secondary neutrons will be greater than in synchrotrons.

Table 5 shows the main types of proton accelerators, the companies that manufacture them, and some parameters of these systems.

As can be seen from Table 5, physicists have tested many different models of proton accelerators in proton therapy. Most often, preference is given to cyclotrons, which have a higher beam current than synchrotrons do. Additional protection against secondary neutrons is installed in them.

Table 5. Parameters of main medical proton accelerators [56].

Company	Name	Accelerator type*	Proton energy, MeV	Power consumption, kW	Weight, t	Diameter, m	Beam current, nA
IBA	C-235	C	235	660	210	4.7	100
IBA	S2-C2	S SC	230	300	50	2.3	150
IBA	C-400 (preliminary)	S C	400 MeV/nucleon	600	660	6.3	8
Mitsubishi		S	(70 – 320) MeV/nucleon	400	40	17	5
Mitsubishi		S	230	200	22	7	5
Hitachi	ProBeat	S	270	300	24	7.5	3
Varian	ProBeam	S C	250	300	90	3.2	800
Mevion	S250 Series	S SC	250	200	20	1.5	~ 100
Sumitomo	SHI	C	250	550	210	4.7	100
ProTom International	Prometheus/ Radiance330	S	330	To 100	15	5.5	0.3/0.6
ProNova	SC360	S C	250	300	60	2.4	600

* Following abbreviations are used for different types of accelerators: C — cyclotron, SC — synchrocyclotron, SC — superconducting cyclotron, S SC — superconducting synchrocyclotron, S — synchrotron.

Proton accelerators are used in radiation therapy less than 1% of the time, since their cost is approximately an order of magnitude higher than that of an electron accelerator (~ 70 million euros). In addition, the number of tumor types that can be effectively irradiated with a proton accelerator is much smaller than with a bremsstrahlung photon beam. The second problem is the significant size of the unit.

Superconducting elements have been developed in recent decades, which will reduce the size and, possibly, the cost of a unit.

Then, physicists measured Bragg curves for many nuclei, including uranium. They analyzed the ratio of the dose at the entrance to the medium and at the maximum of the Bragg peak, and the spread of the beam in the transverse direction. The accuracy of hitting the target for ions was approximately 0.5 mm. They found that a 'tail' appears behind the Bragg peak for ions, which increases with the growth of the atomic weight of the ions. Figure 15 shows the Bragg curves for protons and nuclei of ^{4}He, ^{12}C, ^{16}O. The presence of a fragment range leads to a change in the shape of the Bragg curve, which has a protrusion behind the Bragg peak (Fig. 15), called a 'tail.'

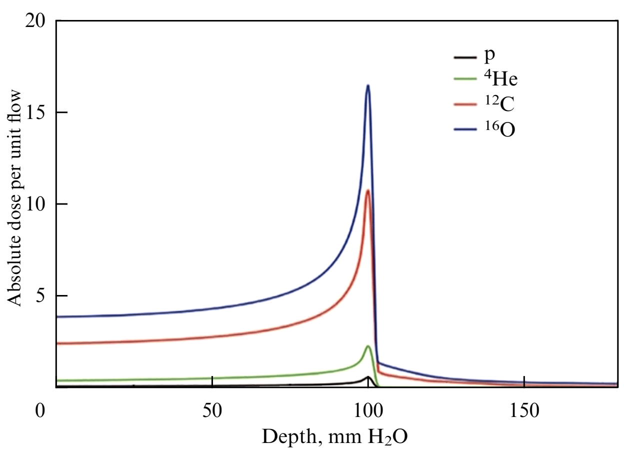

Figure 15. Dose distribution in water for protons and nuclei ^{4}He, ^{12}C, ^{16}O.

The reason for the effect is that, when interacting in tissues, heavy nuclei disintegrate into fragments that have a greater range than the original nuclei. For example, from the ratio of the ranges of two particles

$$\frac{R_2(E_2)}{R_1(E_1)} = \frac{z_1^2}{z_2^2}\frac{m_1}{m_2}\,, \tag{6}$$

it follows that, if $m_2 = m_1/2$, $z_2 = z_1/2$, then the fragment range will be 2 times greater: $R_2 = 2R_1$

As a result of experimental studies, the main advantages of ion therapy have been established:

— the therapeutic effect is achieved at significantly lower radiation doses due to an increased entrance-to-peak dose ratio of carbon ions;

— the average scattering angle of the ion beam in a tissue-equivalent medium is approximately one fourth that of protons;

— a significantly wider range of tumor types is suppressed, including inoperable and radioresistant ones;

— as the ion beam passes through tissues, unstable isotopes are generated, and monitoring their decay makes it possible to control the radiation dose during the treatment.

It has also been shown that, among ions from helium to uranium nuclei, the ratio of the peak dose to the dose at the entrance to the medium is best for carbon ^{12}C nuclei (see Fig. 15). The heavier the ion, the higher the dose from fragments at a depth beyond the Bragg peak.

The scattering angle of carbon ions is many times smaller than that of protons. Fragmentation (the disintegration of nuclei into fragments when they interact with matter) is insignificant for ^{12}C nuclei.

Carbon is harmless to the body. In addition, ^{11}C is formed in biological tissues during irradiation, which decays with a lifetime of approximately 20 min, emitting ^{11}B nuclei and positrons:

$$^{11}_{6}\mathrm{C} \xrightarrow[20.4\ \mathrm{min}]{\mathrm{e}^+} {}^{11}_{5}\mathrm{B} + \mathrm{e}^+\nu_\mathrm{e}\,. \tag{7}$$

They, in turn, annihilate with electrons, emitting gamma quanta:

$$e^+ + e^- \to 2\gamma\,.$$

This allows dynamic monitoring (similar to PET tomography) of the accuracy of carbon nuclei hitting the tumor.

However, with all the positive factors, the cost of a carbon radiation therapy complex reaches 200 million euros, i.e., 2.5–3 times higher than the cost of a proton radiation therapy complex. For example, the gantry in this complex is 20 m long and 13 m in diameter and weighs 670 tons. Therefore, such complexes are rare in the world.

4.5 High-tech facilities based on charged particle accelerators in medicine

In medicine, more than a third (17,108 electron accelerators and 123 proton and ion accelerators) of all operating accelerators in the world are used for the treatment of oncological diseases and diagnostics [32], which operate in 156 countries. We have 569 of them in our country. Table 6 shows that only the number of tomotherapy systems is clearly insufficient. In terms of other accelerator complexes, we are comparable with the most technologically advanced countries in the world.

Table 7 presents all the most high-tech types of units based on ionizing radiation sources. It should be noted that 12,693 medical accelerators operate in 14 leading countries, and today Russia has risen from 13th place in 2018 to seventh place on this list. For each type of unit (except tomotherapy), our country is no lower than seventh place in the world, and 5 years ago we were not among the top ten leading countries in the world. In addition, 1268 cyclotrons are involved in the production of radionuclides, including 60 in Russia.

Table 6. Facilities with medical accelerators in Russia and the world [32, 34, 57–59].

	In the world	In RF	Share of RF, %
Medical electron accelerators	16,600*	569*	3.6
CyberKnife units	413	10	2.4
Tomotherapy units	639	3	0.5
Intraoperative radiation therapy accelerators	260	12	4.6
Proton and ion therapy accelerators	123	5	4.1
Medical proton cyclotrons for isotope production	1268	60	4.7

* According to IAEA, this number includes cobalt units; there are about 1200 of them in the world, ~ 100 of them in our country.

There are about 200 thousand complex high-tech facilities in the world. Working on them requires very high professional training. Therefore, the specialty of medical physics arose, in which nuclear physicists work. Their area of responsibility is the development of a dosimetric treatment plan, checking all the parameters of the system and dosimetric equipment before and during treatment. The usefulness of the procedure and the life of the patient depend on this.

5. Training personnel for nuclear physics technologies in medicine

It is hardly worth discussing the development of nuclear physics for medicine if you do not train personnel. The need for this arose back in the 1930s, when engineers servicing X-ray units were tasked by physicians to evaluate the doses

Table 7. High-tech systems in medicine [32, 34, 57–59].

Country	Medical electron accelerators	CyberKnife units	Gamma Knife units	Intraoperative radiation therapy accelerators	Tomotherapy	Medical proton cyclotrons for isotope production	Proton therapy accelerators	Brachytherapy	X-ray therapy
USA	3892	120	115	72	162	249	42	772	6
China	2931	39	48	13	84	175	7	12	122
Japan	1069	47	53	?	98	218	24	239	0
India	794	12	6	2	29	25	1	413	5
France	570	40	7	12	28	31	4	100	2
Germany	566	12	10	63	12	43	7	229	114
Russia	555	10	7	12	3	60	5	153	86
Italy	523	9	11	5	26	46	3	61	14
Brazil	374	1	4	4	1	14	0	133	39
Great Britain	358	6	10	11	10	27	7	58	49
Canada	288	4	8	2	6	28	0	52	14
Turkey	287	11	18	4	34	20	0	31	0
Spain	262	3	7	3	10	21	3	147	13
Australia	224	2	8	3	4	19	0	11	6
...	...	...	...	...	...	...	...	...	...
Total	16,959	413	396	260	639	1268	123	3469	720

received by patients, since in a significant number of cases negative and even lethal results of radiation treatment were noted. Although patient doses were essentially estimated only in a rough, back-of-the-envelope manner, treatment outcomes improved significantly. The need for specialists dedicated to dose calculation, who were later referred to as medical physicists, became clear. In 1955, the first medical physicists graduated from Uppsala University (Sweden). This new specialty then developed along an increasing trajectory. The first association of medical physicists was formed in 1963 in Chicago (USA) [60].

Then, the International Organization for Medical Physics (IOMP) was formed, which unites national associations from 86 countries comprising a total number of medical physicists of more than 25 thousand. At the same time, the number of medical physicists in different countries fluctuates from a few to 10 thousand in the USA. In 1993, a legally independent public organization, the Association of Medical Physicists of Russia (AMPR), was formed, which numbers approximately 690 medical physicists and 250 engineers. The demand for them in Russia is about 3000 specialists.

The main contribution to the training of medical physicists in Russia is made by Moscow State University, MEPhI, Tomsk Polytechnic University, St. Petersburg State University, St. Petersburg Polytechnic University, Novosibirsk State University, Kazan Federal University, Ural State University, North-Eastern Federal University (NEFU), and other universities. Programs for training medical physicists have been created: the first ones have been implemented at MEPhI.

A unique school for training personnel, including highly qualified medical physicists, has been created based on Moscow University [61]. Graduates receive not only fundamental knowledge and practical skills for working in radiation therapy departments, but also the opportunity to jointly conduct advanced scientific research in the field of radiation medicine throughout their entire professional career. Moscow University collaborates with more than 15 leading nuclear physics and oncology centers in Russia.

5.1 Higher education programs at Lomonosov Moscow State University

The Physics Department of Moscow State University implements three educational programs of higher education: a specialty in Accelerator Physics and Radiation Medicine; a master's program in Accelerator Physics and Radiation Medicine; and a master's program in Radiation Medical Physics. They are aimed at training specialists in theoretical and experimental profiles in the field of radiation medical physics for radiation therapy departments. The programs consist of three components: fundamental knowledge in physics, medical and biological principles, and scientific research practical classes in laboratories or medical institutions. Within the framework of the educational programs, scientific research is carried out in the leading oncology centers of Moscow. Among them are the Herzen Moscow Oncology Research Institute, the Blokhin National Medical Research Center of Oncology, the Burdenko National Medical Research Center of Neurosurgery, the Moscow Regional Oncology Dispensary, the Dmitry Rogachev National Medical Research Center of Pediatric Hematology and Immunology, the Burnazyan Federal Medical and Biomedical Center, the European Medical Center (EMC), and City Clinical Hospital No. 57 named after D.D. Pletnev.

Training in these programs allows graduates to work on high-tech equipment (medical accelerators and other sources of ionizing radiation), solving problems related to the treatment of patients, conducting radiobiological experiments and innovative research in the field of radiation medical physics, and improving existing technologies. By 2024, 210 students had graduated, of which more than 100 work in radiology departments.

5.2 Continuing education programs

To address the pressing issue of the shortage of qualified medical physicists in Russia, Moscow University is implementing programs for professional retraining and advanced training for radiation therapy. The programs are based on the modular principle of constructing an educational process focused on practice in accordance with the needs of radiation therapy departments.

An important achievement of Russian education and science is the creation of a program for professional retraining of specialists for radiation therapy departments at Moscow University [62]. The program is primarily aimed at filling the acute shortage of qualified personnel in the regions and is 530 hours, including 2.5 months of classes (resident and remote) and independent work, as well as one month of practice in leading oncology medical institutions of Moscow. From 2017 to 2024, 56 specialists were trained under this program, including 45 students from Russian regions (Novosibirsk, Donetsk, Orsk, Ryazan, Kaluga, Arkhangelsk, Cheboksary, Khabarovsk, etc.), as well as from Uzbekistan. Graduates of this program can undertake the procedure of primary specialized accreditation.

A number of short programs of advanced training (18 hours, 72 hours, and 144 hours) have been created, which are implemented remotely. Graduates of the advanced training program of 144 hours can undertake the procedure of periodic accreditation.

5.3 Training of highly qualified personnel

An important achievement of Moscow State University is the consistent advancement of professional training for medical physicists. Talented specialists become postgraduate students or external doctoral candidates at the university. In collaboration with radiochemists and radiobiologists, a specialized Dissertation Council (Thesis Committee) has been established at Moscow State University, authorized to confer the degree of Doctor of Sciences.

Over the past decade, the university has been transforming into a nationwide center for research in radiation medical physics. Many innovative ideas proposed by physicists from collaborating oncological institutions are further developed here, refined through scientific work, and subsequently applied in clinical practice. These research efforts form the basis of dissertations defended before the university's Doctoral Thesis Committee. To date, more than 30 dissertations have been successfully defended. Most importantly, the majority of them have been implemented in oncological institutions on accelerators and tomographs, not only in Moscow, but across Russia.

5.4 Accreditation of specialists in field of medical physics

Medical physicists working in healthcare institutions, like medical doctors, are required to undergo accreditation in order to be eligible to practice. To address this demand, a comprehensive assessment system was established at MSU, including a question bank of 2000 items designed to test theoretical knowledge. For the evaluation of practical skills within the accreditation process, developers from the domestic companies RT-7 LLC and Gradiaciya LLC provided specially designed training modules based on their own software, which is currently used in radiotherapy departments. In July 2024, the first such accreditation in Russia took place.

6. Prospects for development of nuclear physics technologies in medicine

This review focuses on the development of physical ideas for nuclear technologies in medicine. It is a continuation of a series of reviews prepared earlier [63–67].

To summarize, it should be emphasized that, despite the challenging economic and political circumstances both in Russia and worldwide, new physical concepts and medical technologies continue to be developed successfully — and at the highest level.

And some of them are unique and are aimed at the medicine of the future. Let us note some of the most striking projects of the leading scientific centers in Russia, the launch of which should be expected in the coming years.

6.1 Russian ONIX complex of radiation therapy

In 2022, Rosatom registered a radiation therapy system based on the compact electron accelerator ONIX with an energy of 6 MeV, developed by the Skobeltsyn Institute of Nuclear Physics, Lomonosov Moscow State University (SINP MSU), the Laboratory of Electron Accelerators, Moscow State University, and the Toriy Research and the Production Association (RPA) [68].

It allows stereotactic and distant radiation therapy of malignant and benign neoplasms of various etiologies using a bremsstrahlung beam, as well as diagnostic projection imaging for the purpose of precise positioning of the irradiated volume using bremsstrahlung photons with a nominal energy of 2.5 MeV.

6.2 Source of monochromatic X-ray radiation

The Skobeltsyn Institute of Nuclear Physics of MSU, the Laboratory of Electron Accelerators of MSU, and Toriy RPA have jointly designed, and are preparing to construct, a Russian source of monochromatic X-ray radiation with a variable energy of up to 200 keV. Its application in medicine promises to open a new stage in the development of computed tomography, radiation therapy, angiography, and related fields. In radiation therapy, monochromatic X-rays can be used by first accumulating an absorbing substance — such as iodine — within the pathological focus (e.g., a tumor) and then irradiating it with the monochromatic beam. In tomography, diagnostic value can be enhanced by varying the energy of the X-ray radiation.

The first large-scale scientific facility in our country is currently under development at the National Center for Physics and Mathematics (NCPM, Sarov). It is designed as a source of (quasi)monochromatic γ-quanta, generated through the effect of inverse Compton scattering of photons on relativistic electrons [69].

In addition to addressing a wide range of fundamental problems in nuclear and particle physics, the facility allows the study of a wide range of applied problems in medicine, including those mentioned above. At the first stage of the project, monochromatic X-rays with $E_\gamma \sim 10-500$ keV can be generated on a linear accelerator and storage ring with $E_e \sim 70-120$ MeV.

6.3 Flash therapy

In recent decades, one of the original areas of nuclear physics research in radiation therapy has been the influence of beam characteristics on the therapeutic interval.[13] It turns out that this interval depends on the type, energy, and intensity of the particles. Physicists and radiobiologists are studying ways to increase this interval for more reliable protection of healthy tissues.

Within the therapeutic interval, the dose can be delivered to the pathological lesion in several ways. In the first classical case of radiation therapy with bremsstrahlung photons, the dose is divided into fractions, and the total dose for the entire course of treatment is 60–80 Gy (2 Gy in each fraction). In this case, the dose rate of bremsstrahlung radiation does not exceed 10 Gy/min, ~ 0.2 Gy/s. With such a dose, healthy tissues are effectively restored. In the second case of stereotactic surgery, the irradiated tissue volume is reduced and the accuracy of the particle beam hitting it is increased. In this case, the transmitted dose in one fraction is increased to ~ 8 Gy, as, for example, in the CyberKnife. The increase in the transmitted dose in one session occurs as a result of irradiating the target from a large number of directions. The total dose remains approximately the same as in the classical case, but the number of sessions is reduced.

In 2014, physicists proposed a new method of radiotherapy called flash therapy[14] [70]. It involves very rapid delivery of a dose that exceeds the dose rate in classical radiation therapy by 200–500 times. The irradiation time is reduced by orders of magnitude to $10^{-6}-10^{-2}$ s, and the average dose rate exceeds 40–80 Gy/s. This is achieved due to such physical parameters as the repetition rate and duration of pulses. It is assumed that the use of very short pulses (1–10 ns) of high intensity allows increasing the therapeutic interval. This is also indicated by the results of many experimental studies. They point to the fact that one of the fundamental goals of radiation therapy is accomplished — full restoration of normal tissues after the harmful effects of ionizing radiation, and more effectively than in classical radiation therapy. At the same time, the tissues of the pathological focus are better suppressed.

The physical meaning of flash therapy is as follows. The dose is transferred to a biological subject (for example, a protein molecule) at different times, depending on the current of charged particles in the accelerator. The current can be pulsed or continuous. It can reach 400 mA per pulse in modern linear electron accelerators with a bright beam and 600 nA in proton accelerators.

The dose rate or gradient in a linear accelerator depends on the pulse length. For example, with a pulse length of 10 μs and an energy of 10 MeV, it is possible to obtain 10^2 Gy/s or higher.

Flash therapy is a potentially effective tool for radiation therapy. In addition, such organs as the lungs are constantly moving, and it is difficult for patients to lie still even for several minutes. Flash therapy can perform an irradiation

[13] The therapeutic interval is understood as the difference between doses at which cancer and normal cells die.

[14] This discovery was made in 2014 and confirmed in several subsequent experiments for different types of tissue.

session in seconds. Thus, it is possible to reduce both the duration and total number of sessions. Therefore, the development of flash therapy can become a new branch of radiation oncology, using these technologies for human treatment.

Despite the fact that there are currently few accelerators capable of obtaining a dose rate of 50 Gy/s, modern technical capabilities for upgrading electron and proton accelerators make it possible to achieve a dose rate of up to 200 Gy/s.

In Russia, experimental studies on proton flash beams are carried out at the INR RAS [71]. Scientists have proposed a new irradiation mode: an ultra-flash mode, which allows delivering a dose of 40–50 Gy in 100 μs, i.e., 5 thousand times more than in the usual flash mode. (During this time, an entire tumor weighing up to 1 kg can be irradiated.) It turned out that, with such ultra-short irradiation, normal cells were damaged 5–6 times less than with conventional radiation therapy (the experiment took place in March 2020). Radiation damage to radioresistant tumor cells turned out to be 1.5–2 times stronger than that of normal cells.

To conduct experiments on flash therapy using bremsstrahlung, an accelerator with an energy of 6 MeV and a pulsed current of 700 mA of the accelerated beam at this energy is being created at SINP MSU for the Joint Institute for High Temperatures of the Russian Academy of Sciences [72].

6.4 Ion beam therapy

The Institute for High Energy Physics (IHEP) in Protvino has been conducting research for over 20 years to create a carbon beam with an energy of 450 MeV/nucleon. And by now, physicists have come as close as possible to their goal. In 2025, the first carbon beam ion therapy center in Russia is planned to be launched at the IHEP.

6.5 Achievements of nuclear physics for medicine at Joint Institute for Nuclear Research (Dubna)

It should be remembered that the first center for proton beam therapy in the USSR, and one of the first in the world, was opened at JINR in 1967. These advanced traditions of Dubna scientists continue today. At the end of this year, the NICA accelerator for colliding beams of heavy ions will be launched [73].

An entire body of medical and biological research is planned for it. Within the framework of the project, a new type of magnet was created based on the high-temperature superconducting (HTSC) material ReBCO and yttrium ceramics $YBa_2Cu_3O_7$. Such HTSC magnets can become the basis for MRI scanners of the future, which allow obtaining more detailed images than modern MRI can, helping doctors to make more accurate diagnoses.

Following this, the creation of a proton beam therapy center based on a compact superconducting cyclotron with an energy of 230 MeV is entering the final design stage. The creation and improvement of compact superconducting accelerators is an important area of modern applied science in the world. It is important that this project is entirely Russian and is being implemented by JINR jointly with the Efremov Institute of Electrophysical Apparatus (NIIEFA) [74].

6.6 Radionuclides for nuclear medicine

A large share of the radionuclides used in nuclear medicine is produced in Russia. Yet one long-standing issue remains: there is still no closed production cycle. Radionuclides are exported abroad and return as finished medicines needed for healthcare. Building a full production cycle of medical radioisotopes and radiopharmaceuticals in Russia — without relying on foreign companies at the final stage — remains a key task. Only then can we claim a leading role in developing the next generation of radiopharmaceuticals for therapy and diagnostics.

Achieving technological independence requires a substantial acceleration in the realization of our national capabilities. The unique domestic projects presented here provide clear evidence of the significant potential already at our disposal.

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