Form № 24

PROJECT
“Further Development of Methods, Technologies, Schedule Modes and Delivery of Radiotherapy”
for the period 2020-2022
Theme 04–2–1132

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Form № 25

PROJECT ENDORSEMENT LIST
“Further Development of Methods, Technologies, Schedule Modes and Delivery of Radiotherapy”
for the period 2020-2022
Theme 04–2–1132

Co-leaders of the Project: G.V. Mytsin, K.Sh. Voskanyan

Approved by the JINR Director ____________________ _______________

Agreed upon

Vice-director of JINR ____________________ _______________

Chief Sc. Secretary of JINR ____________________ _______________

Chief Engineer of JINR ____________________ _______________

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Approved by the PAC for
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1. 1. Introduction

The main aim of the project “Further Development of Methods, Technologies, Schedule Modes and Delivery of Radiotherapy” is the conducting of medical-biological and clinical research on the basis of the Medico-Technical Complex (MTC) DLNP JINR, to study the effectiveness of hadron radiotherapy for treatment of various tumors, modernization of the equipment and devices and development of new methods of radiotherapy for cancer patients at the medical hadron beams from the JINR Phasotron. The Project is the continuation of research started at JINR in 1967.

By now, the Medico-Technical Complex (MTC) [1, 2] has been established and operates at the Laboratory of Nuclear Problems JINR, on the basis of the 660 MeV proton accelerator (Phasotron) where therapeutic exposure can be conducted of patients with various tumors using the method of 3D conformal proton beam radiotherapy [3] when the maximum of the formed dose distribution conforms most accurately to the shape of the irradiated target. The dose decreases sharply beyond the borders of the tumor that allows conducting the irradiation of inaccessible for earlier radiotherapy localizations that are very close to vital radiosensitive organs of the patient.

In 1999 a specialized Radiological Department of Health Care Facility № 9 of FMBA (Dubna, Russia) was opened in the city that provided an extension of clinical research in hadron therapy for cancer patients at medical beams of JINR.

For example, in the period from 2000 to April 2019, 1287 patients with various tumors (including foreign citizens from JINR Member States) underwent courses of proton radiotherapy at the Phasotron beams with the scientific support of leading specialists of the Medical radiological research center of RAMS (Obninsk) and the Russian Academy of continuing professional education (Moscow).

The irradiation was usually carried out fractionated (on average, about 10-20 sessions in each patient) and from several directions. Annually, the total number of fields (single therapeutic exposures) was about 6000-7000. The Phasotron was used for these studies for about 1000 hours a year.

The activities proposed in the project for the coming 3 years are logical continuation of medical biological research conducted lately, maintaining the basic aims of the studies and the number of participating institutions.

Today, over 200 000 patients in more than 80 centers all over the world have received treatment at proton beams [4]. The results of these clinical studies have shown that proton therapy is a very effective method of treatment of cancer and some other diseases, and in some cases it is almost no alternative. Because to this accumulated positive experience, by the end of the last century, a specialized proton therapy centers were being built at large radiological clinics. Today in the world there are several dozens of projects to create such centers at different stages of implementation.

At the same time, methodic issues of delivering the dose to the abnormal focus, fixing and centering adjustment of the patient and some other aspects have not been solved to the full as for today and are open for further research. The main purpose of the project for the 2020-2022 will be the development of methods of patient’s irradiation with a proton beam that will provide the highest degree of conformability of the dose field for the irradiated target. Clinically it will show in a decrease of the dose that arrives at healthy tissues and organs surrounding the target and in general growth of efficiency of the conducted therapy.

Carrying out works aimed at expanding the range of localizations available for treatment on medical hadron beams of the Phasotron it is also planned.

The high degree of interest in the work of various research and educational institutions both from the JINR member States and from other Russian and foreign organizations it should be noted. Students and postgraduates from these countries regularly carry out their research at the MTC and participate in the workshops, organized by the JINR University Center, within the framework of the annual summer schools. Grants of Plenipotentiary representatives of Poland, Czech Republic and Romania have been allocated to support these works in recent years.

Once the proposed programme is accomplished, evaluations of the efficiency of proton therapy in treatment of a number of malignant tumors will be obtained, practical recommendations will be issued for the choice of optimum variants of radiotherapy treatment of cancer patients and further development of the radiotherapy methods with application of hadron beams, new means, methods and schemes of irradiation fractioning for treatment of cancer patients in these beams will be elaborated and tested.

2. Medical-Physical and Methodical Background

2.1. Prerequisites for the use of hadron beams in radiotherapy

Radiotherapy occupies one of the leading positions in modern oncology. The experience of more than a century of development of radiotherapy has demonstrated sustainable growth of its role in oncological practice. Over 70% of patients with malignant tumors today are in urgent need of one or another variant of radiotherapy [5]. Taking this into account, together with high rate of modern radiation oncology development, it can be stated with confidence that the role of radiotherapy in future will grow more and more.

Upgrading of technical means, elaboration of new methods of irradiation have become the main trend of the modern radiotherapy development. Radiation oncology of today cannot be imagined without extensive planning and irradiation simulation, individual devices of beam shaping, systems of precision immobilization of the patient and its verification that allow achievement of high degree of conformability in radiotherapy.

The development of three-dimensional radiotherapy planning systems laid the groundwork for the rapid progress of radiation technology. It was possible to significantly reduce the radiation of normal tissues volume and improve the quality of patient’s life, and, if necessary, significantly increase the total focal dose, which significantly increased the effectiveness of cancer treatment because to three-dimensional planning.

Along with the upgrading of the irradiation equipment as such, accompanied with optimization of space parameters of dose distribution, the search for optimum modes of dose fractioning, i.e. optimization of irradiation time parameters plays a big role in modern radiotherapy. The development of radiotherapy has led to the emergence of “traditional” dose fractionation methods in different countries. For example, according to the Manchester school, radical radiation treatment consists of 16 fractions and is carried out for more than 3 weeks, while in the US 35-40 fractions are carried out for 7-8 weeks. In Russia, in cases of radical treatment, it is considered traditional to fractionate 1.8-2 Gy once a day, 5 times a week to the total doses, which are determined by the morphological structure of the tumor and the tolerance of normal tissues located in the irradiation zone (usually within 60-70 Gy).

Potentialities of conventional types of radiation (photons, electrons) are well studies. However, their application turns ineffective in a part of cancer patients (from 10 to 30%). To treat such patients it is advisable to apply hadron therapy.

At present, protons, neutrons and carbon ions are used in clinical practice. Space dose distribution in proton radiotherapy and treatment with carbon ions is much better in comparison with analogous values for photons and electrons. Even the application of modern accelerators of electrons with multileaf collimators and beam intensity modulation does not negate this advantage. This is due to the fact that the beams of protons and carbon ions have small angle of multiple scattering in the tissues, well-defined range, and their LET reaches a maximum at a specified depth, forming a Bragg peak. Therefore, the dose in the tumor may exceed the dose on the entrance several times even with radiation from one direction. At the same time, the absorbed dose behind the Bragg peak drops sharply to almost zero.

These properties allows by 2-3 times to reduce the radiation dose on the surrounding tumor normal tissue, which is especially important in the treatment of tumors located near or inside the critical organs, as well as repeated irradiation of recurrent tumors.

It is impossible to apply standard variants of radiotherapy in some cases in order to achieve tumor recovery without growth of complications. The use of hadrons often allows one to solve this problem. For example, excellent geometrical values of dose distribution that permits the achievement of recovery of cancer patients without complications made protons one of most actively studied sources of hadron radiation.

Protons have superiority over "traditional" radiotherapy, when used in patients with tumors of the orbit, pituitary gland, small intracranial tumors, chondromes and chondrosarcomas adjacent to the cervical spinal cord, inoperable and recurrent meningiomas, arteriovenous malformations of the brain, prostate cancer, etc [5].

The benefit from the use of protons can be expected for treatment of recurrent tumors, moderately radiosensitive tumors, when the possibility of increasing the dose in the tumor, reducing the duration of treatment can significantly improve the therapeutic effectiveness of radiation exposure.

The active development of different types of hadron therapy is obvious. However, only about 200 thousand patients have been treated worldwide today [4]. The high cost prevents the widespread introduction of these technologies in the clinical practice of creating specialized medical centers of hadron therapy. Adaptation for medical purposes of existing research accelerators may be an alternative.

2.2. Experience of using hadron beams in radiotherapy

The idea to use heavy charged particles in radiotherapy was expressed by R. Willson in 1946 [6], but it became possible to be implemented only after the introduction of hundreds MeV accelerators of heavy charged particles.

In 1952 Tobias and Lawrence [7] were the first to use beams of protons, deuterons and alpha particles from a synchrocyclotron in Berkeley (USA) for biomedical research. Similar work with 187 MeV protons began Larson (Sweden, Uppsala) in 1956 [8]. Clinical studies on the use of high-energy protons in radiotherapy have been conducted by Kelberg since 1959 at Harvard University (USA) on a synchrocyclotron with 160 MeV protons energy [9]. Russia was the third country where biomedical research in this area began after the USA and Sweden in 1967 [10, 11].

In the mid-1980s of the last century reliable statistical-clinical evidence of the opportunities were accumulated in the world. In the period 1954-1990, the research was conducted by clinicians in 10 experimental centers of proton radiotherapy in scientific physical institutes on accelerators, created for nuclear physics experiments. Created and tested a new generation of the requisite equipment, medical technology (techniques, treatment protocols), tools, dosimetry, specific software, etc.

The positive clinical results of proton therapy, accumulated in these centers, have confirmed expectations and were the reason for the transfer of the work from experimental centers to medical clinics. The first dedicated center of proton therapy was built and launched into operation in 1990 in a big multifaceted hospital of Loma Linda (USA); then rapid application of this method was started in practical health care in developed countries of the world.

Starting from this time, multi-rooms dedicated hospital centers were constructed, each having 3-5 treatment rooms with ray facilities for multifield irradiation of a wide range of tumors localized in different parts of the patient’s body (gantry) with a rotatable beam. As for today, about 80 centers of proton and ion therapy operate in the world and about 40 centers are under construction [12].

The first proton beam in the Soviet Union, with the necessary parameters for radiotherapy, was developed in 1967 on the initiative of V.P. Dzhelepov at the Laboratory of Nuclear Problems JINR, at the 680 MeV proton accelerator [10, 11]. Clinical research was started after a series of physics-dosimetric and radiobiological experiments in 1968, but it was interrupted in 1974 due to reconstruction of the accelerator and development of the multi-room Medico-Technical Complex.

Radiation treatment was performed for 84 patients, mainly for malignant tumors of the esophagus and lung during this initial period of clinical researches [13]. The proton beam was used for medical purposes 2 times a week, with each patient irradiated fractionated (10-15 sessions during 1-1.5 months). Thus, the total number of therapeutic radiation sessions was about a thousand.

The result of this search stage is a proof of the correctness of the basic initial physical, technical, radiobiological and clinical prerequisites, the methods of irradiation of a number of tumor localization have been developed and the expediency of continuing and expanding clinical studies on proton radiotherapy of malignant tumors has been shown.

After the reconstruction of the DLNP accelerator into a high-current Phasotron, sessions of cancer patient’s irradiation were resumed. From 1987 to 1996 40 patients were successfully treated mainly in cases of cervical cancer. Then there was a long pause in the research caused by a number of reasons the main of which was economic slowdown in Russia.

A new round of the development of the present work started in December 1999 when due to efforts of V.P. Dzhelepov again a specialized radiological department of patient capacity of 25 beds was opened in Dubna. Since 2000 regular sessions have been conducted in research of proton therapy efficiency in irradiation of patients with tumors located in head, neck and other parts of the body. By April 2019 1287 patients have received courses of radiotherapy at the Phasotron beams.

The method of 3D conformal proton radiotherapy when the maximum of the formed dose distribution conforms most accurately to the shape of the irradiated target has been put into operation and is used now. In this way, the maximum sparing effect is achieved in normal tissues and organs surrounding the tumor [3].

3. 3. Main characteristics of the experimental equipment

3.1. Medico-Technical Complex at the LNP JINR

To carry out the planned program of activities at the Laboratory of Nuclear Problems JINR, by the end of 1985 the development of the multi-room Medico-Technical Complex on the basis of the 660 MeV proton accelerator Phasotron had been mainly accomplished [1, 2]. The Complex includes six treatment rooms (Fig.1). Room 1 is the most universal and allows to perform the proton irradiation of targets, located in the head, neck and other parts of the patient's body. Room 2 is intended for treatment of gynaecological tumours. Room 3 contains the equipment for stereotactic convergent irradiation of small intracranial targets with a narrow 660-MeV proton beam by the so-called “shoot-through” technique. Room 4 is supplied with the separated negative pion beam of adjustable energy 30-80 MeV. Room 5 accommodates a therapeutic neutron beam to be used, both independently and in combination with the proton beam, for treatment of large hypoxic tumours. The standard unite "Rokus-M" for distant gamma therapy is placed in Room 6 and is used as a back-up radiation source and for combined treatment methods – part of the required dose is collected from gamma radiation to a tolerant value for healthy tissues and after that, the tumour is additionally irradiated with protons.

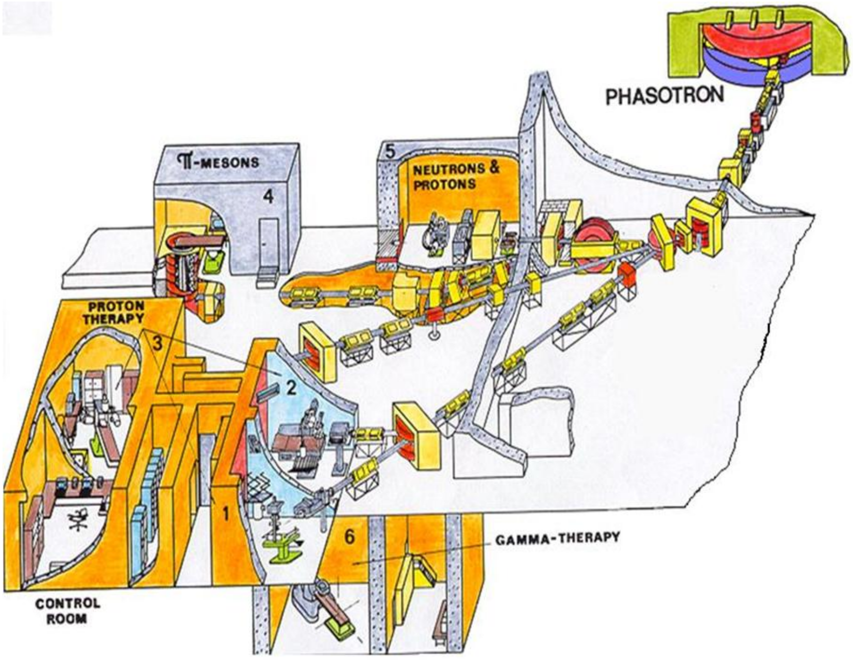

Fig.1. Medico-Technical Complex at the Laboratory of Nuclear Problems JINR

However, for a number of reasons, the main efforts have been lately concentrated on the development of the Room 1 as the most universal one from the point of view of irradiation of a wide range of localizations. This room was upgraded according to requirements of the precision 3D conformal proton radiotherapy (Fig.2).

Fig.2. Treatment Room 1

A wide (8 cm x 8 cm) homogeneous in the cross section decelerated 170 MeV proton beam is delivered to Room 1, to irradiate intracranial targets, and a beam with the energy of up to 220 MeV to irradiate targets localized in the region of pelvis, for example, prostate cancer. The narrow Bragg peak of the initial proton beam is expanded by using of specially designed and manufactured beam energy spectrum modifiers, so-called Range Filter. As a result, at the end of the range, an ionization maximum of Bragg peak is formed with a flat top with a length of 8 to 60 mm (Fig.3). To irradiate the patient, a Range Filter is selected, in which the length of the maximum most accurately corresponds to the size of the irradiated tumor.

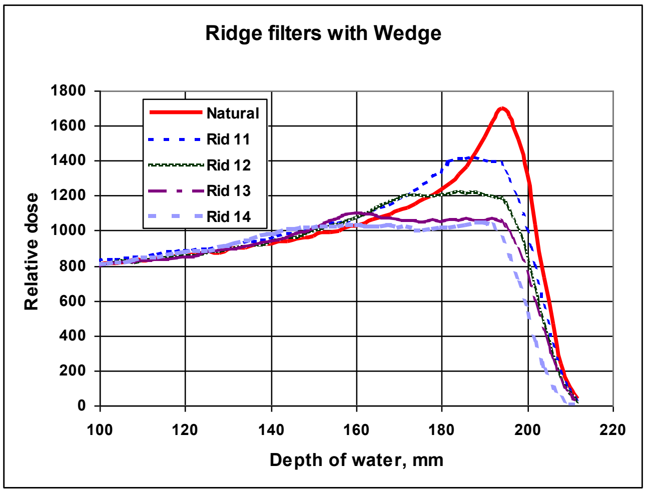

Fig.3. Deep-dose distributions of a therapeutic 170 MeV proton beam with different Range Filters

With an individual collimator of Wood's alloy a profiled beam is formed from the homogeneous one that copies in the cross section the target projection from the irradiation angle. Moreover, the beam is also modified with a profiled decelerator, bolus, on the distance depth in such a way to make all protons stop on the back border of the target. Thus, the maximum sparing mode is achieved for normal tissues beyond the tumor.

During the session the patient is fixed in a special positioner in the form of an armchair, which has four degrees of mechanical displacement - two orthogonal horizontal, one vertical and rotational. All movements can be carried out both manually and from the remote control, as well as by computer commands. The positioner can easily be transformed into a deck for a patient in the lying position (Fig.4).

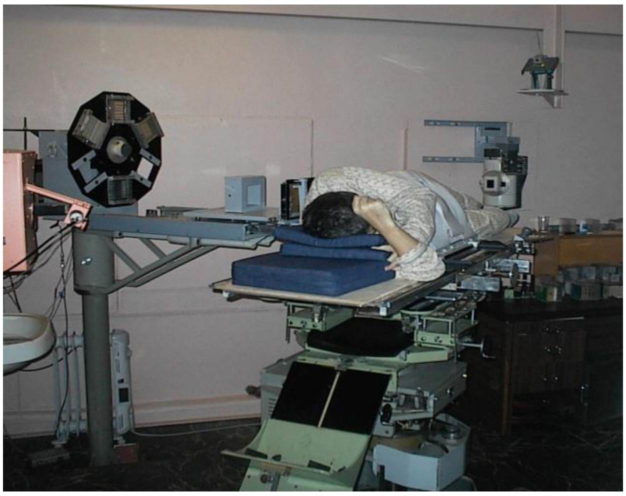

Fig.4. The positioner in Room 1, transformed into a deck for a patient in the lying position

To immobilize (fix) the patient’s head during the pre-irradiation topometric computer tomography (CT) and the subsequent proton irradiation a radiotransparent functional fixator was developed for the head, with an individual mask made of perforated thermoplastic.

An X-ray tube was set-up for centering the beam at the target according to the most reliable rigid bone structures – the orienting points in the beam axis. The digital equipment “Regius-170” of the company Konica-Minolta was purchased and launched for express production of X-ray verification images of the patient and their imaging on the PC monitor screen.

If necessary to treat targets located in the chest area of the patient in a sitting position, there is a problem in planning due to a significant mismatch in the position of the internal organs of the patient in the diagnosis and irradiation. To solve this problem a variant of an X-ray computer tomography device combined with a therapeutic chair was manufactured for topometry [14]. The X-ray tube and the detector unit are fixed on the walls of the treatment room, and the patient, fixed in further irradiated position, rotates in the chair at a speed of 1 rpm. After completion of the full rotation the chair with the patient, the positioner is moved vertically by the specified amount and the measurement is repeated. Tomographic data are reconstructed and entered into the planning system.

3.2. The method of 3D conformal proton radiotherapy

The main methodic and technological stages of pre-irradiation and irradiation are given below. They are the following:

- Immobilization of the irradiate region;
- X-ray and MRI diagnostic and introduction CT sections to the treatment planning system;
- 3D computer planning of irradiation;

- Production of individual devices of beam shaping – profiled collimators and compensating boluses;
- Implementation and verification of the irradiation plan.

As it was mentioned before, heavy charged particle’s beams allow forming dose fields with sharp gradients due to the strictly localized distance and small angle scattering that make it possible to irradiate tumors in the direct neighborhood to the critically radiosensitive structures and body organs of the patient. However, to use these advantages to the full, it is necessary first to hold preliminary thorough planning of irradiation. It is primarily necessary to obtain for it the data on 3D density distribution of the patient’s tissues in the place of the target localization. This is possible to be done with the X-ray computer tomography (CT).

The general requirement is also full correspondence of the position of the irradiated region in diagnostics and in each following session of fractionated irradiation of the patient. In case the target is localized in the region of head or neck, an individual immobilizing mask is manufactured from perforated thermoplastic for each patient, to fix them firmly in tomography session and in the therapeutic chair during irradiation. In irradiation of targets localized in the pelvis region in the lying pose (for example, prostate cancer) special vacuum mattresses are used that keep the form of the patient’s body for a long time and an individual support from thermoplastic is produced.

Tomographic examination is held at the spiral X-ray tomographic scanner in the lying position of the patient, with a fixing mask. Usually, up to 200 sections with 1 mm spacing are measured. The data then are entered in the digital form into the 3D computer system of irradiation planning. To specify the borders of the tumor spreading, magnetic resonance tomography, angiography, etc is additionally conducted.

The conformal radiotherapy is impossible without computer simulation of irradiation. Cooperation with the first in the world hospital center of proton therapy in Loma-Linda (US) resulted in the adaptation of the 3D computer system of irradiation planning “TPN” developed at this center to the equipment and proton beams of the DLNP JINR Phasotron. After a series of dosimetry experiments that verified the dose calculation algorithm the system is used in clinical practice.

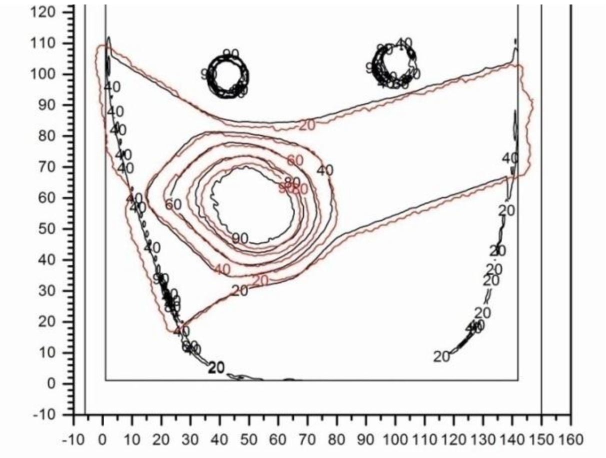

Fig.5. Comparison of the dose distribution calculated by the developed planning program (red lines) with the distribution measured by radiochromic film (black lines). The Figures show a good match.

But this program cannot be modified for correspondence to new methods of irradiation, for example, for dynamic irradiation of tumor with a multileaf collimator. That is why the development of the main components of the 3D program of computer simulation of the conformal proton radiotherapy has been completed by the present time. The developed variant of the program has already been verified dosimetrically with the heterogeneous Alderson phantom and radiochromic films, and now its clinical approbation is being conducted (Fig.5).

The 3D file of topometric data obtained in computer tomography is entered in the digital form into the treatment planning system. In each axial section the radiologist marks the borders of the irradiation target and critical structures, for example, brain steam, optic nerve, etc (Fig.6). Besides, the number of irradiation fields and their directions are given. The planning system generates 3D models of marked structures according to these data.

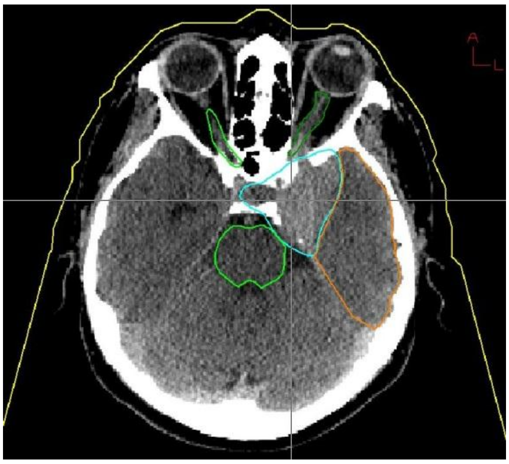

Fig.6. Contoured border of the irradiation target and critical structures on the axial CT slice

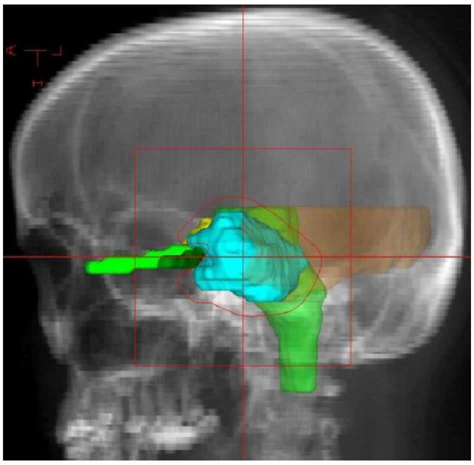

Fig.7. Digital reconstructed X-ray of the patient's skull with the projection of the target, critical structures (brain stem, optic nerves, temporal lobe) and the shape of the Figure collimator for this direction of irradiation.

With the function “beam’s-eye-view” in the program and digital reconstructed X-ray radiograms for each direction of irradiation the proton beam of a definite form in the cross section is determined and marked (Fig.7). In real irradiation it is formed with the individual collimator of the Wood’s alloy.

Compensating boluses – moderators of a complex shape that take into account the heterogeneous structure of tissues and the patient's organs located in the way of the beam – are calculated and then manufactured for conformability of the dose distribution of the proton beam for the target shape in depth (Fig.8).

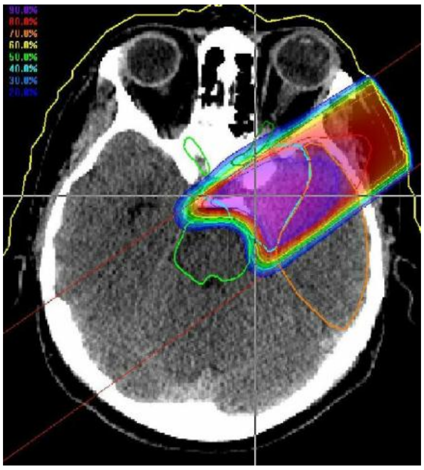

Fig.8. An example of the boluse's operation. A conformal proton beam is formed along the penetration depth

When adding all single beams from different directions, the total dose distribution is calculated (Fig. 9). Sections of three-dimensional structures of the irradiated area and dose distribution can be visualized in three inter-orthogonal projections: axial, sagittal, coronary.

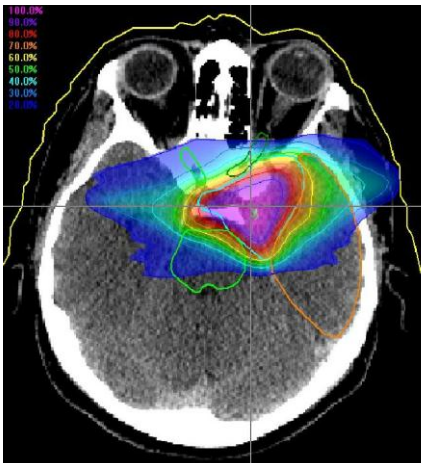

Fig.9. Calculation of the total dose distribution. The sum of four beams from different directions

The final stage of preparation for irradiation ends is production in the MTC workrooms of individual profiled collimators and boluses that are calculated by the planning program (Fig.10); for these purposes all necessary technological devices and facilities have been designed and manufactured.

The proton irradiation is conducted by fractions, as usual – daily, except days-off, during 3-7 weeks (so-called, accelerator cycle). Every day, before an irradiation session starts a therapeutic proton beam is delivered to the treatment room and is thoroughly checked in dosimetry. The beam profile, its depth-dose distribution, dose rate are measured. Then these parameters are controlled directly during the patient's irradiation.

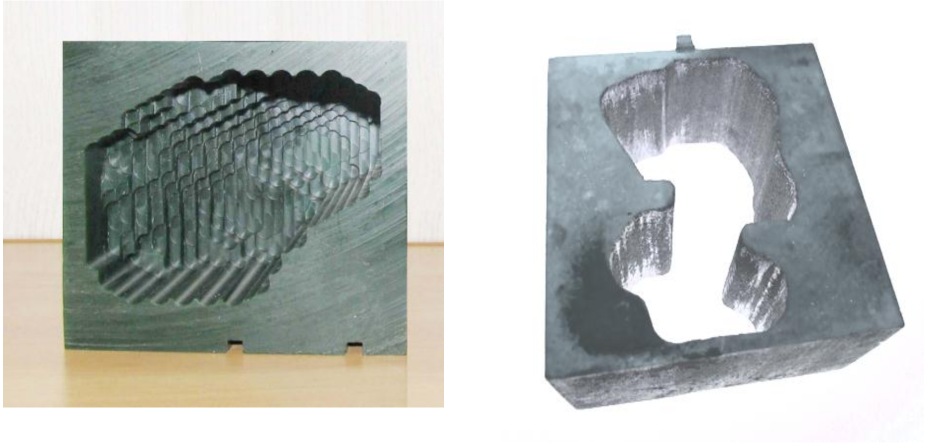

Fig.10. The final stage of pre-irradiation preparation is the production of individual boluses and collimators in the MTC workrooms

For each irradiation direction, before the exposure, an X-ray image of the patient is produced with an X-ray tube installed behind the patient on the beam axis and with the flat panel digital detector. Moreover, at the same time the detector is exposed to the proton beam of low intensity. As a result, the image shows clearly the position of the proton beam in regard to the anatomical structures of the skull (Fig.11). If this position is not the same with the accuracy of 1 mm as that calculated by the planning program a correction of the chair with the patient is done in regard to the beam. Immediately after that the therapeutic irradiation with the proton beam is conducted.

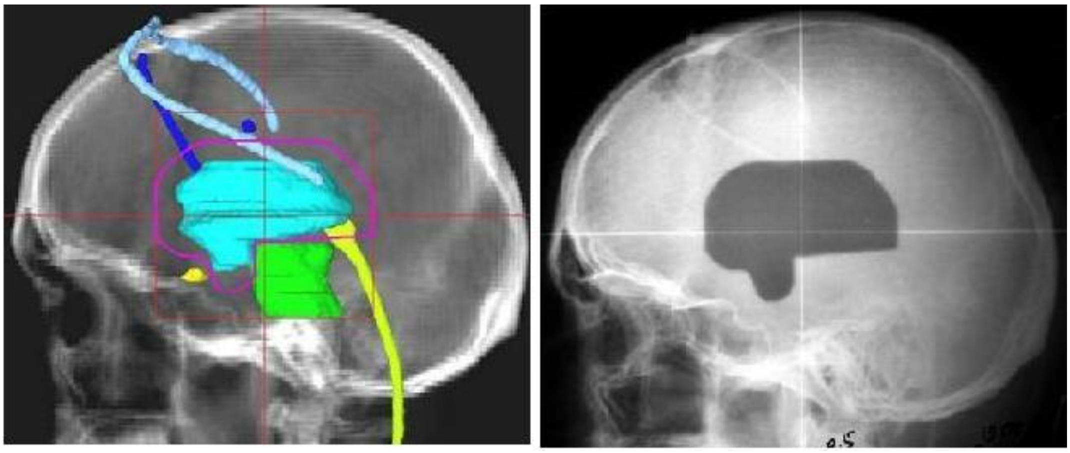

Fig.11. Verification of the proton irradiation plan: on the left - a digital X-ray of the skull from the irradiation direction with the projection of the target, critical structures and the collimator aperture; on the right – an X-ray of the skull before irradiation with mark of low-intensity proton beam exposed. The position of the beam relative to the bone structures-reference points and its shape exactly correspond to the plan of irradiation.

3.3. Dosimetry accompaniment of proton therapy

The adequate dosimetry accompaniment of the proton radiotherapy is an indispensable part of the provision of its “Quality Assurance”. This notion includes the definition of absorbed radiation dose in the tumor and healthy tissues and many other aspects connected to the forming of therapeutic proton beam, calculation of dose distributions, micro-dosimetry peculiarities of interaction of radiation with tissues and cells, etc.

Thus, to control the parameters of the therapeutic proton beam in real time-scale, a special system was developed. The system consist of parallel plate and multiwire ionization chambers; it allowed high accuracy control the horizontal and vertical beam profiles and the dose in the irradiated target, with automatic switch-off of the accelerator when the its given value is achieved. Besides, a system of the proton beam energy (range) control was worked out and implemented on the basis of semiconductor detectors [15].

Original measuring electronics blocks based on TERA chips were developed and manufactured for these systems. Each block contains 64 high-precision current-frequency converters. All software has also been developed in the MTC.

For a number of recent years, studies have been conducted together with staff members of the Department of Radiation Dosimetry of the Nuclear Physics Institute (Prague, the Czech Republic) on dosimetry calibration of a gamma-therapeutic apparatus “Rokus-M” possessed by MTC in the absorbed dose units, according to the IAEA recommendations. A stand for calibration of clinical dosimeters is developed on its basis [16]. The use of the stand makes it possible to keep the accuracy of dosimetry calibration of the therapeutic proton beam on the level of 3 % that complies with the world standard.

LET spectra were measured at the proton beam of the DLNP JINR Phasotron [17]. On the basis of the measured LET spectra evaluations were conducted of the relative biological efficiency of the proton beam that is an important parameter for proton therapy and radiobiological research.

Measurement experiments of the LET spectra by track detectors on carbon beams of the Nuclotron (Dubna) and HIMAC (Chiba, Japan) were also carried out [18]. For carbon beams, the value of LET is much higher than for protons, this leads to a significant increase in the relative biological efficiency (up to 3-3.5 in the Bragg peak area), which should be taken into account when planning radiotherapy.

Dose distributions beyond the irradiated target were measured by thermoluminescent and track detectors at proton beams of DLNP JINR Phasotron and the Proton Therapy Center in Prague [19]. The measured doses were compared with the doses of irradiation beyond proton beams that were formed passively with application of collimators, additional moderators and ridge filters at the proton beam of the Phasotron. This research is very important for evaluation of the irradiation risk of healthy tissues.

In collaboration with staff members of the Physics Department of Bucharest University (Magurele, Romania) and the Department of Radiation Dosimetry of the Nuclear Physics Institute (Prague, the Czech Republic) work was done to define errors that occur in proton therapy planning with standard programming means in case a patient has metallic implants in the irradiation region. The research is conducted by simulation methods and experimentally with application of special phantoms. The similar measurements were carried out at the Proton Therapy Center of Chicago (USA) using the technique of the proton computed tomography and the Monte-Carlo treatment planning software developed in this center.

It was shone that in case of presence of titanium alloy implants in the vicinity of irradiated target the shape of dose distribution is far from the calculated one both in case of irradiation with a wide fixed beam and in case of a pencil beam scanning technique irradiation. But if one uses proton CT data instead of X-ray CT data for calculation of dose distribution the situation becomes much better.

A PhD dissertation was defended on the results of this work.

In collaboration with staff members of the Greet Poland Cancer Center (Poznan, Poland), methods of verification were developed of all technological stages of preparation and holding therapeutic irradiation of patients with the use of radiochromic films and the heterogeneous “Alderson phantom” [20, 21]. Radiochromic films are specially designed detectors of ionizing radiation, which darken after exposure to radiation. The two-dimensional distribution of the absorbed dose in the film can be restored after scanning the film and processing of the received data. This method produces a very good geometric resolution with a dose determination accuracy of about 5 %, which makes it indispensable in case of measurement the dose fields of a proton beam with sharp gradients.

Alderson phantom is almost identical to the human anatomy and is made of tissue-equivalent materials. It consists of separate layers 25 mm thick, between which radiochromic film is placed and planning and irradiation is carried out in the same way as in the case of the patient. The need for such measurements often arises at the beginning of the use of new X-ray CT, with some changes in the technological process of planning and irradiation, to study the effectiveness of new irradiation techniques, etc.

A prototype of the automated multileaf collimator for the proton therapy for 4 leaf pairs was also designed and manufactured. After its testing and adjusting of all techniques, a full-scale version of the collimators for 33 pairs of leaf will be created (Fig.12). That is necessary for implementation of the so-called dynamic method of irradiation of various tumors with a proton beam. Patent RU2499621 of 27.11.2013 for the invention of this construction was obtained.

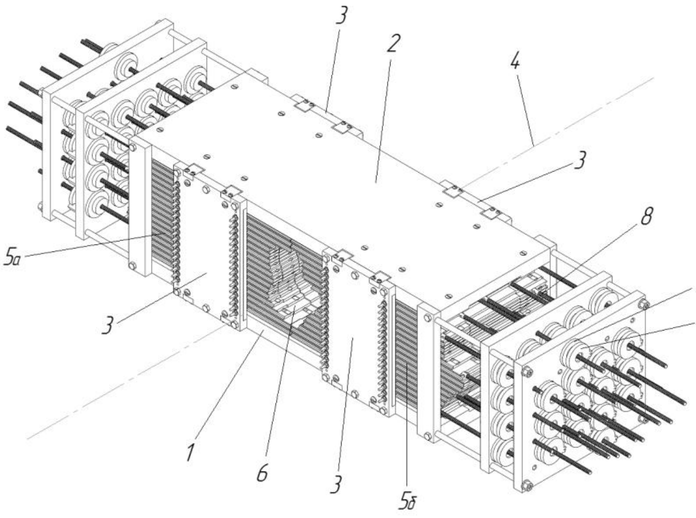

Fig.12. The design of the multileaf collimator 33 pairs of leaf

The invention solves the task maximally quickly and accurately to form any given aperture of the therapeutic proton beam and implement various irradiation methods to bring the maximum absorbed dose to the tumor and minimize irradiation of healthy tissues.

Besides, the application of the proposed multileaf collimator will allow shorter irradiation sessions, lower irradiation dose load on the personnel produced by the collimator radioactivity, less man-hour and lower costs, in comparison to the application of individual collimators.

3.4. 3.4. Clinical approbation

The first systematic data on patient irradiation at the Medical and Technical Complex of the JINR Laboratory of Nuclear Physics, together with the WONC staff, was presented in the mid-1990s based on the results of cervical cancer treatment [22].

Since December 1987, a combined proton-gamma-ray treatment of 34 patients for cervical cancer was performed on the medical proton beam of the JINR Laboratory of Nuclear Research. Of them: 6 patients received preoperative irradiation, 25 – radical proton-gamma irradiation in a separate version and 3 – palyative radiation treatment.

The results of the combined proton-gamma radiation treatment of cervical cancer are presented in Table 1 [22]. Directly 100% of patients were cured. Of the 34 patients, 18 were observed over 3 and 5 years. 83% of patients with three- and five-year follow-up are alive without a relapse or metastasis. Three patients died 2 years after irradiation due to: relapse of a radioresistent tumor, metastasis to the upper third of the vagina (outside the irradiation zone), intercurrent disease (stroke).

Radiation reactions and complications from normal organs (bladder and rectum) adjacent to the irradiated target (uterus) and tissues were not observed in all patients.

The obtained immediate and long-term results of proton-gamma radiation treatment showed the advantages of using protons over other types of radiation treatment for cervical cancer – the absence of radiation damage to normal organs adjacent to the uterus.

Table 1. The results of proton-gamma irradiation of cervical cancer

Stage	Number of patients	Directly cured	Alive without relapse or metastasis more		Died from:		
			3 years	5 years	relapse	metastases	intercurrent disease
IB	11	11	10	5	–	1[*]	–
IIA,B	4	4	3	–	1	–	–
IIIB	3	3	2	–	–	–	1[**]
Total	18	100%	15/18 (83%)	5/6 (83%)	1	1[*]	1[**]

[*)] 2 years after irradiation - from metastasis to the upper third of the vagina (outside the irradiation zone).

[**)] 2 years after irradiation - from stroke.

Unfortunately, the economic crisis that befell the Russian Federation in the nineties led to a complete halt of these studies. In addition, over time, new, fairly effective ways of dealing with this ailment were developed, so work in this direction was discontinued.

Of course, there is no doubt that proton therapy proves to be the most advantageous method if necessary to irradiate new growths located in the head and neck. Firstly, due to the presence in the field of irradiation of a large number of critical radiosensitive structures that prevent the required dose to be taken to the tumor in the case of conventional therapy, secondly, due to the fact that these organs can be fixed well for the time of topometry and subsequent exposure, which makes it possible to precisely plan and administer therapy.

Nevertheless, it became possible to realize all the advantages of protons only after creating an adequate diagnostic base (X-ray and PET CT, MRI, etc.) that can thoroughly determine the area of spread of the tumor, as well as the rapid development of computer technology, allowing medical physicists and programmers to create very complex software for three-dimensional planning of radiotherapy.

At the beginning of the last decade, the 3D conformal proton radiotherapy technique was implemented in one of the treatment rooms of MTC LNP, JINR, in which the maximum of the dose distribution formed most closely matches the shape of the irradiated target. Due to this, the possibility of radiotherapy of brain tumors localized near critical organs appeared. The structure of the nosological forms treated in the MTC from 2000 to April 2019 is presented in Table 2.

Table 2. Structure of nosological forms

Nosological forms	Patients
AVM	85
Adenocarcinoma	2
Pituitary adenoma	29
Jaw Ameloblastoma	1
Cavernous angiomas	9
Astrocytoma	59
Glioma, glioblastoma	89
Lymphoma	1
Melanoma	32
Meningioma	230
Lymph node metastases	1
Brain metastases	83
Skeletal metastases	3
Neuroma, neurolemma	27
Tumors, lung cancer	9
Brain tumors	15
Paranglioma	6
Skin cancer	83
Mammary cancer	54
Prostate cancer	1
Sarcoma	21
Chordoma and Skull Chondrosarcoma	57
Chordoma spine	6
Head and Neck Tumors	344
Other	36

Due to the already quite solid accumulated clinical experience in one of the numerous nosologies treated in MTC, namely arterial-venous malformations (AVM) of the brain, a statistical analysis of the results of treatment was carried out [23, 24]. From 2002 to 2010, 61 patients with this non-oncologic, but also very dangerous disease underwent a proton therapy course on the Phasotron beams. The volume of formations varied from 1 cm^3 to 82 cm^3. An international irradiation protocol was used, according to which the therapeutic dose was delivered in 2 days (radiosurgery). The total absorbed dose ranged from 20 Gy to 25 Gy, depending on the size of the formation and the proximity of its location to critical structures.

Evaluation of treatment results was based on information obtained using magnetic resonance imaging, carried out every 6 months after a course of radiotherapy. This is due to the fact that the process of overgrowth of the pro-light of the pathological vessels of the brain by endothelium cells as a result of radiotherapy (obliteration) proceeds gradually, usually from 6 to 24 months (Fig. 13).

At the time of the statistical analysis, the observation period exceeded 2 years in 55 patients. Of this number, communication with 6 patients was lost due to unexplained reasons, two died from other diseases, one died from hemorrhage while waiting for the effect. Thus, the analysis was carried out according to the results of treatment of 46 patients.

Full obliteration of pathological vessels occurred in 19 patients (41.3%), partial - in 25 (54.4%). From the latter group, almost complete obliteration (80-99%) was observed in 11 patients, in 7 patients it was 50-70%, and in 7 patients it was from 10% to 49%. Without a noticeable effect, there were only 2 patients who, apparently, had biochemical features of the formation.

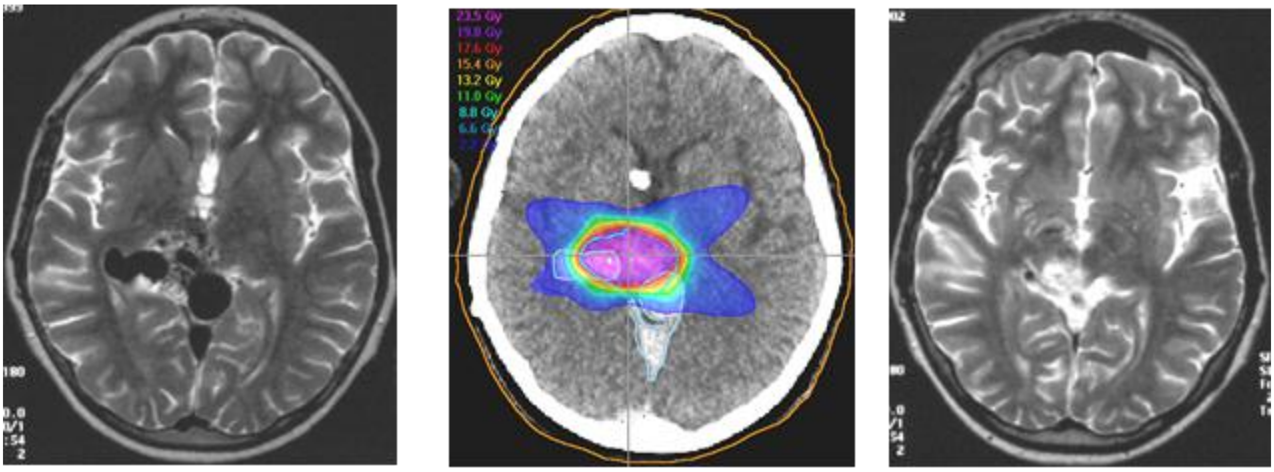

Fig. 13. An example characterizing the effectiveness of radiosurgery: the AVM irradiation plan for a 13-year-old boy (center), as well as magnetic resonance tomography before irradiation (left) and 40 months after (right) - there is a full spill -ration of pathological vessels

Radiation reactions inevitable with this method of treatment were distributed as follows: asymptomatic swelling was noted in 13 patients, swelling with the development of neurological symptoms and its subsequent regression - in 4 patients, radiation necrosis developed in one patient, followed by complete regression obliteration of the AVM.

Over the past 3 years, a statistical analysis of proton therapy of chordomas and chondrosarcomas of the skull base has also been performed. These are rare malignant tumors, constituting less than 0.5% of the number of primary intrahepatic tumors. Chordoma develop from the remnants of the embryonic chord. Intracranial chondrosarcomas - from embryonic residues of the cartilage matrix of the skull or from primitive mesenchymal cells. In the process of growth, these tumors destroy the bones of the skull base and, penetrating intracranially, cause damage to brain structures, cranial nerves and co-vessels. With all the similarity of localization, clinical manifestations, X-ray data and treatment tactics, the prognosis for chondrosarcomas is more favorable than for chordomas.

The main method of treatment of the chordoma and chondrosarcoma of the skull base remains surgical, but the infiltrative nature of growth and close proximity to critical brain structures make it difficult to perform radical operations. Almost 90% of patients after surgery have residual volume, and for a number of patients, for various reasons, surgery is not performed. In the absence of therapy, the average life expectancy of patients with chordomas of the base of the skull is from 18 to 28 months.

From 2002 to 2016 three-dimensional proton conformal therapy was performed in 28 patients with chordomas and skull base chondrosarcomas (Fig. 14). The average tumor volume was 42 cm^3 (3.9 cm^3-154 cm^3). The average total focal dose per isocenter was equal to 73 Gy (63-80 Gy). Dose loads on critical structures did not exceed tolerant values. The average dose on the surface of the brain stem was 62 Gy (56.6-64 Gy). The chiasm of the optic nerves received an average of 46 Gy (9-56 Gy).

The follow-up period for patients averaged 59 months (2-160 months). Of the 28 patients, 18 people maintain tumor control. Seven patients for various reasons dropped out of observation. In 3 patients, marginal relapse developed.

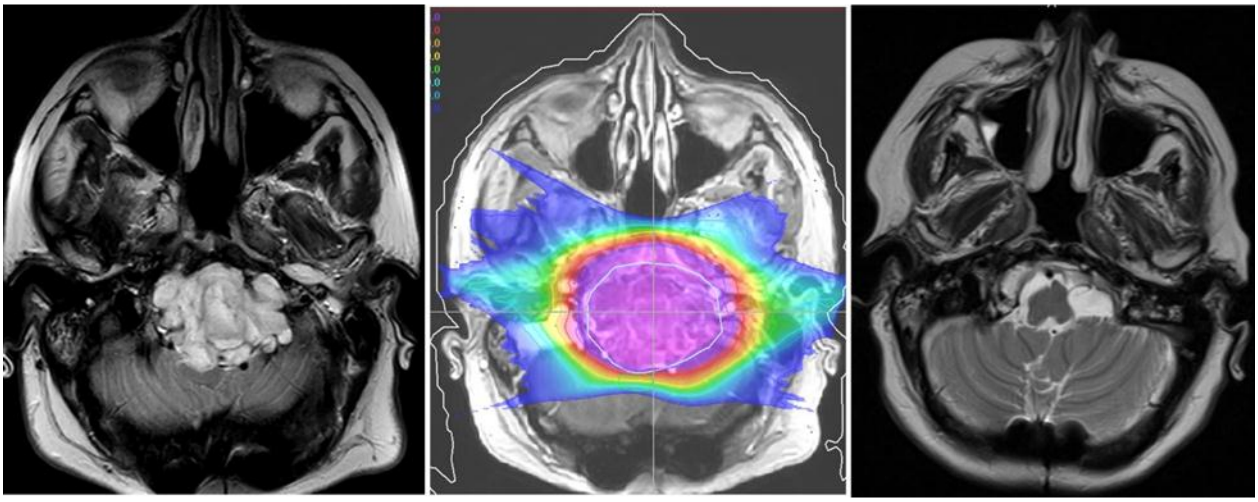

Fig. 14. Example of proton finely divided therapy for skull base chordoma: MRI before treatment (left), irradiation plan (in the middle) and MRI 2 years after - significant tumor regression

Radiation reactions and complications developed in 4 people (16.6%). There were acute radiation reactions that corresponded to the 2-nd points on the RTOG scale: on the part of the mucous membranes of the oropharynx and nasopharynx, the conjunctiva of the eye and the skin in the area of the irradiation fields. Neither the side of the brain stem, nor the side of the visual apparatus showed signs of radiation toxicity and radiation complications.

According to the statistical analysis, the following conclusions can be drawn: proton radiosurgery and radiotherapy conducted with the beams of the JINR Phasotron is a highly effective and safe method of treatment of AVM of the brain, including AVM of large size, as well as the chordomas and chondrosarcomas of the skull base, which, due to the close location to the critical structures of the brain, are the most complex of all intracranial targets. The results obtained are close with the data of foreign centers of proton therapy.

3.5. Radiobiological research

At the present stage of development the treatment of oncological diseases is practically in all cases conducted in a combined way, i.e. several methods of treatment are combined at the same time: surgery with chemotherapy, radiotherapy, hypo- and hyperthermia, etc. Besides, in radiotherapy more and more often additional medicated and hardware facilities are applied that in one way or another modify the effects of the ionizing radiation action on cells and tissues.

Such research, aimed at revealing the opportunities to produce effect of the laser radiation of various spectra combined with ionizing radiation, on the modification of results of the latter have been conducted at MTC for several years. For example, we had proved earlier that irradiation, both preliminary and subsequent and simultaneous with laser radiation (with wave length of 633 nm), of mice's fibroblasts leads to the increase in survival of cells that underwent the action of γ - radiation or protons.

The maximum radioprotective effect was observed at the energy density of laser irradiation of 1 mJ/cm^2 (patent for invention RU 2 330 695 C2). The given results were used to develop "A Device for radiation protection of biological objects in experiments" (patent for invention RU 2 428 228 C2). Then a new device was constructed; its launching, like the start of the previous one, takes only a few seconds but allows protection of the body area up to 300 cm^2 (patent for invention RU 2 515 405 C1).

The method of laser radiation protection of biological objects has a number of advantages compared with various chemical radioprotectors – it can be used before, after, as well as simultaneously with the impact of ionizing radiation on biological objects; the effectiveness of the protective effect does not depend on the repair genotype of cells and on the linear energy transfer (LPE) of ionizing radiation; it is not necessary to introduce into the body, can be used locally; is not toxic; has not only protective, but also therapeutic effects. In addition, our laser devices allow us to quickly and accurately irradiate a biological object with the desired dose of laser radiation.

The above mentioned devices are used on the doctor's recommendation and with the consent of the patient to protect the skin of radiosensitive patients that have a course of radiotherapy at the Medico-Technical Complex of the Laboratory of Nuclear Problems.

The idea to develop a new device for radiation protection of biological objects with the use of a laser module with a wave length of 532 nm is based on the results obtained earlier of radiobiological research where it was shown that both the preliminary irradiation and the subsequent laser irradiation of bacteria cells with laser radiation with that wave length decreases the damaging action of α - particles [25]. The studies on lethal and mutagenic action of laser radiation with the wave length of 532 nm also showed that this radiation can produce the same biological action on the cells of the E.coli K-12 bacteria as radiation with the wave length of 633 nm. These facts are in favor of the supposition that cell cytochromes included into the cell breathing system can be initial photoreceptors under the action of optical radiation of a visible range.

It is known that cytochrome C induces apoptosis (programmed cell death) when you exit from the mitochondria into the cytoplasm, and serves to strengthen the signal pathway of apoptosis, but also has a number of not apoptotic functions. Cytochromes also play an important role in the metabolism of steroids, bile acids, unsaturated fatty acids, phenolic metabolites, as well as in the neutralization of xenobiotics (drugs, poisons, etc).

The urgency of the given research is related to the fact that the search for ideal protective means, efficient for application in radiotherapy and in various cases of radiation damage of biological objects is still one of the most important issues of radiation and space biology and medicine. Radio epidermal effect that is accompanied with the sense of itching and tense skin is widely spread and is a serious problem in patients that undergo radiotherapy for cancer treatment.

From the perspective of probable scenarios of excessive exposure to ionizing radiation on humans, the most relevant are the search for means of experimental use for the treatment of acute radiation injuries, as well as means of reducing the adverse effects of prolonged radiation exposure with low dose rate.

In addition, special attention should be paid to the development of radiation protection agents that have low toxicity, practical control mode, long shelf life and a wide window of protection.

Studies conducted by us earlier in mice showed that the reduction of radiation damage to mice by laser radiation with a wavelength of 650 nm at a dose of 1 mJ/cm^2 is possible within 30 minutes after the impact of acute and prolonged exposure to ionizing radiation regardless of the dose (in the dose range up to 7 Gy), as well as 24 hours after exposure to ionizing radiation at a dose of 5 Gy, leading to the bone marrow form of acute radiation diseases. At a lethal dose of ionizing radiation of 7 Gy, leading to a transitional form of acute radiation diseases, the increase in the life expectancy of mice is observed when using laser irradiation both 2 and 24 hours after exposure to ionizing radiation, but the laser efficiency when used 2 hours after the defeat of ionizing radiation is significantly higher [26-28]. All this testifies to the competitiveness of laser devices in comparison with chemical radioprotective means.

As a result of research on fibroblast cells quantitative ratios will be obtained of the death forms of fibroblasts at the action of only ionizing radiation, at combined irradiation with laser and ionizing radiation and at the action of laser radiation in doses that cause lethal effect in mice fibroblasts cells. These results are of great interest for radiobiology and photobiology. The data of the studies will also help to understand the radioprotective action mechanism of laser radiation.

The effectiveness of the radioprotective effect of the device based on the laser module with a wavelength of 532 nm will be investigated in mice, then the clinical trials of the device will be scheduled.

Experimental data indicate high radiosensitivity of certain parts of the brain to the effects of high-energy heavy charged particles. However, to date, many aspects of the manifestation of neurophysiological effects of exposure to ionizing radiation with different physical characteristics remain unclear.

In 2018-2019, work was carried out to study the neurochemical parameters of the brain and behavioral reactions in rats after exposure to carbon ions, protons, neutrons and γ-quanta at a dose of 1 Gy. A generalized map of brain structures in which the most significant changes in the metabolism of norepinephrine, dopamine and serotonin after irradiation are observed is obtained. It is shown that the neurochemical response of brain structures to the effects of different ionizing radiation varies and depends on the quality of radiation. There were found evidence of hyperactivation of compensatory-restorative mechanisms that lead to partial restoration of functions of some brain areas and, at the same time, participate in the formation of long-term effects of radiation in other radiation-sensitive areas. Data on the regularities of neurochemical changes after exposure to radiation with low and moderate values of linear energy transfer were obtained. It is shown that an increase in LET from relatively low to moderate values leads to various neurochemical consequences depending on the considered brain structure. The hypothesis is proposed that hyperactivation of neurochemical mechanisms under the influence of radiation with moderate LET smoothes deviations in the metabolism of monoamines at the considered time intervals (30 and 90 days) after irradiation, but subsequently can lead to long-term violations of brain functions. Based on the results obtained, conclusions were made about the possible contribution of the observed changes in to behavioral disorders of laboratory animals.

In 2018-2019, joint work is being carried out within the framework of the program of cooperation with South Africa (iThemba LABS) on the topic "Neurochemical studies of neurotransmitters in brain tissues after exposure to neutrons, protons and gamma quanta" [29]. Works on this topic are focused on the study of radiation effects in the Central nervous system — a problem that has been relevant for the last decades mainly due to the increasing use of ionizing radiation in the treatment of brain tumors and the issues of radiation protection of astronauts in long-term space flights outside the earth's magnetosphere. The work includes a series of behavioral and neurochemical experiments using laboratory animals (rats) irradiated with proton and neutron beams at iThemba LABS facilities. The project is implemented in close cooperation with the South African medical research Council (SARBC) and entered an active phase at the end of 2018.

Over the past few decades, there has been significant progress in the radiotherapy of malignant tumors of the head and neck. At the same time, the high rhythm of modern life, lack of interest of patients in the prolonged (and economically more costly) radiation treatment course are forced to seek alternative ways of solving problems, one of which is hypofractionation.

Our studies using extreme hypofractionation (10 Gy once a week, on Mondays, the total dose of 20 Gy) for irradiation of the head of mice showed that the chosen option of extreme hypofractionation can successfully replace the traditional fractionation, which is mainly used in the conduct of radiotherapy for the treatment of brain tumors. The use of this type of fractionation can lead to a reduction in the duration of radiotherapy, as well as increase the capacity of medical centers conducting radiotherapy. In this regard, it is planned to continue the study (on the fibroblast cells of mice and on the mice) of the possibility of using different fractionation schemes during radiation therapy.

Improving the effectiveness of radiotherapy is important in the treatment of cancer. This fact makes it necessary to improve the methods of irradiation in order to increase the absorbed dose of radiation in the tumor and reduce the risk of damage to healthy tissues. Hadron therapy has great potential in this direction. Protons allow 2-3 times reduction the radiation load on the surrounding tumor normal tissue compared to γ-rays. Heavy ions are characterized by a high value of linear energy transfer, which contribute to the generation of significant damage in cells. Although modern conformal radiation therapy gives relatively good results, one of the main reasons for the failure of treatment is the ability of tumor cells to repair damage after irradiation. Therefore, to increase the therapeutic effect, combined technologies are often used, as an example, radiation therapy in combination with metal nanoparticles [30].

The increase in local energy depositions in the tumor is achieved by incorporating particles with large Z (^{53}I, ^{64}Gd, ^{78}Pt, ^{79}Au, etc.) into the tumor. The lesion of tumor cells is formed by both primary and secondary short-range radiation resulting from the interaction of initial particles with atoms of heavy elements concentrated in tumor cells.

Such induced radiation can be used to increase the target dose during radiotherapy of malignant tumors without increasing the non-target dose deposited in healthy tissues.

Secondary particles generated in interactions of protons with nanoparticles, it is possible to visualize and determine, for example, using the detector “Timepix-3”. The development of this new direction in the project is expected to start together with colleagues from several centers of Russia, Romania and the Czech Republic.

4. Планируемые в проекте исследования и методические разработки

Today, over 200 000 patients in more than 80 centers all over the world have received treatment at proton beams. The results of these clinical studies have shown that proton therapy is a very effective method of treatment of cancer and some other diseases, and in some cases it is almost no alternative. Because to this accumulated positive experience, by the end of the last century, a specialized proton therapy centers were being built at large radiological clinics. Today in the world there are several dozens of projects to create such centers at different stages of implementation. At the same time, the methodological issues of delivering the dose to the pathological volume, fixation and alignment of the patient and some others have not been fully resolved to date and represent a field of activity for further research.

The main objective of the project for the period 2020-2022 will be to develop methods of irradiation of patients with a proton beam, providing the highest degree of conformity of the created dose field to the irradiated target. Clinically, this will be expressed in a decrease in the dose to healthy tissues and organs surrounding the target, and to an overall increase in the efficiency of therapy. It is also planned to carry out works aimed at expanding the range of localizations available for irradiation with the Phasotron medical hadron beams.

In accordance with modern standards and rules existing in the field of health care of the Russian Federation, any equipment used in the treatment of patients should be registered (certified) accordingly, even if it is used for research purposes. The process of registration of equipment for proton radiotherapy of the MTC JINR is not easy, given its specificity, and can take 1 year or even longer. However, it was already started in 2019 and will continue in 2020. In any case, clinical trials can be resumed only after obtaining all the permits.

A wide program of research in the field of radiobiology is also planned, which meets the needs of both practical clinical radiology and such as determining the degree and mechanisms of influence of different types of ionizing radiation on the central nervous system of animals.

In the coming three years we propose to conduct the following activities in the frame of the project:

Clinical research:

- To continue clinical studies on proton therapy of various neoplasms at the JINR Phasotron beams in treatment room Num. 1 (after receiving all permits from the Ministry of Health of the Russian Federation).
- To carry out a statistical analysis of the results of proton therapy clinical studies on the irradiation of patients with different diagnoses.

Development and upgrade of proton therapy methods:

- Further development and construction of equipment for dynamic conformal proton beam irradiation of deep seated targets will be continued, including the creation of a computer-controlled moderator of variable thickness and a full-scale version of a multileaf collimator.
- It is supposed to design and construct a computerized dose control system for proton therapy.
- Work will continue to expand the functionality of the three-dimensional conformal proton radiotherapy planning software being developed at the MTC and its clinical testing in irradiation sessions.

Dosimetry and microdosimetry of therapeutic hadron beams:

- Activities will be continued on LET spectra measurements of clinical proton beam of DLNP Phasotron with Si detectors Liulin and Medipix.
- During radiotherapy, in devices of proton beam forming secondary particles appear, in particular neutrons and photons that irradiate surrounding healthy tissues. Doses from such fields should be minimized as they can lead to negative effects, up to formation of secondary radiation-induced tumours. Work is planned at the medical proton beam of the Phasotron to measure background conditions in the proton therapy room. Such measurements will also be con-

ducted at the scanning clinical proton beam in the Proton Therapy Center in Prague (PTC). The obtained data will be compared with the results of measurements at the proton beam DLNP JINR.

Radiobiology:

- Continuation of studies to determine the forms of fibroblast cell death depending on the dose of ionizing radiation. To study the lethal effect of laser radiation with a wavelength of 532 nm on the survival of fibroblast cells. In order to clarify the mechanism of radioprotective action of laser radiation (633nm and 532 nm) on biological objects to determine the ratio of forms of death after exposure to ionizing radiation, as well as after the combined effect of ionizing radiation and laser radiation.
- Study of the effects of increased cytotoxic effects of radiation therapy in the presence of metallic nanoparticles in animal cells. Determination of characteristics of radiation produced during radiotherapy (with and without nanoparticles) inside cells. These parameters can be calculated with a high degree of accuracy based on measurements with the Timepix-3 detector. Identification of new mechanisms of combined methods of treatment of tumor cells using metal nanoparticles and identification of their role in enhancing the effect of γ-rays and protons on tumor cells.
- Study of regularities and mechanisms of functional and neurochemical disorders in the central nervous system under the action of radiation with different values of linear energy transfer. Obtaining comparative data on the laws of induction of functional disorders in the brain structures under the action of rare and dense ionizing radiation used in the treatment of cancer diseases. Search and study of drugs with neuroprotective effect to the influence of ionizing radiation of different quality.

The implementation of the planned programme will give evaluations of the hadron therapy efficiency for a number of neoplasms, practical recommendations will be issued on the choice of optimal variants of radiation treatment of oncological patients and further development of radiotherapy methods with the use of hadron beams, new means and methods will be elaborated and tested of irradiation of oncological patients at these beams. New experimental and fundamental results will be obtained in the field of radiobiology as well.

TIMETABLE

activities on the project “Further Development of Methods, Technologies, Schedule Modes and Delivery of Radiotherapy”

2020

1. To continue clinical studies on proton therapy of various neoplasms at the JINR Phasotron beams in treatment room Num. 1 (after receiving all permits from the Ministry of Health of the Russian Federation).
2. To carry out a statistical analysis of the results of proton therapy clinical studies on the irradiation of patients with different diagnoses.
3. Testing of the prototype multileaf collimator on the accuracy of the positioning of the plates. Check of operability of electronic control units of the collimator. Development of test software for automatic aperture setting. Experimental verification on a proton beam. Troubleshooting identified problems.
4. Development of the project of a computerized dose control system. Development of a test unit of the system on the basis of the MC Board. Testing unit, identify problems in the work.
5. Continuation of work on widening functional opportunities of the 3D software developed at MTC for planning of conformal proton radiotherapy and on its clinical approbation in irradiation sessions.
6. Dose calibration of the Phasotron proton beam of DLNP JINR and gamma-apparatus ROKUS-M together with NPI, Prague, the Czech Republic.
7. Measurement of radiation dose beyond the proton beams generated by the passive technique of irradiation using collimators, moderators and additional filters with proton beam of the JINR Phasotron and using active scanning beam generated with the use of gantries in the Proton Therapy Center in Prague.
8. Measurement of LET spectra of proton beams with detectors Liulin and MEDIPIX.
9. Verification of radiotherapy treatment planning systems for proton beam irradiation. Measurements of spatial dose distributions using radiochromic films and other detectors in various phantoms, including the heterogeneous Alderson phantom.
10. Continuation of research to determine the forms of fibroblast cell death depending on the dose of ionizing radiation.
11. Study of mechanisms of functional and neurochemical disorders in the central nervous system under the action of radiation with different linear energy transfer. Study of neurochemical and behavioral effects after exposure to ionizing radiation, widely used in radiation therapy in ground-based experiments to simulate the biological effects of cosmic radiation. To study the effect of radiation with different LET on the functions of glutamate and GABA receptors.
12. Mastering of new methods for evaluating the effectiveness of cytotoxic action of nanoparticles on tumor cells. Effects will be assessed using a variety of microscopy techniques (optical microscopy and fluorescence microscopy).

2021

1. To continue clinical studies on proton therapy of various neoplasms at the JINR Phasotron beams in treatment room Num. 1 (in case of receiving all permits from the Ministry of Health of the Russian Federation).
2. To carry out a statistical analysis of the results of proton therapy clinical studies on the irradiation of patients with different diagnoses.
3. Designing and development of an irradiation stand to implement methods of dynamic proton radiotherapy with components of the multileaf collimator and the variable thickness moderator. Work out of the software to control the collimator-moderator system.

4. Development of the electronic devices for automated dose control system, manufacturing, testing.
5. Elaboration and implementation of algorithms for the 3D treatment planning software for the conformal radiotherapy with methods of dynamic irradiation of deep-seated targets with a wide homogeneous beam.
6. Dose calibration of the Phasotron proton beam of DLNP JINR and gamma-apparatus ROKUS-M together with NPI, Prague, the Czech Republic.
7. Measurement of LET spectra of proton beams with detectors Liulin and MEDIPIX.
8. Measurement of background conditions in the treatment room for proton therapy.
9. Verification of radiotherapy treatment planning systems for proton beam irradiation. Measurements of spatial dose distributions using radiochromic films and other detectors in various phantoms, including the heterogeneous Alderson phantom.
10. Investigation of the lethal effect of laser radiation with a wavelength of 532 nm on the survival of fibroblast cells.
11. Obtaining an integral assessment of the CNS state under the influence of different types of ionizing radiation on the basis of a comprehensive analysis of neurochemical brain parameters and behavioral characteristics of laboratory animals. Search and study of drugs with neuroprotective action against radiation-induced effects on the central nervous system. A study of the dose dependence of the functional response of the brain under different combinations of radiation and pharmaceuticals. The study of molecular mechanisms of radiation effects on the cultures of neuron-like cells.
12. Combined irradiation with γ-rays and proton beam of tumor cells with metal nanoparticles. Identification of effective combinations and differences in radiobiological effect of γ-rays, proton beams and metal nanoparticles.

2022

1. To continue clinical studies on proton therapy of various neoplasms at the JINR Phasotron beams in treatment room Num. 1 (in case of receiving all permits from the Ministry of Health of the Russian Federation).
2. To carry out a statistical analysis of the results of proton therapy clinical studies on the irradiation of patients with different diagnoses.
3. Approbation of mechanical and electron blocks of the system collimator-moderator. Checking of the working capacity of the software. Finding out technical, electron and software malfunctions and troubleshooting. Experimental irradiation of the phantom by the technique of dynamic proton radiotherapy.
4. Development of the project of a three-dimensional dose field analyzer. Selection of the system elements, purchase of necessary equipment.
5. Completing the design and implementation of algorithms of the 3D treatment planning software for conformal proton radiotherapy for technique of dynamic irradiation of deep-seated targets with a wide homogeneous beam. Testing and modification.
6. Dose calibration of the Phasotron proton beam of DLNP JINR and gamma-apparatus ROKUS-M together with NPI, Prague, the Czech Republic.
7. Measurement of LET spectra of proton beams with detectors Liulin and MEDIPIX.
8. Verification of radiotherapy treatment planning systems for proton beam irradiation. Measurements of spatial dose distributions using radiochromic films and other detectors in various phantoms, including the heterogeneous Alderson phantom.
9. In order to clarify the mechanism of radioprotective action of laser radiation (633 nm and 532 nm) on biological objects, it is proposed to study the ratio of forms of cell death after exposure to ionizing radiation, as well as after combined exposure to ionizing radiation and laser radiation.

10. To establish the rules of functional disorders induction in the brain structures under the action of ionizing radiation used in radiation therapy. Application of computer simulation techniques to the analysis of the results of experimental studies on the effects of ionizing radiation on the central nervous system. Establishment of the regularities of the influence of different doses of pharmaceuticals having a neuroprotective effect during irradiation; formulation of concepts of their practical application in order to minimize the negative impact of radiation in radiotherapy and for radiation protection of astronauts in long-range space flights.
11. Determination of the "dose change factor", as well as the maximum permissible concentrations of nanoparticles to achieve the cytotoxic effect in tumor cells. Analysis of the features of inactivation of normal and tumor cells of animals induced by ionizing radiation with various physical characteristics, as well as the presence of metal particles in combination with irradiation.

REFERENCES

1. В.П.Джелепов и др. Шестикабинный клинико-физический комплекс. Медрадиология 8, стр. 81 (1987).
2. В.М.Абазов и др. Шестикабинный клинико-физический комплекс Лаборатории ядерных проблем ОИЯИ для лучевой терапии пучками протонов, отрицательных пи-мезонов и нейтронов. Сообщение ОИЯИ, 18-90-496, Дубна, 1990.
3. А.В.Агапов и др. Методика трехмерной конформной протонной лучевой терапии. Письма в ЭЧАЯ, 2005, т. 2, № 6 (129), с. 80-86.
4. http://www.ptcog.ch/index.php/ptcog-patient-statistics
5. Терапевтическая радиология. Под редакцией А.Ф. Цыба и Ю.С. Мардынского. Медицинская книга, 2010 г.
6. R.R.Wilson, Radiology, 47, 487 (1946).
7. C.A.Tobias et al. Am. J. Roentgenol, 67, 1 (1952).
8. B.Larsson. The British J. of Radiology, 34, 143 (1961).
9. R.N.Kiellberg and W.H.Preston. Exerpta Med. Int. Cong. series No 36 (1961).
10. В.П.Джелепов и др. Создание возможностей для проведения на синхроциклотроне Лаборатории ядерных проблем ОИЯИ исследований по лучевой терапии и другим медико-биологическим проблемам. I. Формирование пучка протонов с энергией 100-200 МэВ. Препринт ОИЯИ, 16-3491, Дубна, 1967.
11. В.П.Джелепов и др. Вывод протонного пучка синхроциклотрона с энергией 100-200 МэВ для медико-биологических исследований. Медрадиология, 4, стр. 54 (1968).
12. https://www.ptcog.ch/index.php/facilities-under-construction
13. Протонные пучки высоких энергий и лучевая терапия злокачественных опухолей. Под редакцией В.П.Джелепова и А.И.Рудермана. ОИЯИ, 9035, Дубна (1975).
14. В.М.Абазов и др. Простой вариант рентгеновского компьютерного томографа для получения топометрической информации. Сообщение ОИЯИ, 13-87-702, Дубна, 1987.
15. Будяшов Ю.Г. и др. Система контроля параметров протонного пучка при радиотерапии. Письма в ЭЧАЯ. 2006. Т.3, №1 (130). С.101-110.
16. Р. Вагнер и др. Дозиметрическая калибровка гамма-терапевтического аппарата Рокус-М и клинических дозиметров ЛЯП ОИЯИ. Сообщение ОИЯИ, Р16-2000-186, Дубна, 2000.
17. Я.Кубанчак, А.Г.Молоканов. ЛПЭ – спектрометрия радиотерапевтического протонного пучка фазотрона ЛЯП ОИЯИ. VI Троицкая конференция МЕДИЦИНСКАЯ ФИЗИКА И ИННОВАЦИИ В МЕДИЦИНЕ (ТКМФ-6), Троицк, 2014, стр. 689-691.
18. O. Ploc et al. Dosimetry measurements using Timepix in mixed radiation fields induced by heavy ions; comparison with standard dosimetry methods. Radiat. Res. 55 (2014) i141-142.
19. J. Kubančák et al. Measurement of out-of-field doses in the clinical proton beam at the Czech Proton Therapy center. JINR Communication P16-2015-33, Dubna, 2015.
20. M. Mumot et al. Measurements of spatial dose distributions of proton beam with the use of radiochromic films. JINR Communication, E18-2006-62, Dubna, 2005.
21. M. Mumot et al. A comparison of dose distributions measured with two types of radiochromic film dosimeter MD55 and EBT for proton beam of energy 175 MeV. Astracts of PTCOG46, Zibo, Shandong, China. May 2007, p. P22
22. Б.В.Астрахан и др. Лечение рака шейки матки на медицинском протонном пучке фазотрона ОИЯИ. Сообщение ОИЯИ, Е18-95-99, Дубна, 1995.
23. Цейтлина М.А. и др. Протонная радиохирургия артериовенозных мальформаций головного мозга средних и больших размеров. Материалы Всероссийской научно-практической конференции «ПОЛЕНОВСКИЕ ЧТЕНИЯ», Санкт-Петербург, 2012. Стр. 212

24. Цейтлина М.А. и др. Протонная трехмерно-конформная радиохирургия артериовенозных мальформаций головного мозга. // Журнал «Вопросы нейрохирургии», 2013, № 4, т. 77, с. 43-50.
25. К. Ш. Восканян, Г.М. Арзуманян - Радиозащитное действие лазерного излучения с длиной волны 532нм // Радиационная биология, радиоэкология, т.36, вып.5, 1996, с. 731-733
26. Voskanyan K. et al. Laser device for the protection of biological objects from the damaging action of ionizing radiation // J. of Phys. Science and Application. 2012. № 6. P. 152–157;
27. Voskanyan K. et al. Reduction of radiation damage in mice after acute and prolonged irradiation with gamma rays by means of laser device // J. of Phys. Science and Application. 2014. № 4. P. 501–506
28. Восканян К.Ш. и др. Эффективность лазерного подавления радиационных поражений мышей в зависимости от интервала времени между облучениями // Медицинская Физика, № 4, 2015, ст.81-84
29. Belov O.V. et al. Neurochemical insights into the radiation protection of astronauts: distinction between low- and moderate-LET radiation components // Physica Medica. 2019. V. 57. P. 7–16
30. Peukert et al. Metallic nanoparticle radiosensitization of iob radiotherapy: a review // Physica Medica. 2018. V 47. P. 121-128

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Timetable suggested and necessary resources to implement the project "Further Development of Methods, Technologies, Schedule Modes and Delivery of Radiotherapy"

For the period 2020-2022

Facility's blocks and systems, resources, sources for financing	Cost of blocks (thous.doll.); need in resources	Proposals to distribute financing and resources		
		I **year**	II **year**	III **year**
Main blocks and equipment				
1. Conducting proton therapy	21	7	7	7
2. Dosimetric equipment	12	4	4	4
3. Materials and equipment for radiobiological research	12	4	4	4
Necessary resources (standard hour)				
DLNP Phasotron	2700	900	900	900
DLNP Workshop	500	500		
Sources of financing Budget sources				
Expenses from budget, including foreign exchange means	45	15	15	15
Extra-Budgetary means on agreements and grants	0	0	0	0

Project Leaders G.V.Mitsyn

K.Sh.Voskanyan

Форма № 29

Budget for the project
“Further Development of Methods, Technologies, Schedule Modes and Delivery of Radiotherapy”
for the period 2020-2022

NN	Costs	Total costs	1 year	2 year	3 year
	Direct costs for the project				
1.	DLNP Phasotron	hours	900	900	900
2.	DLNP workshop	hours	500		
3.	Materials	USD	5000	5000	5000
4.	Equipment	USD	10000	10000	10000
5.	International cooperation	USD	10000	10000	10000
	Total:	75000	25000	25000	25000

DLNP Director	V.A. Bednyakov
DLNP Chief Engineer Economist	G.A. Usova
Project Leaders	G.V.Mitsyn K.Sh.Voskanyan