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

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 neoplasms, 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) 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 neoplasms using the method of 3D conformal proton beam radiotherapy 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 neoplasm 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 neoplasms (including foreign citizens from JINR Member States) underwent courses of proton radiotherapy at the Phasotron beams.

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.

So far, over 200 000 patients in more than 80 centres all over the world have received treatment at proton beams. 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 patients’ 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.

A wide research program in the field of radiobiology intended to necessities of clinical radiology as well as determination of power and machinery of different kinds of ionizing radiation effect on the central nervous system of animals.

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

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. 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.

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.

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.

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.

The idea to use heavy charged particles in radiotherapy was expressed by R.Willson in 1946, but it became possible to be implemented only after the introduction of hundreds MeV accelerators of heavy charged particles. First usage of proton and other heavy charged particles' beams for medical biological research was done in the USA and Sweden in the 1950s. JINR was one of the first world centers where such research started in 1967.

The first dedicated centre 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, many-box 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 60 centers of proton and ion therapy operate in the world and about 30 centers are under construction.

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. 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.

After the reconstruction of the DLNP accelerator into a high-current Phasotron, sessions of cancer patients' 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 neoplasms 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 beam radiation therapy 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. Main characteristics of the experimental equipment

To carry out the planned programme 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. The Complex includes six treatment rooms.

Due to a number of reasons, the main efforts have been lately concentrated on the development of the first treatment room as the most universal one from the point of view of irradiation of a wide range of localizations. This box was upgraded according to requirements of the precision 3D conformal proton radiotherapy.

Besides, box 6 is also included into the research. A standard gamma-therapy device Rokus-M with a Co-60 source is installed in it to conduct combined irradiation, when part of the required dose is taken from gamma radiation up to the value tolerant for healthy tissues, while the tumor nucleus is additionally irradiated with protons.

A wide (8 cm x 8 cm) homogeneous in the cross section decelerated proton beam with energy of 170 MeV is delivered to box 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. 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. The positioned can easily be transformed into a deck for a patient in the lying position.

To immobilize (fix) the patient's head during the pre-radiotherapy 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 manufactured 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.

In case targets located in the patient’s chest need therapy, in the sitting pose, a problem arises in the planning as there is a minor maladjustment of the position of the patient’s inward parts of the body during diagnosing and irradiation. To solve this problem a variant of an X-ray computer tomography device combined with a therapeutic chair was manufactured for topometry.

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

- Immobilization of the region to be irradiated;
- X-ray and magnetic resonance diagnostic research and introduction CT sections to the treatment planning programme;
- 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 particles’ beams allow forming dose fields with sharp gradients due to the strictly localized distance and small angle scattering that make it possible to irradiate neoplasms 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 jacket 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 neoplasm 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 centre of proton therapy in Loma-Linda, US resulted in the adaptation of the 3D computer system of irradiation planning “TPN” developed at this centre to the equipment and proton beams of the DLNP JINR Phasotron. After a series of dosimetric experiments that verified the dose calculation algorithm the system is used in clinical practice.

But this programme cannot be anyhow 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 programme of computer simulation of the conformal proton radiotherapy has been completed by the present time. The developed variant of the programme has already been verified dosimetrically with the heterogeneous Alderson phantom and radiochromic films, and now its clinical approbation is being conducted.

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. Besides, the number of irradiation fields and their directions are given. The planning system generates 3D models of marked structures according to these data.

With the help of the function “beam’s-eye-view” in the programme 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. In real irradiation it is formed with the individual collimator of the Wood’s alloy.

Compensating boluses – moderators of a sophisticated 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.

The preparative stage for irradiation ends with production in the MTC workshops of individual profiled collimators and boluses that are calculated by the planning programme; for these purposes all necessary technological devices and facilities have been designed and manufactured.

The proton irradiation in itself 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 patients’ irradiation.

For each irradiation direction, precisely 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. If this position is not the same with the accuracy of 1 mm as that calculated by the planning programme 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.

The adequate dosimetric 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 dosimetric 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 that consisted 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.

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 dosimetric 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. The use of the stand makes it possible to keep the accuracy of dosimetric calibration of the therapeutic proton beam on the level of 3 % that complies with the world standard.

LET (Linear Energy Transfer) spectra were measured at the proton beam of the DLNP JINR Phasotron. 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.

Dose distributions beyond the irradiated target were measured by thermoluminescent and track detectors at proton beams of DLNP JINR Phasotron and the Proton Therapy Centre in Prague. 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 Centre of Chicago (USA) using the technique of the proton computed tomography and the MC treatment planning software developed in this centre.

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 Centre (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”.

A mock-up model of the automated multileaf collimator of the proton beam for 4 plate pairs was also designed and manufactured. After its testing and adjusting of all techniques the mock-up model will serve a prototype of a full-scale variant of the device for 33 plate pairs that is necessary for implementation of the so-called dynamic method of irradiation of various neoplasms with a proton beam. Patent Num. 2499621 of 27.11.2013 for the invention of this construction was obtained.

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, i.e. to observe the utmost conformability of the treatment.

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.

4. Clinical trials

First systematized data on patients’ irradiation in the Medico-Technical Complex of DLNP JINR were presented together with staff members of VONC in mid 1990s, on the example of cervical cancer treatment. The obtained direct and distant data on the proton-gamma radiotherapy showed advantages of proton application in comparison to other types of radiotherapy of cervical cancer – the absence of radiation damage in normal organs lying close to the uterus.

Regretfully, the economic crisis in RF in the 1990s led to the complete stop of this research. Furthermore, eventually new effective methods to fight this disease were developed, and the above studies were stopped.

It is obviously without any doubt that proton therapy is the most advantageous method if irradiation of neoplasms in the region of the head and neck is necessary. Firstly, it is due to the presence of a big number of critically radiosensitive structures in the irradiation region that may hinder the delivery of the necessary dose to the tumor in case of conventional therapy, secondly, as these organs can be well fixed for the topometry time and further irradiation it is possible to plan and accomplish with precision the therapy session.

Nevertheless, it became possible to implement all the advantages of the protons only after the development of an adequate diagnostic base (X-ray and PET CT, MRI, etc.) that allows detailed definition of the region of the neoplasm spreading, and rapid development of computer technology that enabled medical physicists and programmers to develop very sophisticated software for 3D planning of radiotherapy.

The technique of 3D conformal proton radiotherapy was implemented at MTC DLNP JINR in the early last decade, in one of the treatment rooms. The maximum dose distribution formed there most accurately corresponds to the shape of the irradiated target. In this way a possibility appeared to conduct radiotherapy of neoplasms of the brain localized near critical organs. The structure of nosologic forms treated at MTC since 2000 is quite extensive and contains over 20 titles.

Due to quite extensive accumulated clinical experience in one of the numerous nosologic diseases treated at MTC, i.e. arteriovenous malformations of the brain (AVM), a statistical analysis was done of the treatment results. From 2002 to 2010 61 patients with this non-oncological but very dangerous disease had a course of proton therapy at Phasotron beams. The volume of formations varied in the limits of 1 cm^3 to 82 cm^3. The international protocol of irradiation was used according to which the therapeutic dose was delivered during 2 days (radiosurgery). The integral dose was from 20 Gy to 25 Gy depending on the size of the formation and its closeness to localization of critical structures.

For the time of the statistical analysis the observation duration exceeded 2 years in 55 patients. Of them, connections were lost with 6 patients due to uncertain reasons, 2 patients died of other illnesses, one patient died of a blood stroke while waiting for the effect. Thus, the analysis was done on the treatment results for 46 patients.

The full obliteration of pathological vessels was in 19 patients (41.3%), partial – 25 patients (54.4%). In the latter group almost full obliteration (80-99%) was in 11 patients, 7 patients had 50-79%, 7 other patients had 10-49%. Only 2 patients had no visible effect; they possibly had biochemical specificities of formations.

The inevitable radiation reactions in this treatment method were distributed in the following way: 13 patients had asymptotic swelling, 4 patients had a swelling with growing neurological symptomatic and consequent regress, a patient developed radiation necrosis which later regressed, with AVM fully obliterated.

Over the past 3 years, a statistical analysis of proton therapy of chordomas and chondrosarcomas of the skull base was also carried out. These are rare malignant tumors that make up less than 0.5 % of the number of primary intracranial tumors. Chordoma grows from the remains of the embryonic chord. Intracranial chondrosarcoma – from embryonic remains of the cartilaginous 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 the structures of the brain, cranial nerves and vessels.

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

From 2002 to 2016, proton three-dimensional conformal radiotherapy was performed for 28 patients with chordomas and chondrosarcomas of the skull base. The average tumor volume was 42 cm^3 (3.9 cm^3-154 cm^3). Average total dose at the iso-center was equal to 73 Gy (63-80 Gy). Radiation doses to critical structures did not exceeded tolerant values. The average dose on the surface of the brain stem was 62 Gy (56.6-64 Gy). The optic chiasm received an average of 46 Gy (9-56 Gy).

The follow-up period of patients was averaged 59 months (2-160 months). Of the 28 patients, 18 people still have tumor control. Seven patients for various reasons fell out of the observation. Three patients have got a regional relapse.

Radiation reactions and complications developed in 4 people (16.6 %). There were acute radiation reactions corresponding to the 2-nd score on the RTOG scale: from the mucous membranes of the oropharynx and nasopharynx, conjunctiva of the eye and skin in the field of irradiation. There were no signs of radiation toxicity or radiation complications of the brain stem or the visual organs.

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.

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. 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 neuropetides 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.

В результате проведения исследований на клетках фибробластов будут получены количественные соотношения форм гибели фибробластов при действии только ионизирующего излучения, при комбинированном облучении лазером и ионизирующим излучением, а также при действии лазерного излучения в дозах, приводящих к летальному действию на клетки фибробластов мышей. Эти результаты представляют большой интерес для радиобиологии и фотобиологии. Данные исследований также помогут в понимании механизма радиозащитного действия лазерных излучений.

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.

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". 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.

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.

6. Research and methodic elaborations planned in the project

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 of 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 conducted 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.

Form Num.26

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 JINR Phasotron	2700	900	900	900
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

Project Leaders G.V.Mitsyn

K.Sh.Voskanyan