Report on the Project:
“Further development of methods, technologies, schedule modes and delivery of radiotherapy”
for the period 2017-2019

Theme 04-2-1132
“Biomedical and Radiation-Genetic Studies Using Different Types of Ionizing Radiation”

The main goal of the research is to carry out medico-biological and clinical investigations on cancer treatment, to upgrade equipment and instrumentation, and to develop new techniques for treatment of malignant tumours and for associated diagnostics with medical hadron beams of the JINR Phasotron in a Medico-technical complex (MTC) of DLNP. Also within the framework of the project, radiobiological studies aimed at improving the effectiveness of radiotherapy and reducing its toxicity are carried out.

The following main results with the project were achieved during the period 2017-2019.

Clinical trials

In collaboration with the Russian Medical Academy for Continuous Professional Education (Moscow) and the Radiological Department of the Dubna hospital the regular sessions of proton therapy aimed to investigate its efficiency to treat different kinds of neoplasm were performed. During the last 3 years, 21 so-called treatment sessions with a total duration of more than 80 weeks have been carried out. The DLNP accelerator was used for these studies for about 2700 hours.

About 150 patients were fractionally treated with the medical proton beam during this period. The total number of the single proton irradiations (fields) exceeded 12000. Other 75 patients were irradiated with the Co-60 gamma-therapy unit "Rokus-M".

A statistical analysis of clinical data for different nosologies treated at the MTC was continued. Over the last 3 years, the statistical analysis of proton therapy for chordomas and chondrosarcomas of the skull base has been carried out. 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. 1). 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.

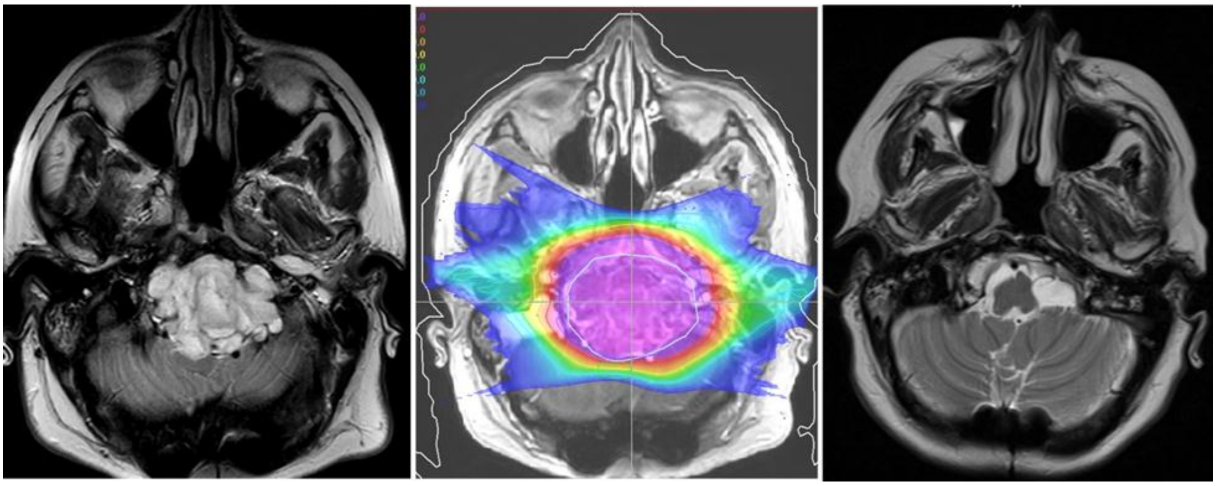

Fig. 1. Example of proton therapy for skull base chordoma: MRI before treatment (left), irradiation plan (in the middle) and MRI 2 years after - significant tumor regression

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 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.

Development and upgrading of the techniques and instrumentation

Tests of a software-hardware complex for the model of a 4-pairs leaves model of a multileave collimator of a proton beam have been continued. After completion by the end of 2019 testing of all the technology the model will serve as a prototype of a full-scale version of the device for 33 pairs of leaves necessary for the implementation of the so-called dynamic method of irradiation with a proton beam of various tumors (Fig. 2).

The devise 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.

The design and testing of the main components of a 3D treatment planning software for the proton conformal radiotherapy was continued. At present for irradiation planning we use a dedicated software elaborated at the proton therapy centre of Loma-Linda, USA, which has been adapted to the DLNP Phasotron proton beams. But this software can not be modified for new techniques of irradiation such as the dynamic tumour irradiation using a multileave collimator and an energy decelerator. The elaborated variant of the software has been successfully experimentally verified with the use of the heterogeneous “Alderson phantom” and the radiochromic films and now it is under clinical tests (Fig.3).

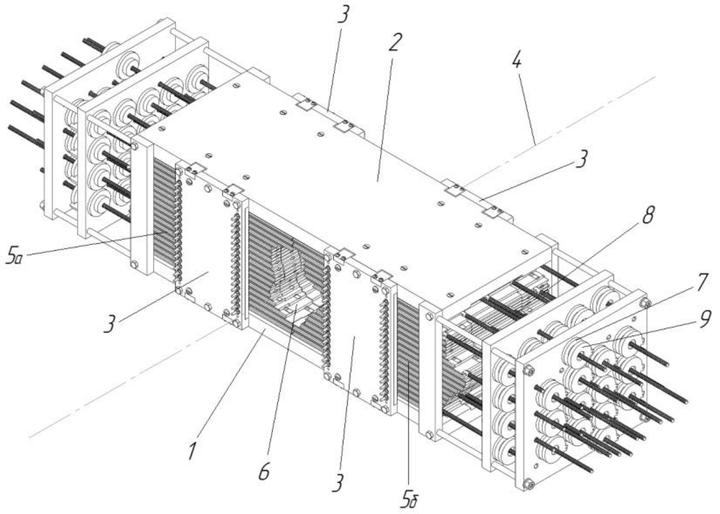

Fig. 2. The design of the multileaf collimator for 33 pairs of leaf

The establishment of a software-hardware complex for the automated verification of the patient position relative to the proton beam during irradiation based on a digital X-ray detector has been completed. The system will allow us to shorten the time required for radiotherapy conduction and on the other hand to increase the accuracy of the beam delivery to the target. At present this system is under clinical tests.

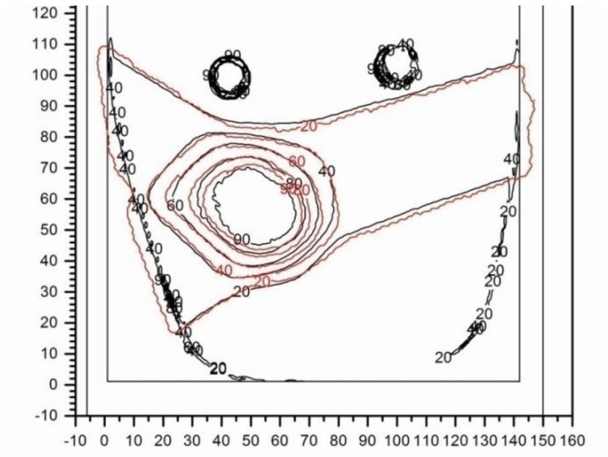

Fig.3. Comparison of the dose distribution calculated by the developed planning program (red lines) with the distribution measured by radiochromic film (black lines). The Figures show a good match.

Dosimetry of hadron beams

Together with the Department of Radiation Dosimetry of the Institute of Nuclear Physics (Prague, Czech Rep.) dosimetry calibration of gamma-source Co-60 in a water phantom on the basis of the IAEA recommendation was curried out. Due to this, the accuracy of measurement and dose delivery during proton therapy is at the level of 3 %, which corresponds to international standards.

Together with the staff of the Department of Radiation Dosimetry Institute of Nuclear Physics (Prague, Czech Republic) measurements of the dose distributions outside a target volume in the MTC proton therapy treatment room using thermoluminescent detectors and radiochromic films were carried out. Together with the staff of the LRB JINR measurements of background neutrons in the treatment room were performed. These studies are important for estimation of risk to healthy tissues during the proton therapy conduction and, as a consequence, the possibility of induced cancer.

Together with the staff of the Department of Radiation Dosimetry Institute of Nuclear Physics (Prague, Czech Republic) measurements of the LET spectra of the proton beam of the JINR phasotron were carried out. On the basis on the measured LET spectra the relative biological efficiency of JINR proton beams was estimated, which is fundamental for their applications in radiotherapy and radiobiology. Together with the staff of the Institute of Bio-Medical Problems and LRB JINR the influence of protons with different LET on biological objects were studied.

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.

Radiobiology

A clinical trial of the radioprotective effect of a laser device with a wavelength of 532 nm (on the doctor's recommendation and with the patient's consent) on the skin of the face, neck, nasopharynx and larynx of radiosensitive patients undergoing radiation therapy in MTC was conducted. Laser radiation had a significant radioprotective effect, both in the preliminary and subsequent laser irradiation.

Currently, studies are being conducted on the forms of inactivation of mouse fibroblast cells after exposure to ionizing radiation, as well as combination irradiated by ionizing radiation and laser radiation.

Previously, we have shown that both preliminary and subsequent, and one-time laser irradiation (with a wavelength of 633 nm) of fibroblasts of mice C3H10T1/2 leads to an increase in the survival of cells exposed to gamma radiation or protons. To clarify the mechanism of radioprotective action of laser radiation, it is of great interest to check the assumption that the primary photoreceptor under the radioprotective action of laser radiation is cytochrome-C-oxidase, a component of the respiratory chain localized in cellular mitochondria. To this end, we created a device based on a laser module with a wavelength of 532 nm, since this wavelength also falls into the absorption spectrum of cytochrome-C-oxidase.

Кривые выживания клеток фибробластов, облученных гамма-лучами, а также комбинированно облученных гамма-лучами и лазером (0,56 мДж/см^2) показали, что лазерное облучение оказывает эффективное радиозащитное действие по критерию выросших клеточных колоний. При этом значение фактора изменения дозы (ФИД), рассчитанное по ЛД50, равно 1,4.

Determination of cell survival C3H10T1/2 using automated counter ST20 (Bio-Rad Laboratories, USA) after exposure to ionizing and combined irradiation showed that the radioprotective effect of laser radiation with a wavelength of 533 nm as well as radiation with a wavelength of 633 nm, is transmitted by the mechanism of “bystander” effect. In addition, it was found that the radioprotective effect of laser irradiation is observed by the criterion of the number of survivors of single cells, compared with cells exposed to gamma rays.

The survival curves of fibroblast cells irradiated with gamma rays, as well as combined irradiated with gamma rays and laser (0.56 mJ/cm^2) showed that laser irradiation has an effective radioprotective effect on the criterion of grown cell colonies. The value of the dose change factor calculated by LD50 is 1.4.

The results obtained support the assumption that the cytochrome-C-oxidase presenting in the inner membrane of the mitochondria of all eukaryotes is the primary photoreceptor under the radioprotective action of small doses of laser radiation with wavelengths of 633 nm and 532 nm.

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.

New papers on a series of experiments on the exchange of monoamines and their metabolites in the rat brain after exposure to carbon ions with an energy of 500 MeV/nucleon of the Nuclotron and gamma quanta of ^{60}Co of the ROKUS-M unit at a dose of 1 Gy have been published.

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 (SARMC) 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.

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.

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