Report on the Project:
"Further development of methods, technologies, schedule modes and delivery of radiotherapy"
for the period 04.2022 - 03.2023

Theme 04-2-1132-2017/2023
"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 reporting period.

Development and upgrading of the irradiation techniques and instrumentation

A new Dose control unit (DCU) based on the Atmega2560 microcontroller has been developed and tested. The block is a fast counter of input pulses (with a frequency of up to 300 kHz) and allows switching the beam of the accelerator off upon reaching a predetermined by the operator delivery dose of the proton beam in the treatment room. The input pulses come from the current-to-frequency block, which converts the current of the monitor parallel-plane ionization chamber (PPIC) into pulses of a certain frequency signal (depending on the dose rate of the proton beam). The DCU has two display panels for displaying the current count and the set number of pulses (in terms of the required dose) and keypad for entering values. The time delay of the DCU in forming the signal to switch off the accelerator dos not exceed 50 μs. The new DCU was tested on the medical proton beam of the DLNP Phasotron in the treatment room of the MTC, which showed its full operability and compliance with its inherent characteristics.

As part of the flash-effect study on biological objects during high dose rate proton beam irradiation, a specialized Dose control unit for flash (DCUF) was developed and tested. The DCUF allows setting the required number of accelerator macropulses to be delivered during irradiation in flash-mode by means of a combination of key switches. The unit allows the selection from 1 to 63 acceleration pulses, which corresponds to a time interval of 40 μs to 248 ms at a pulse rate of 250 Hz. The experiments showed that in the irradiation site there is on average 0.3 Gy of absorbed dose per 1 macropulse of the accelerator. The speed of the DCUF electronics operation allows delivering the dose with the accuracy of 1 pulse. The unit was tested with the proton beam in the flash-mode and was successfully used for radiobiological experiments at the Phasotron.

A special parallel-plane ionization chamber with ultra-thin interelectrode gap (~500 μm) was designed and manufactured to monitor the beam of high dose rate. The case of the chamber is made by 3D printing technology from ABS plastic. The diameter of its working area is 80 mm. External dimensions of the ionization chamber are 140x150 mm with a total thickness of 15 mm. Anode and cathode planes are made of 0.5 mm thick fiberglass board with copper coating of 35 microns. The gap between the planes is set by a gasket - a dielectric ring made of the same material. The final effective thickness of the chamber across the beam is 1.9 mm water equivalent, which, given the high energy of the protons (660 MeV), is not critical. The electrodes on the cathode and anode planes were made by etching method. To reduce leakage currents, a grounded guard ring was formed on the anode plane. Linearity of the chamber operation was confirmed experimentally.

In order to obtain real-time data of the proton beam profiles in the flash-mode, a multichannel pixel ionization chamber (MPC) was created. It including 14 vertical and 16 horizontal channels, which allows significantly shortening the procedure of beam delivery to the irradiation site (Fig. 1). There are electrically isolated pixels in the shape of a crosshair located in the central area of the MPC anode plane, each pixel represents an independent channel. To reduce the effect of leakage currents through the dielectric, a guard electrode connected to "ground" is formed around the pixels at a distance of 0.5 mm. Each pixel has a size of 4.5x9.5 mm and the distance between neighboring pixels is 0.5 mm. To make the pixel electrode, 0.35 mm thick foil-glass fiberglass with a copper coating of 20 μm was used. To prevent oxidation of the copper surface, the electrode was coated with a 15 μm thick layer of tin.

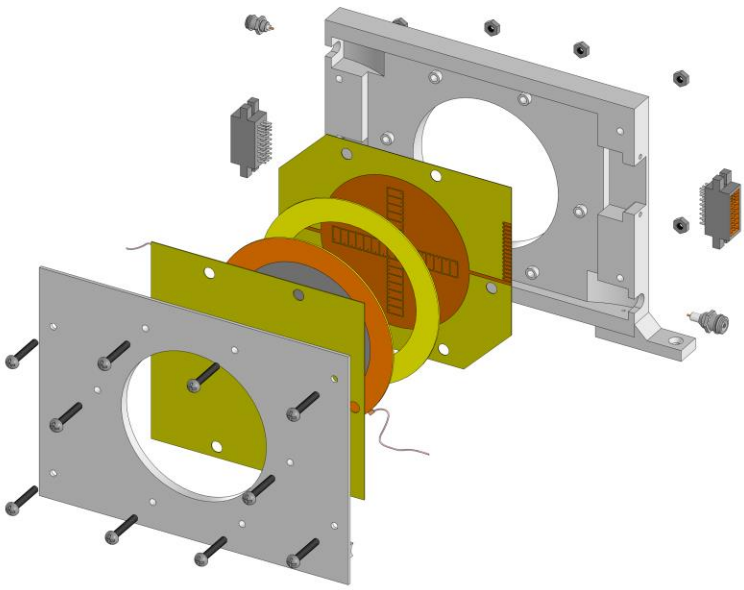

Fig. 1. Design of the Multichannel pixel ionization chamber (MPC)

The cathode electrode is made of a thin (12 μm) aluminum foil, stretched on a fiberglass ring, 1 mm thick. On the other side of the cathode, also with a gap of 1 mm, there is other anode made of the same thin fiberglass (0.35 mm), but already completely covered with copper. Thus, this chamber simultaneously gives information about the beam profiles and serves as a monitor of the delivery dose.

The control electronics consisting of two blocks was developed to collect data from the MPC and transfers it to a computer. The first analog block processes current signals from each MPC channel. The architecture is based on a 64-channel Tera06 chip (INFN, Italy), in which each channel consists of a current-to-frequency converter with a sensitivity of about 200 fC per sample, followed by a 16-bit counter. A second digital unit, the industrial programmable logic controller ICPDAS WP-8128-CE7 (Taiwan), is used to poll the output register of the Tera06 chip. ADC control and data collection is performed through a 32-channel parallel I/O module ICPDAS I-8042W. The controller is used for data collection and transmission via network cable to a personal computer. Developed software displays on the computer screen the current signal value from each MPC channel in the form of histograms on two axes - horizontal and vertical. The MPC was calibrated at the proton beam with a radiochromic film.

The MPC was tested at the proton beam in the flash-mode, which showed full operability of the whole system and linearity of its readings at ultrahigh dose rates.

Studies have also been initiated for a new center based on the MSC-230 accelerator. A new type of range filters (RF) allowing modification of the narrow Bragg peak of the proton beam into a depth-dose curve with a spread-out plateau (in the range of 10 to 110 mm of water equivalent) has been developed. The new concept of RF consists in selection of weight characteristics of its profile, which will allow creating universal RFs with variable plateau in some range in depth by turning the filter in a certain plane before irradiation. The uniformity of dose at the plateau for different angles of the filter should not be worse than 5 %. At the moment, a method for calculating the weight characteristics of such filters has been developed, the manufacturing technology (3D printing from ABS plastic) and the methodology for testing the filters at the proton beam has been selected. A series of test RFs has been created and tested.

The previously developed one-dimensional dose-field analyzer with a water phantom and a movable semiconductor detector was used to measure depth-dose curves of the proton beam in the MTC. At the moment, this analyzer is being totally upgraded, both mechanically as well as in its control and data acquisition system. For this purpose, a new linear movement system part of the analyzer has already been made. Electronic components have been purchased to upgrade the detector readout channel and the motion control system.

Radiobiology research

Together with the staff of the University "Alexandru Ioan Cuza", Faculty of Physics, Iaşi, Romania, we studied the effect of irradiation of soft wheat seeds (Triticum aesticum L.), a widely cultivated crop in many countries, with a proton beam at high dose rate of irradiation. Ionizing radiation is used in plant biotechnology to produce a new mutagenic source for genetic modification. The study focused on the content of photosynthetic pigments and polyphenols in seedlings obtained from irradiated wheat seeds. The study will continue with antioxidant enzymes to look for evidence of some of the biophysical and biochemical changes caused by irradiation at the molecular level.

During the reporting period, new scientific results were obtained in the field of studying the effect of different quality on the structure and function of the central nervous system (CNS). New information was obtained about the role of functional changes in receptors, as well as on the role of neuroglial interactions and brain neuromodulatory systems in response to ionizing irradiation. The work done pays special attention to the comparison of various molecular mechanisms in interaction with functional changes at the level of behavior, as well as to molecular mechanisms important for the development of promising drug countermeasures against the negative effects of cosmic radiation.

A number of questions related to the mechanisms of CNS radiation damage, functioning at the level of brain hierarchical networks, were studied from the same aspect. Induction and modulation of emotional, motivational behavior and cognitive functions in laboratory animals have been studied on the basis of the results of neurochemical studies of the metabolism of neurotransmitters present in the morphological structures of the brain. The data on neurochemical studies were compared with the assessment of behavioral changes induced by exposure. Concepts have been formulated against the action of space radiation in long-term manned flights beyond the Earth's magnetosphere.

For the last several years we have been studying the cytotoxic and cytogenetic effect of gold nanoparticles of human lung carcinoma cells A 549 under the influence of radiation with different LET (photons, protons).

Over the last year, studies have been conducted to increase the efficiency of proton beam irradiation in the presence of gold nanoparticles of human lung carcinoma cells A 549.

Changes in the radiosensitivity of A 549 tumor cells were studied, as well as an increase in the genotoxic effect of proton irradiation in the presence of gold nanoparticles. The studies were carried out using clonogenic analysis, a micronuclear test, an analysis of the formation of γ-H2AX foci, the formation of reactive oxygen species was studied as well.

Work has been carried out to compare the reactions to the irradiation of tumor cell culture with an ultra-high dose rate (70 Gy/s) and a standard dose rate (0.1 Gy/s). In collaboration with the colleagues from ITEB RAS (Pushchino, Russia) and IMBP RAS (Moscow, Russia) we performed irradiation of cell cultures and irradiation of about 80 laboratory mice. The results of these experiments are currently being systematized.

Publications during the reporting period:

1. A.V. Rzyanina, G.V. Mitsyn, S.V. Shvidkiy, A.G. Molokanov, K.N. Shipulin, A.V Agapov., V.N. Gaevsky, I. Khasenova. Improvement of proton irradiation effectiveness of human lung carcinoma cells A549 in the presence of gold nanoparticles. Medical Physics, 2022, № 4, P. 21-29. (RUS)
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3. L. Oprica, G. Vochita, M. N. Grigore, S. Shvidkiy, A. Molokanov, D. Gherghel, A. Les, D. Creanga. Cytogenetic and Biochemical Responses of Wheat Seeds to Proton Irradiation at the Bragg Peak. Plants 2023, 12, 842. plants12040842, Published: 13 February 2023.
4. Yakovleva M.A., Feldman T.B., Lyakhova K.N., Utina D.M., Kolesnikova I.A., Vinogradova Y.V., Molokanov A.G., Ostrovsky M.A. Ionized Radiation-Mediated Retinoid Oxidation in the Retina and Retinal Pigment Epithelium of the Murine Eye. Radiation Research, V. 197, ISSN 0033-7587/22, 2022, pp.270–279.
5. Yu.S.Severyukhin, M.Lalkovičová, D.M.Utina, K.N.Lyakhova, I.A.Kolesnikova, M.E.Ermolaeva, A.G.Molokanov, V.N.Gaevsky, D.A.Komarov, E.A.Krasavin. Comparative Analysis of Behavioral Reactions and Morphological Changes in the Rat Brain After Exposure to Ionizing Radiation with Diferent Physical Characteristics. Cellular and Molecular Neurobiology, 2022, doi.org/10.1007/s10571-021-01187-z
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7. A.V. Rzyanina, G.V. Mitsyn, S.V. Shvidkiy, A.G. Molokanov, K.N. Shipulin, A.V Agapov., V.N. Gaevsky. Improvement of human lung carcinoma cells A549 radiosensitivity in the presence of gold nanoparticles. Proceedings of the V INTERNATIONAL FORUM ONCOLOGY AND RADIOTHERAPIY, September 19-22, Moscow, Book of Abstracts, pp. 95-96. https://forum-forlife.ru/ (RUS)
8. A.V. Rzyanina, G.V. Mitsyn, S.V. Shvidkiy, A.G. Molokanov, K.N. Shipulin, A.V Agapov., V.N. Gaevsky. Improvement of proton irradiation effectiveness of human lung carcinoma cells A549 in the presence of gold nanoparticles. Materials of the Annual All-Russian Scientific School-Seminar "Methods of Computer Diagnostics in Biology and Medicine - 2022", November 23-25, 2022, Saratov State University, Saratov, p. 56-60. (RUS)
9. K. Belokopytova, O. Belov. Emerging roles of CNS neurochemical mechanisms in health, radiation damage and disorders. COSPAR 2022, 44-rd Scientific Assembly. 16 – 24 July 2022. Abstract F2.2-0025-22

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