MODERNIZATION OF THE MEDICAL PROTON COMPLEX FOR STEREOTACTIC RADIOSURGERY AT NRC "KURCHATOV INSTITUTE" – PNPI

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This paper is dedicated to the memory of professor Aleksey Alekseevich Vorobyov, who proposed in november 1971 to use a 1 GeV proton beam of the SC-1000 for clinical radiation therapy.

1. Introduction

Radiotherapy (stereotactic radiosurgery) using a proton beam of the synchrocyclotron SC-1000, was conducted from 1975 to 2013. It confirmed its viability and effectiveness, and received recognition in the scientific community. This article considers the method of proton therapy with 1 GeV beam energy based on the Medical Proton Complex (MPC) of the National Research Centre "Kurchatov Institute" – PNPI, created by the joint efforts of the PNPI and of the Russian Scientific Centre for Radiology and Surgical Technologies (RSC RST). The main results of the current activities of the Laboratory of Medical Physics of the Department of Medical Radiology of the PNPI on the modernization of the MPC, which consists in updating the material and technical base, expanding verification methods for quality assurance (QA) of dose planning and dose delivery for stereotactic radiosurgery using protons with an energy of 1 GeV at the PNPI, are presented. The modernization program will bring the treatment of oncological diseases in Gatchina to a new level.

Nowadays, thanks to technological advances of developed countries, radiation therapy has reached a qualitatively new level and has made a significant progress in terms of achieving the main aim, which is bringing the required dose to the therapeutic focus area while maintaining healthy tissues. About 40% of patients in Russia and up to 70% of patients in other developed countries receive at one stage or another the disease radiation treatment alone or in combination with other methods of cancer treatment. One of the most perspective and actively developing type of radiotherapy is proton beam therapy (PBT). The main advantage of using protons is a more efficient dose distribution within a target than with other types of radiation therapy.

Currently, there are more than 80 functioning PBT centres in the world [1], four proton therapy centres operating in Russia:

- A medical and technical complex in Dubna based on the Joint Institute for Nuclear Research phasotron, which accelerates protons to 660 MeV and protons are slowed down to 200 MeV for medical purposes;
- A proton complex at the A. Tsyba Medical Radiological Research Centre in Obninsk, opened in 2016 on the basis of a synchrotron with variable proton energy in the range from 70 to 250 MeV;
- The medical and diagnostic centre of the Sergey Berezin Medical Institute in Saint Petersburg, launched in 2017 on the basis of a Varian cyclotron with an energy of 250 MeV;
- A multicabin centre in Dimitrovgrad, launched in 2019 on the basis of an ion beam applications (IBA) cyclotron with an energy of 235 MeV.

2. Bragg peak method and on-through method

A typical depth dose distribution curve for a proton beam (Bragg ionization curve) in a tissue-equivalent medium (Fig. 1) has certain features. Depending on which part of the Bragg curve falls on the irradiation focus, there are two options for radiation therapy with proton beams: irradiation method using the Bragg peak (the method of stopping) and the method of irradiation with the plateau region (the "on-through" method). The last method is expedient to use for narrow beams. Protons up to 250 MeV are used when appliying the Bragg peak method. Their range in biological tissues corresponds to the depth of the irradiated objects. A successful experience was gained in radiotherapy of patients with intracranial pathologies using higher energy protons in the USSR, which will be discussed in the article. The treatment of patients was started in 1975 in Gatchina (Leningrad region, Russia), at the Leningrad Nuclear Physics Institute (LNPI, and PNPI nowadays). The radiation therapy was carried out by the “on-through” method with 1 GeV protons of the LNPI synchrocyclotron SC-1000 [2]. It is worth noting that the first experience of proton therapy at Berkeley was just the “on-through” method.

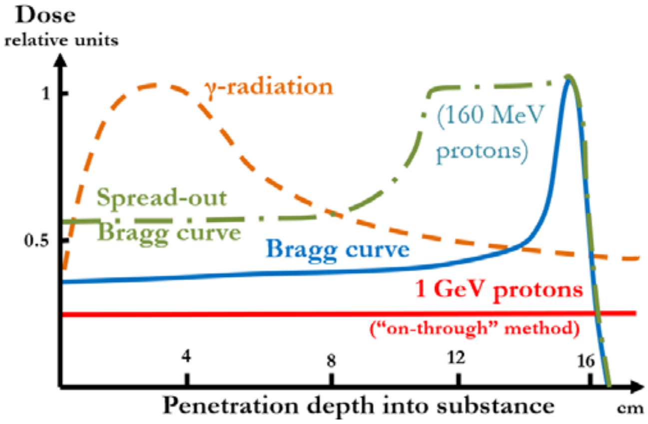


Fig. 1. Absorbed dose radiation distribution depending on the penetration depth into substance

The method of proton therapy using a beam of such energy is fundamentally different from other methods. There is no experience in the world practice of clinical use of beams of such energy in matters of their formation and dosimetry. The proton beam of the accelerator is monoenergetic and it has a small cross section. In order to enhance the effect in the irradiated tumor and to reduce the irradiation of healthy tissues, the technique of multifield irradiation from different directions is applied, which is implemented by rotating the irradiation stand relative to a monodirectional stationary beam.

The therapeutic installation (UPST) designed to implement the multifield irradiation technique in PNPI is shown in Fig. 2. The main elements of the UPST are a treatment table, a head fixation device (HFD) and an *X*-ray centralizer. The treatment table can rotate around the vertical axis (*Z*), passing through the isocentre of the installation by ±40°. The HFD can perform pendulum movements at an angle of up to ±36° around the horizontal axis (*X*) perpendicular to the beam axis (*Y*). Both rocking axes, as well as the axis of the proton beam, intersect at one point, which is the isocentre of the UPST. At any rotation of the head fixation device and the treatment table, the object located in the isocentre of the UPST remains motionless. Thus, the proton beam is directed to the set-up isocentre (target centre) at different angles. The *X*-ray centralizer is a specially adapted *X*-ray diagnostic apparatus with the ability to rotate around the isocentre. It has two fixed positions: horizontal and vertical, which makes it possible to produce a lateral and frontal *X*-ray image, respectively, for precise targeting at the isocentre of the UPST.

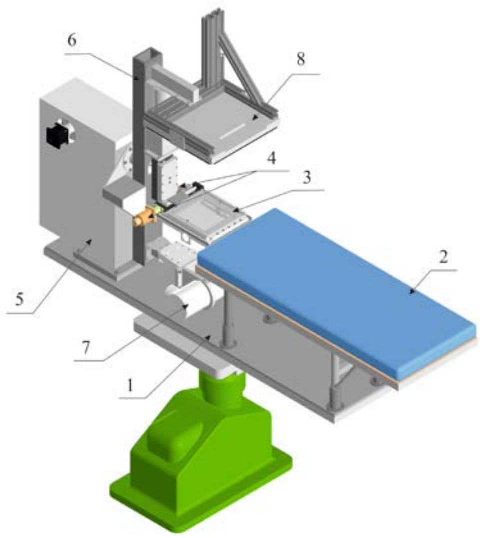
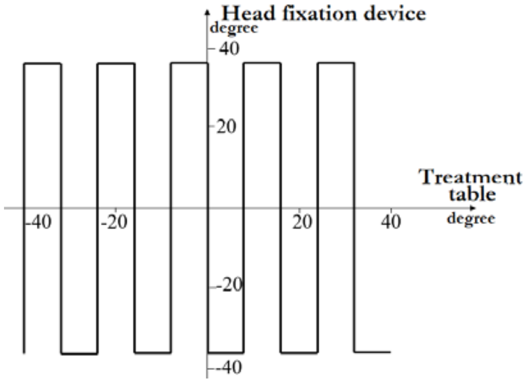


Fig. 2. Scheme of the installation of proton stereotaxic therapy: *1* – treatment table; *2* – treatment table deck; *3* – head fixation device; *4* – drives for movement of the deck of the HFD along the *X* and *Y* axes; *5* – HFD drive rack; *6* – rocker for rotation of the *X*-ray centralizer; *7* – *X*-ray monoblock; *8* – flat panel *X*-ray detector

The irradiation procedure begins with setting the initial position of the UPST: the HFD is set to –36°, the treatment table is set to –40° (depending on clinical requirements, other angles can be chosen). Simultaneously with switching on the beam, the movement of the UPST is started in accordance with the preset irradiation program. The HFD rotates from –36° to +36°, after which the treatment table rotates to a fixed angle, depending on the planned number of passes (for example, 8° for 10 passes). This cycle of movement corresponds to one pass. Then the second pass begins: the HFD makes a reverse movement from +36° to –36°, the treatment table again turns to a fixed angle, *etc*. (Fig. 3) until the irradiation program is completed.



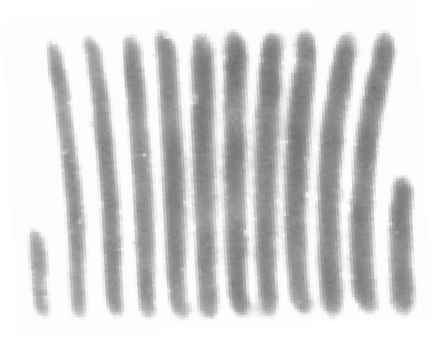


Fig. 3. Diagram of movement of the head fixation device and treatment table during 10 passes (*left*); radioautograph of a proton beam (*right*)

As a result, the beam describes a trajectory on the patient's head, shown in Fig. 4. The concentration of the dose at the desired point occurs due to the following factors:

- Changing the direction of the patient irradiation by slowly turning it in two planes relative to the beam axis;
- Focusing of the proton beam by quadrupole magnetic lenses to the irradiation point;
- Small angular scattering of protons with an energy of 1 GeV in the patient's body.

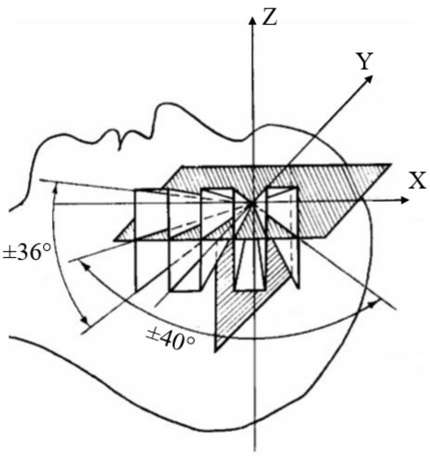


Fig. 4. Irradiation scheme. Direction of the proton beam passing through the centre of the target during stereotaxic irradiation using rotation of the stereotaxic proton therapy unit

Based on the results of clinical trials, it was found that the medical proton beam formed at the SC-1000 can be rationally used in the field of radioneurosurgery to affect small pathological areas of the brain (up to 2 cm) in order to destroy them. The main advantage of this method is the possibility of forming small dose fields with a high edge gradient, which makes it possible to concentrate the absorbed dose in the tumor with minimal radiation exposure of the surrounding tissues. Due to the high energy of the particles, the angular divergence of the 1 GeV proton beam is much smaller with the PBT than with the standard energy for PBT (using the Bragg peak), which simplifies the treatment planning. Using the gantry system is not provided due to the high energy of protons: guide magnets would be too heavy and cumbersome, so the technique of rotating the object of irradiation on a special installation is used.

The first full-scale dosimetric and radiobiological studies to analyse the effectiveness and at the same time the safety of using 1 GeV proton beam of the SC-1000 for radiation therapy, as well as to determine the scope of its application, were carried out back in 1971–1974. By 2013, the proportion of patients receiving proton therapy from the RSC RST–PNPI was approximately 2% of the global number of patients treated in the world. Using of proton stereotactic therapy (radiosurgery) proved to be effective in the treatment of various brain diseases, especially pituitary adenomas and cerebrovascular malformations, as well as in adenohypophysis irradiation for palliative purposes in breast and prostate cancer [3]. After 40 years of successful experience in treating patients, studies conducted in 2013–2017 led to the decision on the advisability of upgrading the stereotaxic proton therapy (radiosurgery) unit to meet modern requirements and world standards in radiation therapy, as well as for UPST registration as a medical device and the resumption of medical activities. The key stages of the modernization were: updating the material and technical base and software, including the replacement of the *X*-ray centering complex, updating the clinical dosimetry system, creating an automated control system for the UPST, a system for dose-anatomical planning and expanding methods for verifying of exposure plans.

3. Modernization of the medical proton complex

3.1. Replacement of the main elements of the X-ray centralizer

The *X*-ray centralizer is an integral part of the UPST, which is necessary to point the irradiation focus at the isocentre of the UPST. Previously, a TURDE-19 *X*-ray machine manufactured in 1982 was used with an electron-optical converter (EOC) and an *X*-ray television installation, on the monitor of which the resulting image was displayed. The issue of replacing the old *X*-ray centralizer with a more modern one is long overdue. The obsolescence of the equipment was considered the main obstacle to the beginning of the formalization of the complex as a medical device. The main parts of the *X*-ray centralizer (the *X*-ray emitter, the power supply and EOC) were replaced in 2018 with new equipment that meets modern requirements for *X*-ray studies. The EOC device was replaced with a digital flat panel detector DFP 4343 (Fig. 5). The size of the active area of the detector is 430×430 mm^2, the matrix resolution is $3\,072 \times 3\,072$, and the pixel size is 140×140 μm^2. For the new detector, a protective cover was made of plexiglass, and a radiopaque crosshair was applied, corresponding to the centre of the detector.

The updated *X*-ray centralizer based on a flat-panel detector surpasses the previously used one based on an image intensifier tube in most characteristics. The advantage is high spatial resolution, large dynamic range, high resistance to direct *X*-ray radiation, absence of spatial distortions and unevenness, insensitivity to magnetic fields, remote control, reduction of radiation exposure to staff. The high sensitivity of the flat panel detector makes it possible to obtain a high-quality image with a wide exposure range. In addition, it became possible to visualize small and low-contrast structures, which simplifies the procedure of laying the patient. Also, an automated workplace for the operator was organized to control the system and to work with the research results (Fig. 6). The digital format allows additional computer processing of the obtained images; the results of the study are stored in the system.

Fig. 5. *X*-ray centralizer in vertical position

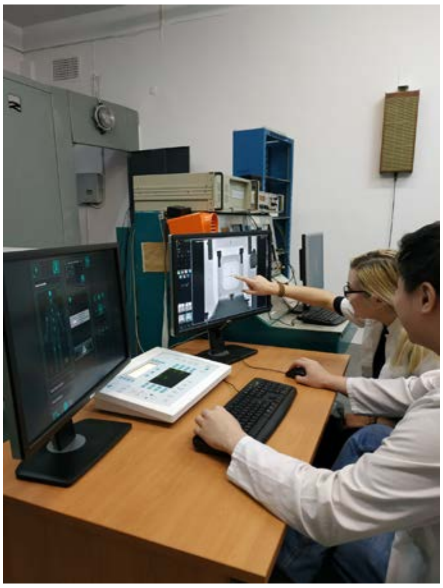


Fig. 6. Operator workstation

3.2. Update of the clinical dosimetry system

In 2018, the clinical dosimetry system was supplemented with a set of dosimetric equipment, which includes a Unidose^{webline} PTW (Physikalish-Techische Werkstatten) Freiburg GmbH T10021 single-channel dosimeter with built-in firmware for absolute dosimetry of therapeutic and diagnostic beams and ultrasmall PinPoint ionization chambers of the type TM31014 (0.015 cm^3) and TM31015 (0.03 cm^3). This device is included in the register of Rosstandart. The dose measurement range is from 200 μGy to 450 MGy, the dose rate being from 1.2 mGy/min to 7.5 kGy/min simultaneously in three measurement ranges. The dosimeter has the ability to correct readings by entering various corrections. Multiplication by correction factors is done automatically by the instrument. The device is easy to use. Setting up, adding and changing the necessary parameters of the device and detector for the study is rather simple. The device can be controlled remotely with a local personal computer *via* the Internet using the virtual network computing program.

Measurements of the dose of a proton beam with an energy of 1 GeV during the verification of the new system (using Unidose^{webline}) were compared with the results of the existing equipment – thermoluminescence dosimetry (TLD) detectors. The analysis of the data showed that the difference in the dispensed dose does not exceed 5%, which indicates good agreement between the data. Figure 7 shows 2 Gy "dose binding" data using the chambers of clinical dosimeter Unidose^{webline} and a comparison with the clinical dosimeter, type 27012, with hose ionization chamber, type 70107 (0.05 cm^3). As can be seen from the diagrams, the differences in the absorbed dose for beams 1 and 2 cm in diameter do not exceed 5%. The difference in the dose at a narrow beam with a diameter of 8 mm arises due to different active volumes of the compared ionization chambers.

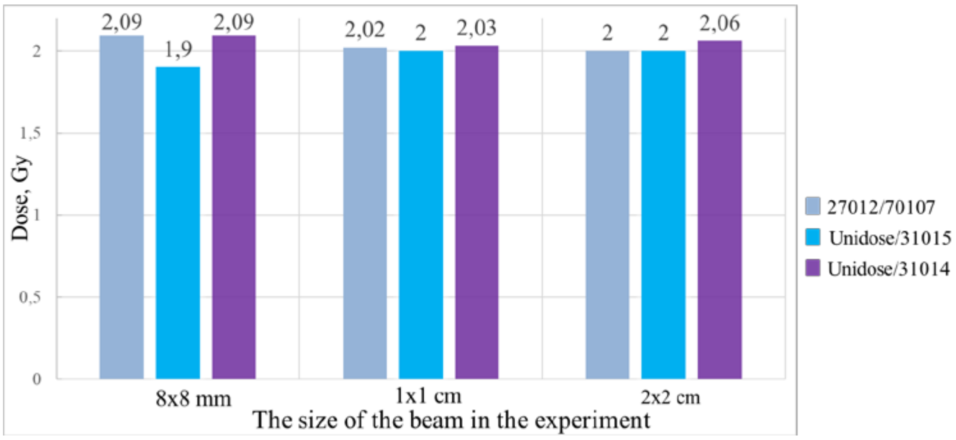


Fig. 7. Comparison of the "dose binding" using PTW Unidose^{webline} and clinical dosimeter type 27012

3.3. Replacement of the control system, and equipment layout

The third-generation UPST control scheme was created back in 1989. Accordingly, the existing element base has become obsolete over the years and cannot meet the current requirements for ensuring the quality of the proton therapy. In 2014–2016, in order to improve the exploitative characteristics (speed of movement, positioning accuracy) of the electromechanical units and elements of the UPST, unipolar stepper motors were replaced with bipolar ones, which made it possible to significantly improve the dynamic characteristics of the moved units of the UPST and to use the mode of reducing the step of the motors during their movement, which improves the smoothness of movement. Magnetic-modulatory sensors of angular displacements were replaced by optical multidigit sensors "angle–code". This measure makes it possible to significantly improve the displacement measurement result and the overall safety of the obtained results. The replacement of the equipment required the development of a new hardware and software (see below). Two types of drivers and a power source for controlling the operation of bipolar stepper motors, three two-channel adapter–coordinator–distributors and a manual control panel for electromechanical units of the UPST were developed and manufactured. In order to respond promptly to emergency situations, the control drivers were moved in 2018 from the irradiation room to the control room. On the whole, the synchronization of the system has been simplified: two workstations have been merged into one; the UPST is controlled by a single program, which also receives data from ionization chambers and profilometers.

3.4. Creation of an automated control program for the installation of proton stereotaxic therapy

The development of a program for the automated control of the UPST was required in connection with the replacement of the hardware for controlling the drives of the treatment unit. The first version of the control program "Proton Therapy", intended to control the patient irradiation system, was developed in 2015. This program was used in conjunction with the previously developed "Profilometer" program, designed to display the data obtained using multiwire proportional chambers that measure the spatial characteristics of the beam online during irradiation. The program "Proton Therapy" had two drawbacks:

- The forced use in conjunction with the "Profilometer" program installed at another workstation, as a result of which it became necessary to involve at least two operators to monitor the irradiation process;
- The development of the program was stopped at the testing stage.

To expand the capabilities of the first version of the program of the control, it was decided to rework it at a new level and to combine it with the program for monitoring the parameters of the proton beam. So, in 2019 a software was created for controlling the UPST with the function of controlling the parameters of the proton beam [4]. The program is designed to automate proton therapy and provides the following modes of operation:

- Manual control of five axes of movement of the UPST;

- Output of information about the beam parameters: beam profiles (size, position), background, statistical parameters, intensity;
- Calculation of the monitor unit per absorbed dose unit;
- Setting exposure parameters or loading patient exposure plans;
- Conducting irradiation according to the given algorithm;
- The ability to interrupt and continue the irradiation process;
- Display of complete information about the course of the irradiation process in the form of 3*D* animation, graphs, tables;
- Generating reports;
- Formation of daily logs of actions of the program and operator, the ability to view the log for any date;
- Editing and storage of the parameters of the movement of the elements of the UPST, setting the parameters for registration of the proton beam.

The developed program has a flexible and understandable interface (Fig. 8). It allows one to manage the UPST in the manual mode as efficiently as possible and to receive complete information about the state of the installation. There is full control over the beam parameters and the possibility of linking to the dose ("dose binding"). The beam profiles are controlled directly in the control program, and not at a separate station. These additions have increased the work efficiency and led to a reduction in the time spent on the commissioning. The irradiation process has become more understandable in terms of visual component and information content, which contributes to the standardization of treatment protocols. The control of the irradiation process (beam profiles) has become automated.

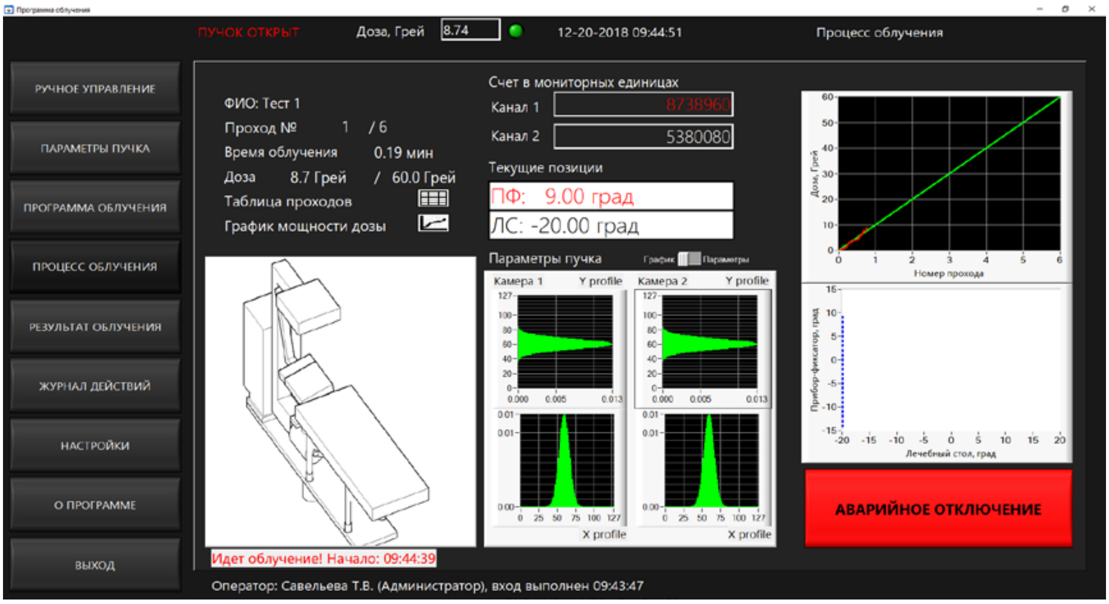


Fig. 8. Operating window of the stereotactic proton therapy unit control system

3.5. Development of a planning and verification system

A narrow proton beam with 1 GeV energy in combination with a stereotaxic irradiation method makes it possible to form strictly localized and concentrated dose fields. However, to realize this opportunity, it is necessary to carry out preliminary dose-anatomical planning of irradiation. At the first stage of proton therapy (1975–2013), irradiation planning was carried out manually according to experimental data. Dose distributions were obtained in a spherical phantom imitating the patient's head using TLD detectors, which were placed in the phantom in two mutually perpendicular planes with a step of 5 mm in the central region and 10 mm at the periphery. In this way, several tens of isodose maps were obtained and analysed for various irradiation parameters, which were combined into an atlas of dose distributions. As a rule, due to the limited shape and size of formations recommended for proton stereotaxic therapy with 1 GeV protons, the irradiation parameters in most cases did not change. The constructed isodose curves were plotted on a transparent film and superimposed on the magnetic resonance images of patients, performed in the frontal and sagittal planes, at the same scale. Then, the distance from the isocentre to the critical structures was determined. The measured distance was used to calculate the dose load on them. The areas of the target, and of the dose fields were calculated by simple arithmetic calculations. Manual scheduling is currently considered obsolete. Experimental data continue to be used, but only to verify the calculated dose distributions, and not as the main planning method.

The planning system and the verification system, along with the clinical dosimetry system, form the basis of radiotherapy quality assurance. The existing commercial software cannot be applied to the 1 GeV proton beam treatment method, since this method is unique and does not fit into the existing requirements. The work on the creation of a computerized treatment planning system (TPS) ProtoPlan, the algorithm for calculating the predicted dose of which is based on the Monte Carlo method with parameterization of integral properties, was started in 2018. The three-dimensional geometry of the TPS takes into account such features as:

- Energy of 1 GeV;
- Beam size of 6–10 mm at 50% isodose;
- Beam convergence and divergence;
- Lack of a gantry system;
- “On-through” irradiation;
- Change in linear energy transfer along the trajectory;
- Isocentric irradiation technique implemented with the help of the UPST;
- Scattering in the irradiated object;
- “Blurring: of the dose distribution due to secondary particles that are born in the process of interaction of protons with biological tissues.

Due to the uniqueness of the method of irradiation with 1 GeV protons, as well as the system of rotation of the irradiation area relative to the beam axis fixed in space, the main abilities of a non-standard proton therapy planning system became:

- Receiving data from diagnostic devices, support for the format of digital imaging and communications in medicine;
- Reconstruction of images from the original data set;
- Segmentation target volumes and organs of a risk;
- Calculation of the absorbed dose from a given beam and its presentation in the form of two- and three-dimensional isodose distributions superimposed on anatomical images (Fig. 9);
- Construction of “dose-volume” histograms for targets and critical organs;
- Export of the irradiation plan to the control program of the UPST.

One of the complex tasks of the formation of the modern concept of the MPC, along with the planning system, is the verification of the calculated exposure plans. The verification system is designed to compare the actual dose that the patient will receive with the dose calculated in the planning system. This stage of radiation therapy allows to be sure of the exact implementation of the radiation plan and additionally check the correct operation of the planning system for various radiation parameters. The dose distribution measured during the implementation of the verification plan (QA-plan) is compared with the calculated dose distribution using the γ-analysis method, which is currently the global standard. This method combines two criteria:

- Comparison of the percentage difference between the calculated and measured dose values;
- Comparison of the smallest distance from the measurement point to the isodose surface of the calculated dose value corresponding to the measured value.

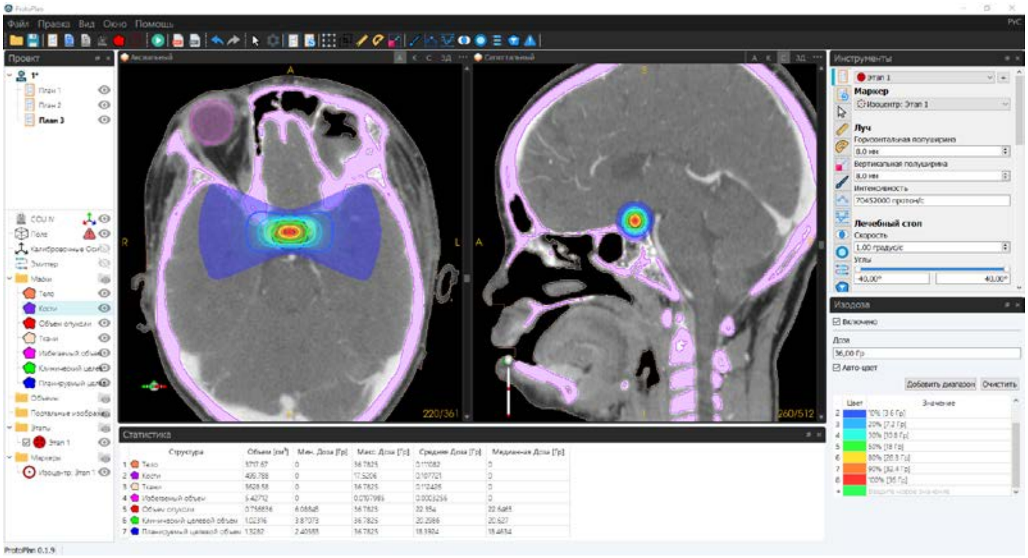


Fig. 9. Isodose curves superimposed on magnetic resonance images of patients in the frontal (*left*) and sagittal (*right*) planes obtained in ProtoPlan

Currently, the work is underway to build up a dosimetric phantom for verification, and a possibility of using radiochromic films as detectors for relative dosimetry is being considered. As a result, the commissioning of a system of planning and verification will make it possible to proceed to the registration of the UPST as a medical device and the resumption of medical activities.

4. Conclusion

On April 17, 2023 it will be 48 years since the start of treatment of patients with proton therapy based on the synchrocyclotron SC-1000. There is no doubt that the unique method of proton radiosurgery for brain diseases using 1 GeV protons should be used with maximum efficiency. To resume proton therapy, it is necessary to obtain a registration certificate for the UPST as a medical device. To this end, a program was launched to modernize the equipment in order to bring the MPC in line with modern quality requirements, as well as to improve the reliability of therapy based on the SC-1000.

As part of the modernization, the main elements of the MPC have been replaced with more modern analogues, including: an *X*-ray centering system, a clinical dosimetry system, a control system, and technical tests of the updated systems were carried out. The last stage of modernization, which made it possible to proceed to the registration of the UPST as a medical device, was the development of a system for dose-anatomical planning and verification of exposure plans. This stage was performed in 2021. By the end of 2022, all planned engineering and technical works have been completed to bring the MPC to modern standards. The proton therapy based on SC-1000 can now be resumed.

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